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***Intractable & Rare Diseases Research*** devotes to publishing the latest and most significant research in intractable and rare diseases. Articles cover all aspects of intractable and rare diseases research such as molecular biology, genetics, clinical diagnosis, prevention and treatment, epidemiology, health economics, health management, medical care system, and social science in order to encourage cooperation and exchange among scientists and clinical researchers.

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## Review

**151-161** **Rare but not to be overlooked: Epidemiology and strategies for rare dermatological diseases in China.**
*Yue Han, Qianwei Zhuo, Nuo Chen, Haosong Zhang, Lihang Lin, Peipei Song*

**162-174** **Literature analysis and implication of biologic therapy for children with non-systemic juvenile idiopathic arthritis in real-world settings.**
*Albert Fung, Xiaomeng Yue, Patricia R. Wigle, Jeff J. Guo*

**175-182** **Secondary musculoskeletal disability and rehabilitation aspects in adults with thalidomide embryopathy: A narrative review.**
*Nobuhiko Haga, Junko Fujitani, Takeshi Kobayashi, Sayaka Fujiwara, Hiroji Tsujimura, Shinichi Shirahoshi, Akiyo Tanabe*

**183-191** **Unraveling the genetic and pathophysiological mechanisms underlying disorders of sex development.**
*Yundi Wang, Hongjuan Zhao, Hongli Yan, Yu Wang*

**192-202** **Towards an Asian paradigm of inflammatory bowel disease management: A comparative review of China and Japan.**
*Qi Sun, Zhixian Jiang, Lichao Yang, Hao Liu, Peipei Song, Lianwen Yuan*

## Brief Report

**203-209** **The effects of mindfulness-based cognitive behavioral group program for patients with intractable disease and high depression.**
*Yukihiko Ueda*

**210-215** **Three-year real-world outcomes of lanadelumab prophylaxis in hereditary angioedema: Complete disease suppression and psychosocial benefits in two East Asian patients.**
*Saori Takamura, Tomoo Fukuda*

**216-222** **Clinical and genetic analysis of X-linked nephrogenic diabetes insipidus caused by a novel *AVPR2* mutation (NM_000054.6:exon3:c.245G>A (p.Cys82Tyr)) in a Chinese boy.**
*Jianmei Yang, Yan Sun, Chen Chen*

**223-231** **Identification of a novel *de novo AFF4* variant (c.778A>G) associated with CHOPS syndrome.**
*Xinyue Deng, Lingling Zhao, Ming Chen, Qin Xiang, Hongbo Xu, Jiangang Wang, Hao Deng, Lamei Yuan*

## Letter

**232-235** **Renal oncocytoma mimicking chromophobe renal cell carcinoma: Management using proposed diagnostic algorithm with emphasis on 99mTc-sestamibi SPECT/CT.**
*Ryan K.W. Chee, Mitchell P. Wilson, Gavin Low*

***Review***

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# Rare but not to be overlooked: Epidemiology and strategies for rare dermatological diseases in China

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**SUMMARY**: Rare skin diseases in China, recognized through the 2018 National Rare Disease List (121 conditions), pose substantial epidemiological and systemic challenges. The National Rare Diseases Registry System (NRDRS) documented 62,590 cases (2016–2020) of 166 diseases, and yet data remain fragmented: only 53.1% of rare diseases are prevalent and they are found in 94.1% of regions. Eight diseases have an incidence of ≥ 1/1,000. Regional disparities persist, as 60% of cases originate from affluent East/North China, contrasting with lower utilization of genetic testing in Western regions (71.9% *vs*. 79.2% in the East). Diagnostic delays average 1.4 years, with patients visiting 3.2 hospitals and enduring 1.6 misdiagnoses, exacerbated by limited physician awareness — only 5.3% of clinicians report moderate familiarity with rare diseases. Therapeutic advances, including B cell-targeted therapies (*e.g*., rituximab), coexist with barriers like orphan drug affordability, exemplified by projected annual budgets exceeding CNY 179 million for 98 patients. Clinical trials increased at a rate of 28.2% annually (2013–2022), yet China lags behind its global counterparts in trial diversity. Policy initiatives, such as the 2019 Drug Administration Law, prioritize orphan drug development but face challenges in regional implementation and insurance coverage. Critical needs include equitable healthcare access, standardized registries, and clinician education. Collaborative networks (*e.g.*, NRDRS-linked biobanks) and media-driven awareness campaigns are vital to alleviating systemic gaps for China's estimated 20 million patients with rare diseases.

***Keywords***: rare skin diseases, genetic testing, healthcare policy, diagnostic challenges, therapeutic advances

## 1. Epidemiological overview of rare dermatological diseases in China

### 1.1. Definition and classification of rare skin diseases

Rare dermatological diseases are defined based on their low prevalence in the general population. In China, the classification of rare diseases gained significant attention following the release of the first national list of rare diseases in 2018, which included 121 conditions. This list aimed to enhance societal awareness, improve diagnostic and treatment capabilities, and promote research and development of orphan drugs (*1*). While the list encompasses a broad spectrum of rare diseases, specific dermatological conditions are included, reflecting the growing recognition of their impact on public health (Table 1).

The classification of rare skin diseases often involves a combination of clinical presentation, genetic factors, and epidemiological data. For instance, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which includes microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), is not uncommon in China. Among GPA patients, myeloperoxidase (MPO)-ANCA is markedly more prevalent than proteinase 3 (PR3)-ANCA (*2*). This highlights the importance of molecular and immunological markers in the classification and diagnosis of rare dermatological diseases.

The establishment of the National Rare Diseases Registry System (NRDRS) in China has further contributed to the classification of rare diseases. Between 2016 and 2020, the NRDRS registered 62,590 cases involving 166 diseases or disease types (*3*). This registry provides a structured framework for categorizing rare diseases, including dermatological conditions, based on clinical and demographic data. Such efforts are critical to understanding the epidemiological landscape and guiding healthcare policies.

### 1.2. Prevalence and incidence in different regions of China

**Table 1. Rare skin diseases in China (Top 30)**

| No. | Disease |
|---|---|
| 1 | Epidermolysis bullosa (EB) |
| 2 | Ichthyosis (*e.g.*, Harlequin ichthyosis and Lamellar ichthyosis) |
| 3 | Porphyria cutanea tarda |
| 4 | Hereditary angioedema |
| 5 | Scleroderma (Systemic sclerosis) |
| 6 | Dermatomyositis |
| 7 | Xeroderma pigmentosum (XP) |
| 8 | Neurofibromatosis (Type 1 and 2) |
| 9 | Tuberous sclerosis complex (TSC) |
| 10 | Necrobiosis lipoidica |
| 11 | Pseudoxanthoma elasticum (PXE) |
| 12 | Darier disease (Keratosis follicularis) |
| 13 | Hailey-Hailey disease (Familial benign pemphigus) |
| 14 | Erythropoietic protoporphyria (EPP) |
| 15 | Lichen sclerosus |
| 16 | Pachyonychia congenita |
| 17 | Goltz syndrome (Focal dermal hypoplasia) |
| 18 | Incontinental pigmenti |
| 19 | Sturge-Weber syndrome |
| 20 | Ehlers-Danlos syndrome (Vascular or Dermatosparaxis types) |
| 21 | Cutaneous T-cell lymphoma (Mycosis fungoides/Sézary syndrome) |
| 22 | Hidradenitis suppurativa (Severe/rare subtypes) |
| 23 | Aplasia cutis congenita |
| 24 | Congenital melanocytic nevus syndrome |
| 25 | Mastocytosis (Systemic or Cutaneous) |
| 26 | Paraneoplastic pemphigus |
| 27 | Blau syndrome |
| 28 | Lipoid proteinosis (Urbach-Wiethe disease) |
| 29 | Erythrokeratodermia variabilis |
| 30 | Progeria (Hutchinson-Gilford syndrome) |

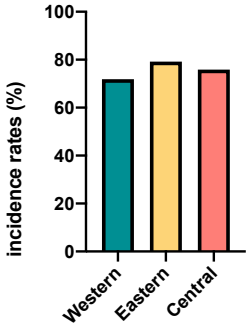


**Figure 1. Regional disparities in the prevalence and incidence of rare diseases in China.**

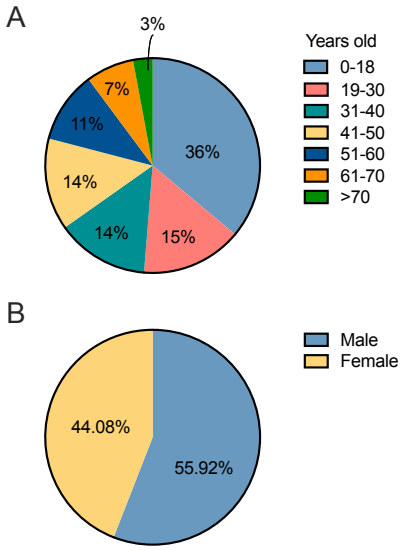


**Figure 2. Characteristics of patients with rare diseases in China. (A) Age; (B) Sex.**

Epidemiological data on rare diseases in China remain limited, with only 1,264 data points on prevalence and incidence found in 277 studies, guidelines, and official websites. These data cover 110 rare diseases (53.1%) and 32 regions (94.1%), excluding the Tibet Hui Autonomous Region and Macao Special Administrative Region. Eight of these diseases have an incidence equal to or greater than 1,000 patients per million (*4*). This highlights the uneven distribution of epidemiological data and the need for comprehensive studies to address gaps in knowledge, particularly for rare dermatological diseases.

Regional disparities in the prevalence and incidence of rare diseases are evident. For example, the NRDRS data indicate that 60% of registered cases are from the wealthier regions of East and North China, underscoring disparities in access to quality care (*3*). Similarly, the rate of genetic testing for rare diseases is highest in the Eastern region (79.2%), followed by the Central (75.9%) and Western regions (71.9%) (Figure 1) (*5*). These disparities reflect broader socioeconomic inequalities that influence the availability and quality of healthcare for rare disease patients.

Rare disease patients in China often face significant challenges in being accurately diagnosed. On average, patients experience a diagnostic delay of 1.4 years and 1.6 misdiagnoses across 3.2 hospitals. Moreover, diagnoses are highly concentrated in 10 large hospitals (43.8%) and 5 major cities (42.1%) (*6*). This concentration of medical resources further exacerbates regional disparities and highlights the need for equitable distribution of healthcare infrastructure.

### 1.3. Demographic and genetic factors influencing disease distribution

Demographic and genetic factors play a crucial role in the distribution of rare dermatological diseases in China. The NRDRS data reveal that the average age of definitive diagnosis for rare diseases is 30.88 years, with 36.07% of cases diagnosed in individuals under 18 years of age (Figure 2) (*3*). This age distribution underscores the importance of early diagnosis and intervention, particularly for pediatric patients who may face lifelong challenges associated with rare dermatological conditions.

Genetic testing has emerged as a vital tool for diagnosing and understanding rare diseases. In China, the overall rate of genetic testing for rare diseases is 76.0%,

with pediatricians performing testing at the highest rate (94.1%) and surgeons performing it at the lowest rate (58.3%). The high rate among pediatricians reflects the critical role of genetic testing in diagnosing congenital and hereditary conditions, which are common among rare dermatological diseases. However, the high cost of genetic testing remains a significant concern for medical personnel (*5*), potentially limiting its accessibility for patients in less affluent regions.

Specific genetic markers have been identified in certain rare dermatological diseases, further elucidating their distribution. In AAV, for instance, there is a significant predominance of MPO-ANCA over PR3-ANCA in Chinese patients. This genetic predisposition highlights the need for targeted diagnostic and therapeutic strategies tailored to the unique genetic landscape of the Chinese population.

Demographic and genetic factors significantly influence the distribution and diagnosis of rare dermatological diseases in China. Efforts to address disparities in access to genetic testing and healthcare are essential for improving outcomes for patients affected by these conditions.

## 2. Clinical features and diagnostic challenges

### 2.1. Key clinical manifestations of rare skin disorders

Rare dermatological diseases in China have varied clinical presentations, often hampering their recognition and diagnosis. For instance, the clinical manifestations of hand, foot, and mouth disease (HFMD), which can occasionally present with dermatological symptoms, vary significantly depending on the causative pathogen. Among 5115 HFMD inpatients analyzed, 4.3% presented with severe symptoms, and there were significant complications in 4.1% of severe cases. While HFMD is not exclusively a dermatological condition, its skin-related symptoms, such as vesicular eruptions, highlight the importance of pathogen identification in understanding disease severity. Coxsackievirus A6 was identified as the predominant pathogen, accounting for 63.5% of mild cases and 36.2% of severe cases. This serotype's association with more severe dermatological manifestations underscores the need for pathogen-specific diagnostic approaches. In contrast, EV-A71, previously considered a major serotype, was responsible for only 15.6% of severe cases and 1.2% of mild cases. Sporadic detection of Coxsackievirus A10 (CV-A10) and A16, with CV-A10 infections tending to increase, further complicates the clinical landscape (*7*).

The variability in clinical presentations among rare dermatological diseases poses significant challenges for clinicians. For example, the overlapping symptoms of different pathogens, such as vesicular eruptions and systemic complications, can lead to misdiagnosis or delayed diagnosis. This complexity is compounded by the lack of standardized diagnostic criteria for many rare skin disorders, which often rely on clinical observation and pathogen-specific laboratory tests. The findings from HFMD studies highlight the importance of understanding pathogen-specific clinical features to improve diagnostic accuracy and patient outcomes (*7*).

### 2.2. Barriers to early and accurate diagnosis

The diagnosis of rare dermatological diseases in China is hindered by several systemic and educational barriers. A survey of physicians revealed that only 5.3% were moderately or well aware of rare diseases, indicating a significant knowledge gap. This lack of awareness is further reflected in clinical practice, where 80.1% of physicians reported suspecting rare diseases in their patients fewer than three times throughout their careers (*8*). Such limited exposure to rare diseases may result in delayed recognition and misdiagnosis, particularly for conditions with subtle or atypical dermatological manifestations.

Physicians with longer careers were more likely to believe that their medical education had not provided sufficient information about rare diseases. This suggests that conventional medical curricula may inadequately address the complexities of rare dermatological conditions, leaving clinicians ill-equipped to identify and manage these diseases. Moreover, the lack of continuing medical education programs focused on rare diseases exacerbates this issue, as practicing physicians have limited opportunities to update their knowledge and diagnostic skills.

The importance of rare disease awareness was emphasized by nine rare disease experts, who highlighted the role of awareness in facilitating early diagnosis and timely treatment (*8*). Increased awareness among healthcare personnel could lead to more proactive diagnostic approaches, reducing the time to diagnosis and improving patient outcomes. However, achieving this requires systemic changes in medical education and training as well as the development of targeted educational campaigns.

### 2.3. Role of advanced diagnostic tools and biomarkers

Advances in diagnostic technologies and biomarker research offer promising solutions to the challenges of diagnosing rare dermatological diseases. The establishment of the NRDRS represents a significant step toward standardizing rare disease registration and improving diagnostic accuracy. This system integrates genomic biobanks and fosters partnerships to share data and collaborate in research, enabling the identification of disease-specific biomarkers and genetic variants (*9*).

Innovative informatics technologies, including ontological and knowledge bases, have been implemented to facilitate the standardization of

diagnostic criteria and enhance diagnostic precision. These tools allow clinicians to access comprehensive databases of rare disease information, facilitating the identification of atypical clinical features and rare genetic mutations associated with dermatological conditions. By using these technologies, healthcare personnel can improve diagnostic accuracy and reduce the reliance on subjective clinical observations.

Long-term research collaboration is encouraged to create additional national rare disease networks, which could further enhance diagnostic capabilities and translate research findings into clinical practice (*9*). Such networks would enable the development of novel diagnostic tools and biomarkers, alleviating the current gaps in rare disease diagnosis. Moreover, the integration of these networks into clinical workflows could streamline the diagnostic process, ensuring that patients with rare dermatological diseases receive timely and accurate diagnosis.

The role of advanced diagnostic tools and biomarkers is pivotal in overcoming the challenges associated with rare dermatological diseases. By integrating genomic data, informatics technologies, and collaborative research efforts, the NRDRS and similar initiatives provide a framework for improving diagnostic accuracy and patient care (*9*).

## 3. Current therapeutic approaches and management strategies

### 3.1. Existing treatment modalities: Efficacy and limitations

The treatment landscape for rare dermatological diseases in China has developed markedly over the past few years, reflecting both advances in therapeutic strategies and persistent challenges. Among the notable developments, the refinement of treatment protocols for AAV, a rare dermatological condition with systemic implications, has been a key focus. In China, a rapid tapering of glucocorticoids has been used to minimize long-term exposure and associated adverse effects. This approach has shown promise in reducing treatment-related complications while maintaining disease control. Additionally, B cell-targeted therapies, such as rituximab, have gained traction as effective options for inducing remission in AAV patients. However, the use of rituximab is not without risks, as infection-related complications and associated mortality remain significant concerns (*2*).

Complement-targeted therapies are another emerging modality for AAV management in China. These therapies aim to modulate the complement system, which plays a critical role in the pathogenesis of the disease. While these approaches are still being developed, they offer the potential for improving outcomes in patients with refractory or severe disease. Moreover, a modified renal risk score model has been validated for early risk prediction in Chinese AAV patients, enabling more personalized and timely interventions (2). Despite these advances, the treatment of rare dermatological diseases in China continues to face challenges, including limited access to specialized therapies, high treatment costs, and the need for more robust clinical evidence to guide practice.

In the broader context of rare diseases, orphan drugs have been a focal point of research and development. These include traditional antibodies, small molecule drugs, gene therapy, stem cell therapy, and small nucleic acid drugs. Clinical breakthroughs in these areas have provided valuable references for the treatment of rare diseases in China, including dermatological conditions. However, the availability and affordability of these therapies remain significant barriers to widespread clinical use (*10*).

### 3.2. Emerging therapies and innovations

The development of innovative therapies for rare dermatological diseases in China has been bolstered by national initiatives and an increasing emphasis on clinical research. Since 2013, China has implemented a pilot project targeting 20 representative rare diseases, which has facilitated the establishment of a national network of approximately 100 provincial or municipal medical facilities. This network has been instrumental in fostering collaboration among clinicians, researchers, and patient organizations, thereby accelerating the development and application of medical guidelines and clinical pathways for rare diseases (*11*).

One of the key outcomes of this initiative has been the promotion of molecular testing for rare genetic disorders, which has significant implications for the diagnosis and treatment of rare dermatological diseases. By enabling precise genetic characterization, molecular testing facilitates the development of targeted therapies and the formulation of personalized treatment plans. Additionally, the establishment of a rare disease patient registry and data repository system has provided a valuable resource for tracking disease progression, treatment outcomes, and long-term patient needs (*11*).

Clinical trials have also played a pivotal role in advancing therapeutic options for rare diseases in China. Between 2013 and 2022, 481 clinical trials on rare diseases were conducted, with an average annual increase of 28.2%. This surge in clinical research has been driven, in part, by supportive policy measures, such as the 2015 policy document that led to an 80% increase in clinical trial applications for rare diseases in 2016 compared to the previous year (Figure 3). Despite these achievements, the number of clinical trials for rare diseases in China remains lower than in the United States, Europe, and Japan, highlighting the need for continued investment and international collaboration (*12*).

Emerging therapeutic modalities, such as gene

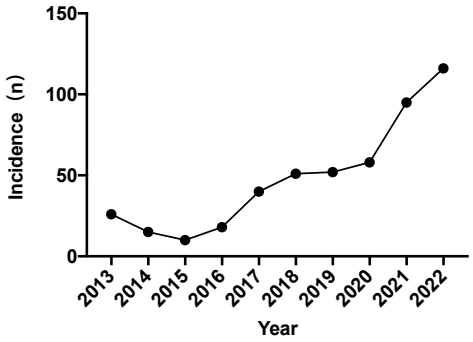


**Figure 3. Annual numbers of clinical trial applications for rare diseases in China.**

therapy and stem cell therapy, have shown particular promise in addressing the unmet needs of patients with rare dermatological diseases. These approaches offer the potential for long-term disease modification and, in some cases, curative outcomes. However, their clinical application is still in the early stages, and further research is needed to establish their safety, efficacy, and cost-effectiveness (*10*).

### 3.3. Patient-centered care and quality of life considerations

In the management of rare dermatological diseases, patient-centered care is increasingly recognized as a critical component of therapeutic strategies. This approach emphasizes the importance of addressing not only the clinical aspects of the disease but also the broader psychosocial and quality of life impacts experienced by patients. Rare dermatological conditions often impose significant physical, emotional, and financial burdens on patients and their families, necessitating a holistic approach to care.

The establishment of a collaborative network among medical facilities, clinicians, and patient organizations in China has been a significant step toward improving patient-centered care. By fostering communication and collaboration, this network has facilitated the development of tailored treatment plans that align with patients' individual needs and preferences (*11*). Moreover, the integration of patient-reported outcomes into clinical practice and research has provided valuable insights into the real-world impact of therapies, enabling more informed decision-making and resource allocation.

Efforts to enhance patient-centered care have also included initiatives to improve access to specialized treatments and reduce the financial burden associated with rare diseases. Government-funded biomedical research programs have been proposed to address challenges such as the high cost of treatment and the shortage of effective drugs for rare diseases (*13*). These programs aim to bridge gaps in care and ensure that patients with rare dermatological conditions receive timely and appropriate interventions.

While significant progress has been made in the therapeutic management of rare dermatological diseases in China, ongoing efforts are needed to address the remaining challenges. By utilizing emerging therapies, fostering collaboration, and prioritizing patient-centered care, the healthcare system can continue to improve outcomes and quality of life for this vulnerable patient population.

## 4. Healthcare and policy challenges in addressing rare dermatological diseases

### 4.1. Access to specialized care and medications

Access to specialized care and medications for rare dermatological diseases in China remains a significant challenge, influenced by factors such as regional disparities, limited healthcare infrastructure, and high costs. The NRDRS, established in 2016, has made strides in standardizing rare disease data collection and promoting research collaboration. This registry includes genomic biobanks and uses innovative informatics technologies to improve rare disease diagnosis and care (*9*). Despite these advances, regional disparities persist, with 60% of registered cases originating from wealthier regions, highlighting inequities in access to quality care (*3*).

The National Network to Collaborate on Diagnosis and Treatment of Rare Diseases, launched in 2019, includes 324 hospitals and aims to create a tiered healthcare alliance for rare diseases. This network focuses on improving collaboration and resource allocation, which is critical to addressing the needs of patients with rare dermatological conditions (*14*). However, physicians in China exhibit a low awareness of rare diseases, with only 5.3% moderately or well aware of those diseases. This lack of awareness underscores the need for improved education in medical schools and the establishment of an online information hub to enhance early diagnosis and treatment (*8*).

Genetic testing plays a pivotal role in diagnosing rare diseases and is performed at an overall rate of 76.0% across China. Regional differences are evident, with testing performed at the highest rate in the Eastern region (79.2%), followed by the Central (75.9%) and Western regions (71.9%). Pediatricians perform genetic testing at the highest rate (94.1%), while surgeons perform it at the lowest rate (58.3%). High costs remain a major concern for physicians, limiting the widespread use of genetic testing in rare disease diagnosis and treatment (*5*).

China's First List of Rare Diseases, established in 2018, includes 121 diseases, with 83 treatments available domestically and 50 covered by national medical insurance. However, challenges such as the lack of a clear definition and coding for rare diseases, difficulty in calculating their economic burden, and limited diagnostic

and rehabilitation services persist. Policy implementation varies across regions, and pilot programs in qualified areas are recommended before national rollout (*15*).

The amended Drug Administration Law of 2019 prioritizes the review and approval of new drugs for rare diseases and encourages domestic development of such drugs. This legal framework provides a basis for improving access to rare disease medications under the Healthy China strategy (*16*). Additionally, recommendations from the Multidisciplinary Expert Seminar on Healthcare Security for Rare Diseases in China emphasize the need for basic data collection and the creation of a healthcare security model tailored to rare diseases. Proposed measures include establishing a special zone for rare disease medical care and classifying healthcare security based on treatment responsiveness (*17*).

### 4.2. Economic burden on patients and healthcare systems

The economic burden associated with rare dermatological diseases in China is substantial, affecting both patients and the healthcare system. A study analyzing the economic burden of 23 rare diseases in Shanghai estimated mean direct medical costs at CNY 9,588 (USD 1,521) for inpatients and CNY 1,060 (USD 168) for outpatients. Factors influencing these costs include age, disease type, complications, and payment type (*18*). High-priced orphan medicinal products (OMPs) further exacerbate the financial strain. For instance, a projected budget of CNY 179 million was required for 98 rare disease patients in Chengdu in 2019, in the absence of reimbursement policies. Under six policy scenarios, the budget ranged from CNY 32 million to CNY 156 million, with annual projections for the next three years ranging from CNY 200 million to CNY 1.303 billion (*19*).

The lack of reimbursement policies for OMPs highlights the need for optimized strategies to alleviate the financial burden on patients. Healthcare policymakers are encouraged to integrate multi-source data and consider financial affordability when designing reimbursement systems (*19*). Additionally, rare disease patients face significant challenges, including delayed diagnosis (1.4 years on average), misdiagnosis, and financial burdens. Recommendations to address these issues include legislating orphan drug acts, expanding medical insurance coverage, and protecting education and employment rights for rare disease patients (*6*).

### 4.3. Policy gaps and recommendations for improvement

Policy gaps in addressing rare dermatological diseases in China are evident, despite ongoing efforts to improve healthcare for rare disease patients. In 2013, China launched its first pilot project focused on 20 representative rare diseases; in concert, it also established a national network of 100 medical facilities, developed clinical guidelines, and promoted molecular testing for rare genetic disorders (*11*). While this initiative laid the groundwork for rare disease healthcare, challenges such as missed or delayed diagnosis, lack of effective drugs, and high treatment costs persist (*20*).

China utilizes a combination of top-down strategies and bottom-up interventions to address rare diseases, with the government leading policy formulation and local authorities and NGOs complementing policy gaps. This approach may serve as a model for other developing countries in improving rare disease healthcare (*21*). However, the lack of a clear definition and coding for rare diseases complicates policy implementation and economic burden calculations (*15*). Recommendations include establishing orphan drug legislation, incentive mechanisms, and reimbursement systems to improve healthcare for rare disease patients (*20*).

China's first national list of rare diseases, released in 2018, aims to improve societal awareness, diagnosis, and treatment of rare diseases. This initiative also seeks to enhance rare disease management and promote international cooperation in drug research and policymaking (*1*). To address regional disparities in policy implementation, pilot programs in qualified regions are recommended before national rollout (*15*). Furthermore, the amended Drug Administration Law of 2019 provides a legal basis for prioritizing the review and approval of new drugs for rare diseases, encouraging domestic development of such drugs (*16*).

## 5. The role of research and collaboration

### 5.1. National and international collaborative efforts

Collaboration at both the national and international level has been a cornerstone in advancing rare dermatological disease research in China. The establishment of the NRDRS in 2016 marked a significant milestone in fostering collaboration among academic institutions and research entities. Over 20 top academic institutions in China are actively participating in the NRDRS, which aims to standardize registration platforms, build genomic biobanks, and create partnerships for sharing data and collaborating in research. This system not only facilitates the collection and sharing of data but also promotes long-term research collaboration, which is essential to translating research findings into clinical applications (*9*).

Internationally, China has increasingly emphasized global cooperation in rare disease research. A national program has been implemented to promote international partnerships, enabling the exchange of knowledge, resources, and expertise. Such collaborations are critical to addressing the unique challenges posed by rare dermatological diseases, which often require specialized knowledge and resources that may not be readily available within a single country. By engaging in international networks, China can capitalize on global

advances in rare disease research while contributing its own findings to the broader scientific community (*22*).

Despite these efforts, challenges remain in aligning national and international priorities, particularly in the context of rare dermatological diseases. The relatively lower number and diversity of clinical trials in China compared to developed countries underscore the need for enhanced international collaboration to bridge these gaps (*12*). Strengthening partnerships with global research entities and patient advocacy groups could further accelerate progress in this field.

5.2. Advancing genomic and epidemiological research

Genomic and epidemiological research plays a pivotal role in understanding the etiology and prevalence of rare dermatological diseases. Since the 1980s, China has made significant strides in rare disease research, with increasing national attention in recent years (*22*). The launch of the first pilot project for rare diseases in 2013 marked a critical step forward, focusing on 20 representative rare diseases and establishing a national network of approximately 100 provincial or municipal medical facilities. This network facilitates collaboration among clinicians, researchers, and patient organizations, aiming to improve healthcare delivery and develop medical guidelines for rare diseases (*11*).

The NRDRS has further advanced genomic research by incorporating innovative informatics technologies, such as ontological and knowledge bases, to support standardization and improve rare disease diagnoses. These technologies enable the integration of genomic data with clinical information, providing a comprehensive understanding of rare dermatological diseases. Additionally, the establishment of genomic biobanks under the NRDRS framework has created a valuable resource for conducting genetic association studies, which are essential for identifying disease-causing mutations and understanding disease mechanisms (*9*).

However, challenges persist in conducting genetic association studies, particularly in handling large volumes of data and identifying small individual effects. These limitations highlight the need for advanced computational tools and collaborative efforts to overcome technical and methodological barriers. Moreover, the field of rare disease epidemiology faces challenges in coding and classification, calculating disease frequency, and conducting comprehensive studies to inform policy decisions (*23*).

China's progress in clinical trials for rare diseases also reflects the growing emphasis on research. Over the past decade, 481 clinical trials have been conducted, with the number of applications growing at an average annual rate of 28.2% from 2013 to 2022 (*24-42*) (supplementary Table S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=265*). This growth was significantly influenced by policy support introduced in 2016, which encouraged the development of clinical trials and molecular testing for rare genetic disorders. Despite these advances, the number and diversity of clinical trials in China remain lower than in developed countries, indicating the need for further investment in genomic and epidemiological research (*12*).

5.3 The need for rare disease registries and databases

The establishment of rare disease registries and databases is critical to advancing research and improving patient outcomes. The NRDRS, launched in 2016, serves as a centralized platform for the nationwide registration of rare diseases in China. By standardizing registration platforms and incorporating genomic biobanks, the NRDRS facilitates data sharing and research collaboration among academic institutions and healthcare personnel (*9*). This system both facilitates the collection of high-quality data and it enables the development of evidence-based policies and clinical guidelines for rare dermatological diseases.

The NRDRS also uses innovative informatics technologies to enhance the accuracy and efficiency of rare disease diagnosis. These technologies include ontological frameworks and knowledge bases, which standardize data collection and improve interoperability across different research and clinical settings (*9*). Such advances are particularly important for rare dermatological diseases, where accurate diagnosis and classification are often challenging due to the limited availability of clinical and genetic data.

Despite these achievements, the need for additional rare disease registries and databases remains evident. Expanding the scope of the NRDRS to include more rare dermatological diseases and integrating it with international databases could further enhance its utility. Long-term research collaboration is also encouraged to create additional national rare disease networks, which can facilitate the translation of research findings into clinical practice (*9*).

In addition to the NRDRS, the pilot project for rare diseases launched in 2013 also emphasized the importance of establishing a rare disease patient registry and data repository (*11*). These initiatives aim to provide a comprehensive understanding of the burden of rare diseases and support the development of targeted interventions. However, challenges such as data standardization, privacy concerns, and resource allocation must be addressed to maximize the impact of these registries and databases (*23*).

**6. Public awareness and education**

6.1. Improving awareness among healthcare personnel

The awareness of rare dermatological diseases among

healthcare personnel in China remains critically low, posing significant challenges to early diagnosis and effective treatment. A study revealed that only 5.3% of physicians in China were moderately or well aware of rare diseases, highlighting a substantial gap in knowledge. Moreover, the majority of physicians (80.1%) reported having suspected rare diseases in their patients fewer than three times throughout their careers, underscoring the limited exposure and diagnostic experience in this domain (*8*). This lack of awareness is particularly concerning given the complexity and rarity of these conditions, which often require specialized knowledge and diagnostic acumen.

Physicians working in Grade A tertiary hospitals demonstrated a slightly better understanding of rare diseases, particularly in terms of the affordability of orphan drugs, where they were rated higher compared to their counterparts in lower-tier medical facilities (*8*). This disparity suggests that healthcare personnel in higher-tier hospitals may have greater access to resources, training, and exposure to rare disease cases, which could account for their relatively higher level of awareness. However, this localized improvement does not address the broader systemic issue of insufficient knowledge among the majority of healthcare personnel across China.

Experts in the field have emphasized the critical importance of improving rare disease awareness among physicians to facilitate early diagnosis and timely treatment. Recommendations include integrating rare disease education into medical school curricula and providing continuing medical education (CME) programs focused on rare diseases. These measures aim to equip healthcare personnel with the necessary skills and knowledge to identify and manage rare dermatological conditions effectively. Additionally, the establishment of an online "information hub" has been proposed as a practical solution to disseminate rare disease-related information among physicians (*8*). Such a platform could serve as a centralized resource for clinical guidelines, case studies, and diagnostic tools, thereby enhancing the overall competency of healthcare personnel in managing rare diseases.

### 6.2. Community outreach and patient advocacy

Community outreach and patient advocacy have played a pivotal role in raising public awareness of rare diseases in China. Efforts by patient organizations and spontaneous campaigns by the public have significantly contributed to heightened awareness. These initiatives have brought attention to the challenges faced by individuals with rare dermatological diseases, including missed or delayed diagnoses, the shortage of effective drugs, and the high costs of available treatments (*13*). Despite these efforts, these challenges remain substantial barriers to improving the quality of life for affected individuals.

Patient organizations have emerged as key stakeholders in advocating for the needs of individuals with rare diseases. Their campaigns often focus on educating the public, lobbying for policy changes, and providing support to patients and their families. These organizations have also been instrumental in fostering collaborations with healthcare personnel and researchers, thereby creating a more inclusive ecosystem for addressing rare diseases. However, the impact of these efforts is often limited by resource constraints and the lack of a coordinated national strategy.

The experiences of other regions, such as the US, EU, and Japan, offer valuable insights for China in addressing rare diseases. Government-funded special biomedical research programs in these regions have successfully advanced the understanding and treatment of rare diseases (*13*). These programs could serve as a reference for China to develop similar initiatives, focusing on rare dermatological conditions. By drawing on international best practices, China can enhance its community outreach and patient advocacy efforts, ultimately improving outcomes for individuals with rare diseases.

### 6.3. Using media and technology to raise disease awareness

Media and technology have emerged as powerful tools for raising awareness about rare diseases, including rare dermatological conditions. In 2013, China launched its first pilot project focused on 20 representative rare diseases, aiming to improve the level of prevention, diagnosis, and treatment (*11*). This initiative underscores the potential of coordinated efforts to use media and technology to disseminate information and foster collaboration among stakeholders.

A key component of the pilot project was the establishment of a national network consisting of approximately 100 provincial or municipal medical facilities. This network facilitates collaboration among clinicians in basic medical facilities, rare disease patient organizations, and other stakeholders. By building close links within this collaborative network, the project aims to enhance the dissemination of knowledge and resources related to rare diseases. Additionally, the development of medical guidelines, clinical pathways, a rare disease patient registry, and a data repository system has been prioritized to support evidence-based practices and improve patient outcomes (*11*).

Promoting molecular testing for rare genetic disorders is another key focus of the project. Advances in molecular diagnostics have the potential to revolutionize the identification and management of rare dermatological diseases, enabling more precise and timely interventions. Media campaigns and digital platforms can play a crucial role in educating both healthcare personnel and the public about the benefits of molecular testing, thereby encouraging its use.

The integration of media and technology into rare disease awareness strategies aligns with global trends in healthcare communication. Digital platforms, social media, and mobile phone apps offer innovative avenues for disseminating information, engaging stakeholders, and fostering community support. By using these tools, China can enhance its efforts to raise awareness about rare dermatological diseases, ultimately contributing to improved prevention, diagnosis, and treatment outcomes (*43-50*).

## 7. Conclusion

In conclusion, rare dermatological diseases in China pose challenges including fragmented data, regional disparities (*e.g.*, 60% cases in the East/North), diagnostic delays (1.4 years), and limited physician awareness (5.3%). While advances like the NRDRS (62,590 cases) and clinical trials (28.2% annual increase) have made progress, equitable policy implementation, enhanced collaboration, and patient-centered care remain critical to improving outcomes.

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***Review***

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# Literature analysis and implication of biologic therapy for children with non-systemic juvenile idiopathic arthritis in real-world settings

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**SUMMARY**: Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease in children. Besides the more severe systemic form, non-systemic JIA is divided into 5 different subgroups. Polyarticular JIA (polyJIA), particularly rheumatoid factor (RF)-positive, which is defined as the disease involving five or more joints in the first 6 months of disease, has the worst prognosis. Biologic disease-modifying antirheumatic drugs (bDMARDs), particularly tumor necrosis factor inhibitors (TNFi), are the backbone of JIA treatment regimens. This research analyzed the published articles for: *i*) optimal sequence, timing and outcomes; *ii*) comparative effectiveness of various bDMARDs; and *iii*) safety concerns for use of bDMARDs. For patients with polyJIA, early effective treatment with bDMARDs is associated with drug-free remission, lower disease activity, better disease control and outcomes. Adalimumab, etanercept and tocilizumab have comparable effectiveness for treating polyJIA, and these drugs are also well-tolerated. JIA patients had a higher rate of hospitalized/serious infection and malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to using methotrexate. Patients treated with IL-1 inhibitors or IL-6 inhibitors reported significantly more serious infections, compared with patients treated with TNFi. Clinicians and patients should consider potential risk in light of benefits of bDMARDs. The reimbursement policy and pricing issue of bDMARDs are out of the scope of the present literature analysis. The current review may help inform shared decision-making discussions between families and physicians as they weigh the risks and benefits of various treatment approaches for children with JIA.

***Keywords***: juvenile idiopathic arthritis, disease-modifying antirheumatic drugs, DMARDs, biologics, children

## 1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease in children and has a prevalence of 1–4 per 1,000 (*1-7*). It is a heterogeneous collection of inflammatory arthritis diseases that begin before the age of 16 and persist for at least 6 weeks during which no other cause is identified (*8*). JIA is associated with short- and long-term disability due to its progressive destruction of cartilage and bones within joints (*9-11*). Around 50% of children with JIA continue to have the active form of the disease in adulthood, causing physical disability and impaired health-related quality of life (*11-13*).

Besides the more severe systemic form, non-systemic JIA is divided into 5 different subgroups, namely oligoarticular, polyarticular, enthesitis-related, psoriatic, and undifferentiated arthritis according to the International League of Associations for Rheumatology (ILAR) (*8*). Table 1 exhibits the major characteristics of these various subtypes of non-systemic JIA (*14*). Polyarticular JIA (polyJIA) is defined as the disease involving five or more joints. A polyarticular course of JIA could occur in most of these categories. Prior research indicated that polyJIA, particularly Rheumatoid Factor (RF)- positive has a worse prognosis and are less likely to achieve disease remission (*15-17*).

First-line pharmacotherapy for JIA usually consists of a combination of nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoids, and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), with methotrexate (MTX) being the most frequently used agent (*14*). In 2019, the American College of Rheumatology (ACR) and Arthritis Foundation updated treatment guidelines for JIA from their 2011 version, which defined patient populations by multiple clinical phenotypes (*18*). In the 2019, and then again in the 2021, treatment guidelines, NSAID monotherapy was removed as first-line treatment for polyarthritis (*19*). For patients with the presence of certain risk factors, such as joint damage or positive anti-cyclic citrullinated peptide (CCP) antibodies, biologic DMARDs (bDMARDs) could be the next first-line

**Table 1. Main characteristics of various non-systemic JIA subtypes**

| Subtype | Gender Predominance | Adult Equivalent Type | Major Physical Findings | Major Lab Findings |
|---|---|---|---|---|
| Oligoarticular (OA) | Female | NA | • Usually, ≤ 4 joints affected and mostly large joints<br>• Asymmetric, often only a single joint (*e.g.*, knee) | 60% ANA positivity |
| Polyarticular (PA) (RF positive) | Female | Sero-Negative Rheumatoid Arthritis | • Usually, ≥ 5 joints affected<br>• Affected both small and large joints; can be either symmetric or asymmetric<br>• Most common affecting TMJ or cervical spine | 40% ANA positivity |
| Polyarticular (PA) (RF negative) | Female | Rheumatoid Factor (RF) positive Rheumatoid Arthritis | • Usually, ≥ 5 joints affected<br>• Mostly symmetric<br>• Affecting mainly small joints (*e.g.*, wrists and metacarpophalangeal joints)<br>• Aggressive and erosive progression | 40% ANA positivity;<br>Rheumatic Factor positivity;<br>Anti CCP positivity |
| Enthesitis-related Arthritis (ERA) | Male | Spondylarthritis | • Affecting mostly lower limb joints affected with axial involvement<br>• Most commonly affect joints are sacroiliac joint, hip or shoulder | 45-85% HLA-B27 positivity |
| Psoriatic arthritis (PsA) | Equal gender | Psoriatic Arthritis | • Asymmetric arthritis<br>• Affects both small and large joints | 50% ANA positivity |

treatment for polyJIA. This is an area of active research where what patients are most likely to benefit from initial bDMARDs is still being determined.

bDMARDs are powerful medications and JIA treatment has been improved dramatically with the introduction of the tumor necrosis factor inhibitors (TNFi) (*20*). Currently, TNFi are the backbone of JIA treatment regimens. TNFi are divided into two classes: monoclonal anti-TNF antibodies [adalimumab (ADA), golimumab (GOL), infliximab (INF), and certolizumab pegol (CER)] and receptor fusion proteins [etanercept (ETA)].

Besides TNFi, other bDMARDs include Interleukin-1 (IL-1) inhibitors (anakinra (ANA), canakinumab (CAN), and rilonacept), IL-6 inhibitors (tocilizumab (TOC), sarilumab) and T-cell inhibitors (abatacept (ABA)) (*14*). Janus kinase inhibitors (JAKi) (tofacitinib, baricitinib, upadacitinib) are a newer class of drug, considered non-biologic DMARDs (or targeted synthetic DMARDs) for the treatment of JIA.

The expanded list of therapies available for JIA increases the complexity of treatment decisions for physicians and patients. The primary goals of treatment for JIA are to control inflammatory signs and symptoms, prevent joint damage and disease progression and achieve disease remission. However, not all patients respond to the first prescribed bDMARDs. The 2011 ACR guidelines recommended switching from one TNFi to another as one treatment approach (*21*). The 2019 ACR guidelines stated that switching to a non-TNFi is conditionally recommended over switching to a second TNFi, as a second TNFi may be appropriate for patients who had a good initial response to the first TNFi (*18*). Prior research indicated that ~17% of patients with JIA switched at least twice, and the most common reason for switching was inefficacy (57%) (*22*). The optimal choice of a second bDMARD remains unclear. No head-to-head trials have been conducted to compare the efficacy or effectiveness of bDMARDs.

In addition, the optimal sequence and timing of csDMARDs and bDMARDs administration in polyJIA patients needs to be further assessed to understand which patients are most likely to benefit from initial bDMARD therapy. Adverse events (AEs) associated with long term use of bDMARDs and targeted synthetic DMARDs need to be further assessed. A recent systematic review of contraindications and special warnings provided by EMA and FDA for bDMARDs and targeted synthetic DMARDs indicates that TNFi, IL-1i, IL-6i and JAKi all had contraindications and/or warning related to serious infections and malignancy (*23*). For JAK inhibitors, other warnings included major adverse cardiac events and thromboembolic events.

The objective of this article was to highlight recent developments on emergent topics related to use of bDMARDs among children with non-systemic JIA in real-world settings. We first described real-world studies that examined the optimal sequence and timing of csDMARDs and bDMARDs administration and associated outcomes in JIA or polyJIA patients. We then summarized real-world studies that examined comparative effectiveness, including treatment response, remission rate, drug adherence and persistence among polyJIA patients who received various bDMARDs. Lastly, we highlighted findings from real-world studies that assessed serious infections and malignancy for use of bDMARDs among JIA patients.

## 2. Research design and literature search strategy

2.1. Literature search

The literature search was conducted using the database PubMed and Google Scholar to identify English language studies in humans that had the predefined key search terms in their title, abstract, or full text and were published from 2004 to 2024. Two review authors (AF, XY) independently screened articles to determine eligibility. Review articles, case reports, studies in children with systemic JIA, studies with different focuses, and articles that were published before 2004 were removed.

Articles were further assessed for quality and those that met the following criteria were retained: *i*) Study objectives were clearly stated, *ii*) Study population was clearly specified and defined, *iii*) The exposure measures (independent variables) were clearly defined, *iv*) The outcome measures (dependent variables) were clearly defined, *v*) Key potential confounding variables were measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s), *vi*) Limitations of the study were included.

Final articles were chosen through consensus process and discrepancies were resolved through discussion. Figure 1 shows a flowsheet of literature review and study selection for analysis.

2.2. Optimal sequence and timing

A combination of search terms – "biologics", "bDMARDs", "timing", "frequency", "pattern", "combination therapy", "juvenile idiopathic arthritis", "polyarticular JIA" – were used. A total of 52 articles were found. After removing non-relevant articles, six studies were retained for the topic of optimal sequence and timing of csDMARDs and bDMARDs administration.

2.3. Comparative effectiveness

A combination of search terms – "biologics", "bDMARDs", "comparative effectiveness", "treatment response", "remission", "drug adherence", "drug persistence", "juvenile idiopathic arthritis", "polyarticular JIA" – were used. A total of 42 articles were found. After removing non-relevant articles, five studies were retained.

2.4. Safety

A combination of search terms – "biologics", "bDMARDs", "serious infections", "medically important infections", "malignancy", "cancer", "juvenile idiopathic arthritis", "polyarticular JIA" – were used. A total of 26 articles were found. After removing non-relevant articles, nine studies were retained.

**3. Key findings based on a literature analysis**

3.1. Optimal sequence and timing of csDMARDs and bDMARDs administration

The studies that assessed optimal sequence and timing of csDMARDs and bDMARDs are summarized in Table 2. The Start Time Optimization of Biologics in Polyarticular JIA (STOP-JIA) was a prospective, observational Childhood Arthritis and Rheumatology Research Alliance (CARRA) patient registry (*24*). The study compared the effectiveness of three different treatment plans for untreated polyJIA: *i*) Step-Up Plan (initial csDMARD monotherapy with a bDMARD added later if necessary), *ii*) Early Combination Plan (csDMARDs and bDMARDs started together), and *iii*) bDMARDs First Plan (bDMARDs monotherapy). Overall, the study

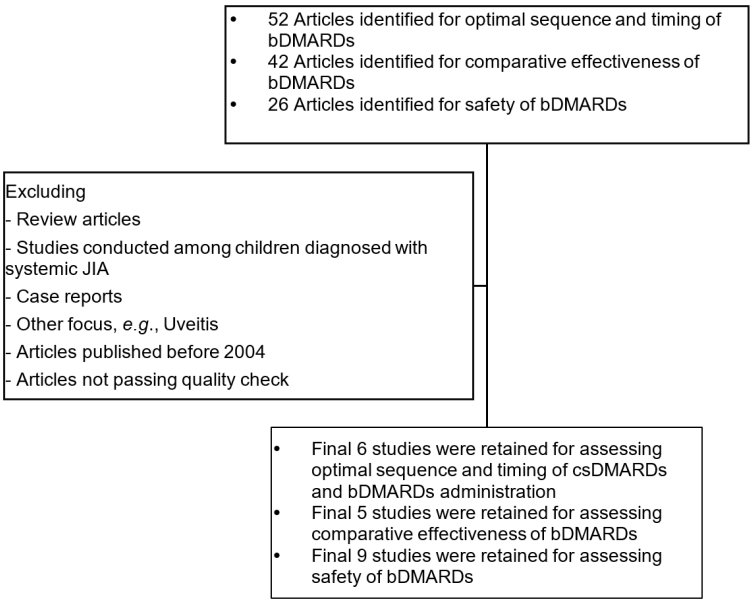


**Figure 1. Flowsheet of literature review and study selection for analysis.**

found no significant differences between the groups in achieving the ACR provisional criteria for clinical inactive disease without glucocorticoids at 12 months. However, there was a significantly greater likelihood of early combination therapy achieving inactive disease according to the clinical Juvenile Arthritis Disease Activity Score 10 (JADAS10) and ACR Pedi 70.

JADAS-10 is a less stringent categorization of disease inactivity. ACR criteria reflect disease inactivity at only one point in time, which may be transient, and may not be the most important target outcome. JADAS-10 may be a better target outcome than clinically inactive disease according to the ACR criteria. A potential benefit of the early combination therapy based on the clinical JADAS-10 merits additional evaluation in future studies. These results show that for many patients with polyJIA, earlier bDMARD treatment may result in more immediate improvement, but the impact on long-term outcomes remains unproven.

The effectiveness of early aggressive use of csDMARD+bDMARD versus the conservative strategy was assessed using the electronic medical record (EMR) system for treating children with newly diagnosed polyarticular course JIA in at a large US Midwest pediatric rheumatology clinic from 2009 to 2018 (*25*). Study results suggest that, compared with csDMARD only, early aggressive use of bDMARD achieves more than two points of additional reduction in disease activity at 6 months. In contrast, adding bDMARD after 6 months to the initial treatment provides very little added benefit. The study suggests timing matters, early use of bDMARDs is more effective than delayed bDMARD use in achieving early and sustained improvement in treating children with newly diagnosed polyarticular course of JIA.

**Table 2. studies assessing optimal sequence and timing of csDMARDs and bDMARDs**

| Author | Year Published | Data Source | Patient Population | Sample Size | Major Findings |
|---|---|---|---|---|---|
| Minden *et al.* (*27*) | 2019 | German BIKER Registry | JIA | 701 | Early bDMARD treatment is associated with better disease control & outcomes. Patients categorized in 3 groups based on time from symptoms onset to bDMARD start (G1: ≤ 2 yrs, G2: > 2 to ≤ 5 yrs, and G3: > 5 yrs). At 10-yr mark, G1 pts (18.5%) more likely in drug-free remission than G2 (10.1%) & G3 (4.9%). G1 pts also had lower disease activity than G3 pts (cJADAS10 = 4.9 *vs.* 7.1), better overall well-being (18.2% *vs.* 8.4%), and higher functional status (59.2% *vs.* 43.7%). G1 pts also required arthroplasty less frequently than G3 pts and had lower disease activity over time than both G2 & G3 pts. |
| Huang *et al.* (*25*) | 2020 | EMRs of Cincinnati Children Hospital | Polyarticular JIA | 2,082 | Compared with csDMARD alone, early aggressive use of bDMARD in treating pts with polyJIA soon after diagnosis achieves > 2 points of additional reduction in disease activity at 6 months. Adding bDMARD after 6 months provides little added benefit. |
| Kimura *et al.* (*24*) | 2021 | CARRA Patient Registry | Polyarticular JIA | 401 | No sig differences among groups in achieving the ACR provisional criteria for clinical inactive disease without glucocorticoids in 1 yr. However, a significantly greater likelihood of early combination therapy achieving inactive disease according to cJADAS-10 & ACR Pedi 70. |
| Yue *et al.* (*26*) | 2021 | EMRs of Cincinnati Children Hospital | Polyarticular JIA | 821 | The timing of bDMARD initiation was influenced by factors such as # of joints with limited range of motion, erythrocyte sedimentation rate, and JIA category. % of pts using bDMARDs within 3 months of diagnosis each yr exhibited a positive correlation with the proportion of pts achieving inactive/low disease outcomes each yr for polyarthritis pts. |
| Montag *et al.* (*28*) | 2022 | JuMBO Registry | JIA | 1,306 | JIA patients with a late start of bDMARDs were significantly more likely to use DMARDs and other medications in adulthood than those with early bDMARD treatment. Early effective treatment in JIA can reduce the need for multiple meds in adulthood. |
| Ramos *et al.* (*29*) | 2023 | Rheumatic Diseases Portuguese Register (Reuma.pt) | JIA | 361 | The patients were categorized into three groups based on the time between disease onset and bDMARD initiation: ≤ 2 years, 2–5 years, and > 5 years. Patients who began bDMARD treatment >5 yrs after disease onset were less likely to achieve drug-free remission (OR = 0.24; 95% CI: 0.06 – 0.92; $p = 0.038$).<br>These patients also had a greater physical disability, worse HRQoL, and required more joint surgeries compared to those who started treatment earlier. |

Another study using the same data source was conducted to investigate time to initiation of bDMARDs, and evaluate the impact of clinical and other baseline factors associated with the time to first bDMARD in treating children with newly diagnosed non-systemic JIA (*26*). The study found that the timing of bDMARD initiation is influenced by multiple factors such as the number of joints with limited range of motion, erythrocyte sedimentation rate, and JIA category. The percentage of patients using bDMARDs within 3 months of diagnosis each year exhibited a positive correlation with the proportion of patients achieving inactive/low disease outcomes each year for polyJIA patients.

To assess long-term outcomes associated with early bDMARD treatment, a study was conducted to assess whether the time of bDMARD initiation determined the outcomes of JIA in young adulthood using data from the German JIA biologic register BiKER (biologics in pediatric rheumatology) and JuMBO (Juvenile Arthritis Methotrexate/Biologics Long-Term Observation) registry (*27*). The researchers concluded that early bDMARD treatment is associated with drug-free remission, better disease control and outcomes in adulthood.

A subsequent study was conducted to evaluate medication and disease burden of young adults with JIA JuMBO registry (*28*). The authors concluded that early effective treatment in JIA can reduce the need for multiple medications in adulthood.

In summary, the collective data above underscore the importance of early and aggressive bDMARD treatment in managing polyarticular course of JIA. Early effective treatment with bDMARDs is associated with drug-free remission, lower disease activity, better disease control and outcomes, as well as reducing the need for multiple medications and joint surgeries in adulthood.

### 3.2. Comparative effectiveness of bDMARDs

The efficacy of bDMARDs such as ADA, ETA, or TOC for the treatment of polyJIA was well established in placebo-controlled trials, but no head-to-head trials have been conducted to compare their efficacy or effectiveness. Observational study design approaches using real-world data are useful to assess comparative effectiveness of these drugs. In addition, treatment persistence computed from real-world data has been considered a surrogate for long-term clinical effectiveness. Poor persistence and adherence have been found to reduce effectiveness of bDMARDs among rheumatoid arthritis (RA) patients (*30*). Below is the summary from real-world studies that examined comparative effectiveness of bDMARDs, including treatment response, remission rate, drug adherence and persistence among polyJIA patients who received various bDMARDs (Table 3).

One analysis was conducted using data from the German BIKER registry to assess comparative effectiveness among patients with polyJIA who started treatment with ADA ($n$ = 236), ETA ($n$ = 419), or TOC ($n$ = 74) from 2011 to 2015 (*31*). A propensity score was computed based on baseline characteristics of each study cohort and an inverse probability of treatment weight (IPTW) was used to create balanced samples of patients. Overall, the researchers concluded that ETA, ADA, and TOC had comparable efficacy for treating polyJIA, and these drugs are also well-tolerated. Treatment adherence was highest among patients receiving TOC and lowest among those receiving ADA.

Another study investigated the treatment effectiveness, safety and drug survival among bDMARD with or without MTX for the treatment of polyJIA using the German BIKER registry (*32*). Efficacy of MTX for the treatment of JIA is established; however, use of MTX needs to be carefully monitored, as a small percentage of patients developed elevated liver enzymes (*33*). In this study, 1464 patients received combination therapy and 684 patients received monotherapy. The bDMARDs include ETA, ADA, TOC, and GOL. A propensity score was computed and IPTW method was used to create balanced samples of patients. The results showed a significant decline in disease activity among patients undergoing combination therapy compared to those on bDMARD monotherapy. The authors concluded that administering additional MTX enhances the effectiveness of bDMARD treatment in polyJIA without seriously affecting safety profile.

Another analysis utilizing longitudinal patient-level data extracted from the EMR at Cincinnati Children's hospital from 2009 to 2018 was conducted to investigate the effectiveness and persistence of TNFi *vs.* non-TNFi among newly diagnosed non-systemic JIA patients following the initiation of bDMARD (*34*). The propensity score approach and IPTW analysis were also performed for this study. Overall, undergoing TNFi experienced a significantly greater reduction in cJADAS at the 6-month visit compared to patients in the non-TNFi cohort. However, the study did not identify significant differences in the effectiveness of TNFi *vs.* non-TNFi after 12 months of treatment.

Dara from the "Pharmacovigilance in JIA patients treated with biologic agents and/or MTX" (Pharmachild) registry was used to assess if ETA and ADA have a differential effect on patient-reported well-being in non-systemic JIA (*35*). The authors concluded that both ETA and ADA improve well-being in non-systemic JIA, with a slightly stronger effect for ETA.

A single-center, retrospective analysis of the EMR from the Wilhelmina Children's Hospital (Utrecht, The Netherlands) was conducted to assess medication prescription patterns for JIA patients receiving systemic therapy (*36*). The results showed that conventional synthetic DMARDs were prescribed to almost all patients with non-systemic JIA (99.5%), while 43.9% received a bDMARD (mostly ADA or ETA). Remission was the most common reason for both bDMARD and

**Table 3. Studies assessing effectiveness of bDMARDs in patients with polyarticular JIA**

| Author | Year Published | Data Source | Patient Population | Sample Size | Major Findings |
|---|---|---|---|---|---|
| Horneff *et al.* (*31*) | 2016 | German BIKER Registry | Polyarticular JIA | 729 Patients (ETA 419, ADA 236, TOC *n* = 74). | Pediatric ACR30/50/70/90 improvement was achieved by ETA (68%/60%/42%/24%), ADA (67%/59%/43%/27%) and TOC (61%/52%/35%/26%) in 3 months. JADAS minimal disease activity was achieved by ETA (61.3%), ADA (52.4%) and TOC (52.4%) in 24 months. JADAS remission was achieved in ETA (34.8%), ADA (27.9%) and TOC (27.9%). There were no statistically significant differences between the three groups in these outcomes, after adjusting for baseline differences between the three cohorts. Lastly, ETA (49.4%), ADA (60.4%), and TOC (31.1%) of patients discontinued therapy, respectively. |
| Thiele *et al.* (*32*) | 2023 | German BIKER Registry | Polyarticular JIA | 2,148 Patients (684 bDMARD monotherapy, 1,464 combination with MTX) | A significant decline in disease activity among patients undergoing MTX combination *vs*. bDMARD monotherapy. Patients who received TNFi experienced greater benefits from the additional MTX compared to patients receiving TOC. Median survival time of bDMARD was significantly longer in the combination group (3.1 years) than in the monotherapy group (2.7 years). |
| Yue *et al.* (*34*) | 2021 | EMR of Cincinnati Children Hospital | Non-sJIA | 667 patients | Median persistence of the first-line bDMARD is 320 days, with TNFi having longer persistence than the non-TNFi (395 *vs.* 320 days). Reduction in the clinical Juvenile Disease Activity Score (cJADAS) of TNFi users was significantly higher than non-TNFi users (6.6 *vs*. 3.0) during a 6-month follow-up. |
| van Straalen *et al.* (*35*) | 2022 | International Pharmachild Registry | Non-sJIA | 134 patients before propensity sore matching (45 ETA and ADA matched patients) | The estimated mean difference in changes in visual analogue scale (VAS) well-being score from baseline for ETA versus ADA was 0.89 (95% CI: -0.01 – 1.78; $p=0.06$).<br>Both ETA and ADA improved patient-reported well-being in non-systemic JIA, with a slightly stronger effect for ETA. |
| Kip *et al.* (*36*) | 2023 | EMR of Wilhelmina Children's Hospital | Non-sJIA | 236 patients | Remission was the most common reason for both bDMARD and csDMARD discontinuation (44.7%), followed by AEs (28.9%) and ineffectiveness (22.1%). |

synthetic DMARD discontinuation (44.7%), followed by AEs (28.9%) and ineffectiveness (22.1%).

In summary, administering additional MTX enhances the effectiveness of bDMARD in polyJIA without seriously affecting safety profile. ADA, ETA and TOC have comparable efficacy for treating polyJIA, and these drugs are also well-tolerated. The reduction in disease activity, as indicated by clinical JADAS for TNFi users was significant greater compared with non-TNFi users at 6-month follow-up visit. Nevertheless, no significant differences in the effectiveness of TNFi *vs.* non-TNFi were recorded after 12 months of treatment. Significantly more patients discontinued ADA due to inefficacy, and significantly more patients discontinued ETS due to remission. A small percent (2–6%) of patients discontinued these drugs due to intolerance.

### 3.3. Safety of bDMARDs

Infections (either serious or medically important) are one of the most common AEs occurring among JIA patients receiving bDMARDs. Due to immunosuppressive effects, bDMARDs may be associated with an increased risk of infections. In addition, most JIA patients receive additional immunosuppressive medications, which may also contribute to an increased risk of infections.

In addition, there are significant concerns about the potential increased rate of malignancy associated with the use of TNFi. Malignancy was first reported by the FDA in 2009 (*37*). There are limitations in this analysis. It did not account for a possible increased risk of malignancy associated with the underlying conditions being treated with TNFi or the increased risk associated with other immunosuppressive drugs, *e.g.*, thiopurines.

bDMARDs, including TNFi, IL-1i, IL-6i all have contraindications and/or warnings related to serious infections and malignancy (*23*). The placebo-controlled trials of ETA, ADA and GOL did not show an increased number of infection or serious infections in patients with non-systemic JIA (*38-40*). Use of TOC was associated

with an increased risk of infections in trials (*41*). Findings on malignancy and other rare AEs associated with bDMARDs from clinical trials are limited. Real-world data is useful to monitor long-term safety of bDMARDs.

Results from real-world studies that assessed serious infections and malignancy among patients receiving bDMARDs are summarized in Table 4.

3.3.1. Serious infections

Risk of serious infections was assessed among JIA patients under treatment of ETA, ADA, and MTX using the data from the German BIKER Registry (*42*). The researchers concluded that the overall rate of serious infections reported was relatively low. Treatment with ETA or ADA slightly increased the risk of serious infections compared to MTX among these patients. Disease activity, as indicated by cJADAS10, was identified as an independent risk factor.

The long-term safety of various bDMARDs (ABA, ADA, ETA, GOL, INF and TOC) was examined for patients with polyJIA using data from the German BIKER registry (*43*). Among 3,873 patients included in the analysis, patients with GOL and MTX combination treatment had the highest rate of medically important infections (5.32 per 100 person-years; 95% CI: 2.2–12.8). It may be related to the low number of patients on GOL ($n$ = 86) included in this analysis. The lowest rate was observed in bDMARD-naïve patients with MTX. Rates in patients undergoing other treatments were comparable. No significant differences in the occurrence of medically important infections were found between patients receiving any TNFi and patients receiving TOC.

Additional analyses were conducted to examine whether treatment with IL-1i (ANA, CAN), IL-6i (TOC), TNFi (ADA, ETA, GOL, INF) and ABA was associated with an increased risk of common infections, infections requiring hospitalization (SAE) among JIA patients using the data from the German BIKER Registry (*44*). IL-1i and IL-6i cohorts had significantly more infections and serious infections, compared to TNFi cohort. The influencing covariates identified for various infectious diseases include the use of corticosteroids, younger age, cardiac comorbidities and higher JIA-activity, this is useful for the choice of a suitable bDMARD for treating JIA.

One study examined the safety of adding MTX to bDMARD treatment among patients with polyJIA using data from the German BIKER registry (*32*). The authors concluded additional MTX moderately affected AE occurrence, primarily due to increased incidence of GI and hepatic AEs. An equal rate of SAEs was found between both cohorts.

All the above analyses conducted were based on the data from the German BIKER registry. Results from other data sources are described below:

The STRIVE registry was designed to evaluate safety and effectiveness of ADA with/without MTX *vs.* MTX monotherapy using new user designs in patients with polyarticular-course of JIA from 16 countries (*45*). Serious infection rates were slightly higher in the ADA ± MTX arm. Similar to those from the German BIKER registry, the authors concluded that ADA with/without MTX is well tolerated.

One study was conducted using the U.S. Medicaid data to assess hospitalized infections among JIA patients who initiated TNFi, ANA and MTX (*46*). The results showed no increased risk of infection associated with TNFi monotherapy *vs.* MTX or with TNFi+MTX combination therapy *vs.* MTX. Baseline high-dose oral glucocorticoid use (defined as ≥ 10 mg/day of prednisone) was associated with infection. ANA was significantly associated with infection, compared with MTX.

Another study was conducted to examine the risk of serious bacterial infection requiring hospitalization among children with JIA who initiated monotherapy with TNFi or csDMARD using the Truven Health MarketScan Commercial Claims and Encounters database (*47*). The results showed that new use of TNFi was associated with a 2.7-fold increase in risk of serious bacterial infection *vs.* new use of csDMARD (aHR = 2.72, 95% CI: 1.08–6.86), adjusting for potential confounders obtained through high-dimensional propensity scores (HDPS) method and time-varying corticosteroid use.

In summary, although most studies indicated that no increased risk of serious infection associated with TNFi monotherapy *vs.* MTX or with TNFi+MTX combination therapy *vs.* MTX. One study showed new use of TNFi was associated with a 2.7-fold increase in risk of serious bacterial infection *vs.* new use of csDMARD in children with JIA. Patients treated with IL-1i or IL-6i reported significantly more infections, compared with patients treated with TNFi. The influencing covariates/factors identified for various infectious diseases include the use of corticosteroids, younger age, cardiac comorbidities and higher JIA-activity. This information is useful in deciding on a suitable bDMARD for treating JIA.

3.3.2. Malignancies

Cases of suspected malignancies documented in patients treated for JIA in the German BIKER Registry were assessed (*48*). A total of 12 suspected cases of malignancies were identified, with 7 being lymphomas. The authors concluded that the occurrence of malignancies in JIA patients was higher than in the general population. Whether JIA patients had an increased risk for malignancies from rheumatic disease, or related to their treatment remains unclear. They did not observe an increase in the rate of malignancy following ETA use compared to no TNFi use.

A retrospective cohort study was conducted among

**Table 4. Studies assessing safety of bDMARDs in patients with JIA**

| Author | Year Published | Data Source | Patient Population | Sample Size | Serious Infections | Malignancies | Other Adverse Events |
|---|---|---|---|---|---|---|---|
| Horneff *et al.* (*48*) | 2016 | German BIKER Registry | JIA | 3,695 JIA patients, totaling 13,198 observation years, the analysis spanning until December 31, 2015 | NA | 1 patients had received MTX, while 9 patients were exposed to bDMARDs: 1 received ETA, 6 received ETA+MTX, 1 received ETA+ADA+MTX, and one patient underwent a sequence of treatments with MTX, ADA, ETA, INF and ABA. A total of 12 suspected cases of malignancies were identified, with 7 being lymphomas.<br>Use of etanercept did not appear to further elevate the risk. | NA |
| Beukelman *et al.* (*46*) | 2016 | Medicaid claim database | JIA | 3,075 new MTX users, 2,713 new TNFi users and 247 new ANA users | No increased risk of hospitalized infection by all organisms associated with TNFi monotherapy or with TNFi+MTX combination therapy *vs.* MTX (adjusted hazard ratio (aHR) 1.19, 95% CI: 0.72, 1.94; 1.23, 95% CI: 0.69, 2.17, respectively). Baseline high-dose oral glucocorticoid was associated with infection (aHR 2.03, 95% CI: 1.21, 3.39). | NA | NA |
| Becker *et al.* (*42*) | 2017 | German BIKER Registry | JIA | 3,350 patients for 5,919 observation-years | Treatment with ETA or ADA slightly increased the risk of serious infections compared to MTX among these patients (MTX *vs.* ETA *vs.* ADA = 1.6 *vs.* 8.1 *vs.* 9.7/1,000 person-years). | NA | NA |
| Beukelman *et al.* (*49*) | 2018 | Medicaid and MarketScan claims database | JIA, pediatric inflammatory bowel disease (pIBD) and pediatric plaque psoriasis (pPsO) | 15,598 children with TNFi use and 73,839 with no TNFi use | NA | There was no significantly increased risk of malignancy among children undergoing treatment with TNFi compared to those receiving other treatments.<br>However, it did show a doubled risk of malignancy in children with JIA overall when compared to an age-matched control of patients with an unrelated condition (standardized incidence risk (SIR): JIA + TNFi: 3.1 (95% CI: 1.3–6.1), JIA without TNFi: 2.1 (95% CI: 1.1–3.5), Control: 0.97 (95% CI: 0.91–1.05). | NA |

*Outcomes were not statistically powered.

**Table 4. Studies assessing safety of bDMARDs in patients with JIA (continued)**

| Author | Year Published | Data Source | Patient Population | Sample Size | Serious Infections | Malignancies | Other Adverse Events |
|---|---|---|---|---|---|---|---|
| Lee *et al.* (*47*) | 2018 | MarketScan claims database | JIA | 482 TNFi initiators and 2013 csDMARD initiators; TNFis included ETA, ADA, INF, CER, GOL, csDMARDs included MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and leflunomide (LEF)) | TNFi initiators were associated with an increased risk of serious bacterial infection compared with csDMARDs initiators (aHR 2.72, 95% CI: 1.08–6.86), adjusting for potential confounders obtained through high-dimensional propensity scores (HDPS) method and time-varying corticosteroid use. | NA | NA |
| Brunner *et al.* (*45*) | 2020 | STRIVE Registry | Polyarticular JIA | 838 patients (MTX 301; ADA ± MTX 537)* | Serious infection rates were slightly higher in the ADA ± MTX arm (MTX: 1.5 events/100 patient-years; ADA ± MTX: 2.0 evens/100 patient-years). ADA ± MTX is well tolerated. | NA | Common AEs included nausea, sinusitis, and vomiting for MTX monotherapy while arthritis, upper respiratory tract infection, sinusitis, tonsillitis, and injection site pain reported in the ADA ± MTX patients. |
| Klein *et al.* (*43*) | 2020 | German BIKER Registry | Polyarticular JIA | 3,873 patients with a cumulative exposure to bDMARDs of 7467 years | No significant differences in occurrence of medically important infections were found between patients receiving any TNFi and patients receiving TOC (RR = 0.85, 95% CI: 0.27–2.70). | Eight cases of malignancy were reported but the significance remains unclear. | The most common AEs were uveitis ($n$ = 231) and medically important infections ($n$ = 101). Cytopenia and elevation of transaminases were more frequently reported for patients on TOC. |
| Thiele *et al.* (*44*) | 2021 | German BIKER Registry | JIA | 3,258 patients – TNFi 3044, IL-1i 105, IL-6i 400 and T-cell activation inhibitors 105 | Patients treated with IL-1i or IL-6i reported significantly more infections (IR = 17.3, 95% CI: 12.5–24; IR = 16.7, 95% CI: 13.9–20), compared with patients treated with TNFi (IR = 8.7, 95% CI: 8.1–9.4). Infections classified as SAEs also occurred more frequently in the IL-1i or IL-6i cohorts. | NA | Incidence of herpes zoster and varicella was higher in patients on TNFi. Other opportunistic infections were rare. |
| Thiele *et al.* (*32*) | 2023 | German BIKER Registry | Polyarticular JIA | 2,148 Patients (684 bDMARDs monotherapy, 1,464 combination with MTX); bDMARDs included ADA, ETA, GOL, and TOC | NA | NA | 1,757 AEs reported, most commonly viral upper respiratory infections, GI disorders (*e.g.* nausea), and transaminase elevation, with 116 classified as SAEs. A higher incidence of AEs in patients on combination therapy was observed. No significant differences in the rate of SAEs between the two groups. |

*Outcomes were not statistically powered.

children with JIA, pediatric inflammatory bowel disease (pIBD) and pediatric plaque psoriasis (pPsO) using the US Medicaid and MarketScan database to assess risk of malignancies among TNFi users compared with no TNFi use (*49*). The study revealed that there was no significantly increased risk of malignancy among children undergoing treatment with TNFi compared to those receiving other treatments. However, it did show a doubled risk of malignancy in children with JIA overall when compared to an age-matched control of patients with an unrelated condition.

In summary, children diagnosed with JIA had a higher rate of malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to not using TNFi.

## 4. Discussion

### 4.1. Biologic therapy for children with non-systemic JIA

The current review summarizes studies that examined the optimal sequence and timing of csDMARDs and bDMARDs administration, comparative effectiveness and safety concerns of these agents in JIA or polyJIA patients in real-world settings.

The collective data from several real-world studies support that early effective treatment with bDMARDs in managing polyarticular course of JIA is associated with drug-free remission, lower disease activity, better disease control and outcomes, as well as reduce the need for multiple medications and joint surgeries in adulthood.

In addition, real-world studies showed that administering additional MTX enhances the effectiveness of bDMARDs treatment in polyJIA without seriously affecting safety profile. ADA, ETA and TOC have comparable efficacy for treating polyJIA, and these drugs are also well-tolerated. The reduction in disease activity, for TNFi users was significant greater compared with non-TNFi users at 6-month follow-up visit.

With regards to safety of bDMARDs, patients treated with IL-1i or IL-6i reported significantly more infections, compared with patients treated with TNFi. Most studies indicated that there was no increased risk of serious infection associated with TNFi in children with JIA. However, one study showed new use of TNFi was associated with a 2.7-fold increase in risk of serious bacterial infection *vs.* new use of csDMARD in children with JIA. This study might have overestimated the TNFi–infection relationship. As TNFi are indicated for moderately to severely active polyJIA, JIA severity was likely higher in the TNFi group. JIA patients who were not currently taking MTX or TNFi were found to have a 2-fold increase in the rate of hospitalized bacterial infection, compared to a comparator cohort of children without JIA after adjusting for potential confounders (*50*). The inflammatory or autoimmune process of JIA may predispose children to infection in the absence of therapy (*51*). Similar findings have also been observed in adults with RA (*52*).

Regarding malignancy, children diagnosed with JIA had a higher rate of malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to not using TNFi.

### 4.2. Limitations of real-world evidence

Limitations of the observational study design including missing data and confounding by indication (*53*) should be noted. First, there are differences in baseline characteristics between the two groups, the early bDMARD group had more patients with RF-positive polyJIA and enthesitis-related arthritis and had higher disease activities, which may be associated with worse outcome measures. Although statistical methods, such as propensity score method were used to adjust for potential bias, residual bias (*54*) may still be present. When assessing comparative effectiveness of bDMARDs, it is important to know that unmeasured confounders, such as physician behavior, patients' comorbidities, insurance reimbursement policies, that were not considered in the analyses may have affected the treatment assignment to patients and associated outcomes.

In addition, some studies included a small number of patients, low sample size plus missing data resulted in few analyzable patients to assess outcomes. Multiple imputation (*55*) was employed to impute missing values. It should be noted that multiple imputations rely on the assumption missing at random, *i.e.*, missing values depend on observed data only.

For studies using EMR, records of actual medication dispensing and treatment adherence are not available. Also, a common approach adopted in clinics is that physicians may prescribe a bDMARD after patients receive 3 months of MTX. Studies that were based on a single center have limited generalizability.

### 4.3. Clinical implications

The influencing covariates/factors identified for various infectious diseases include the use of corticosteroids, younger age, cardiac comorbidities and higher JIA-activity. This information is useful in deciding on a suitable bDMARD for treating JIA. Patients who have one or more of these factors should be monitored closely regarding infections.

For the use of corticosteroids, compared with no use of corticosteroids, use of high-dose oral corticosteroids (≥ 10 mg prednisone daily) was consistently and independently associated with a more than doubling of the rate of subsequent infection. Similar findings have been observed in adults with RA (*56*). One implication is that the use of steroid-sparing treatment strategies may

reduce the risk of serious infections in children with JIA.

Overall, clinicians and patients need to balance the benefits of these highly effective bDMARDs against the risk of infection they pose. To minimize potential risk, risk management plan should incorporate appropriate screening, monitoring and withholding of treatment as needed to mitigate the potential harm to children with JIA.

### 4.4. Future research

For future direction, long-term outcomes from early effective treatment with bDMARDs in children with JIA warrant further assessment. Future studies may also further evaluate the various benefits and detriments of newly approved bDMARDS, especially in a large population to ensure the appropriate use of these therapies.

In addition, long-term assessment of JIA patients treated with bDMARDs into adulthood is an important task. Further studies incorporating a larger cohort of children with JIA would further characterize the risk of serious infection and malignancy across individual TNFi medication.

### 4.5. Future perspectives

The current review did not include new classes of drugs, such as JAK inhibitors (JAKi). Although they provide a useful alternative for some patients, JAKi, including tofacitinib, baricitinib and upadacitinib have a boxed warning regarding risk of cardiovascular disease (CVD), venous thromboembolic events (VTE) and its use should be limited to those failing or intolerant of TNFi. Safety signals from adult RA tofacitinib trials warrant caution, currently data on risk of CVD and VTE in pediatric patients are limited. Future research to assess the risk of CVD/VTE among patients receiving JAKi in real-world settings is necessary before its routine use in patients with JIA.

In conclusion, for patients with polyJIA, early effective treatment with bDMARDs may result in more immediate improvement including drug-free remission, lower disease activity, better disease control and outcomes. Potential impacts on long-term outcomes warrant further assessment.

Additional MTX enhances the effectiveness of bDMARDs treatment in polyJIA without seriously affecting safety profile. ADA, ETA and TOC have comparable efficacy for treating polyJIA, and these drugs are also well-tolerated.

Children with JIA have higher rates of serious infection than children without JIA independent of the treatment effect. The use of TNFi did not seem to significantly increase risk of serious infection further when compared to using MTX. Patients treated with IL-1i or IL-6i reported significantly more infections, compared with patients treated with TNFi. In addition, children diagnosed with JIA had a higher rate of malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to using MTX.

Clinicians and patients should consider potential risk in light of the benefits of bDMARDs. The reimbursement policy and pricing issue of bDMARDs are out of the scope of the present literature analysis. The current review may inform shared decision-making discussions between families and physicians as they weigh the risks and benefits of various treatment approaches for children with JIA.

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***Review***

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# Secondary musculoskeletal disability and rehabilitation aspects in adults with thalidomide embryopathy: A narrative review

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**SUMMARY**: To review musculoskeletal disabilities and rehabilitation in adults with thalidomide embryopathy (TE), the authors reviewed the literature related to musculoskeletal disability, quality of life (QOL) and rehabilitation intervention in adults with TE, obtained through a PubMed search, and their experience in clinical practice with Japanese individuals. Through literature search, 25 studies were included for this review. Literature search results and the authors' experiences revealed that, in adults with TE, upper limb disabilities included neuropathy, mainly due to carpal tunnel syndrome; finger pain due to tenosynovitis; and symptoms caused by osteoarthritis, mainly in the shoulders. Disabilities of the trunk and spine included lower back and neck pain. Although disabilities in the lower limbs were uncommon, pain due to hip and knee osteoarthritis were reported. Regarding the health-related QOL in adults with TE, the physical domain of QOL was reduced, which may be related to musculoskeletal disabilities. Reports on rehabilitation approaches for secondary musculoskeletal disabilities in TE, including physical therapy, environmental modification, and alternative medicine, were scarce. This review of musculoskeletal disabilities and QOL in adults with TE revealed that pain is common in the upper limbs and spine, and is associated with reduced physical QOL.

***Keywords***: limb malformation, rehabilitation approach, health-related quality of life

## 1. Introduction

Thalidomide embryopathy (TE) is a well-known drug-induced tragedy having affected over 4,000 infants worldwide, born in the late 1950s and early 1960s (*1*). These infants were born to mothers who took thalidomide in their early pregnancy. Thalidomide had sedative property, and compound preparations which combined thalidomide with other drugs were marketed for a wide variety of indications, including asthma, hypertension, and migraine. The most common phenotype of TE is congenital limb malformation. The second most common group of defects involves developmental abnormalities of the ear and eye and abnormalities in the innervation of the external ocular muscles, facial muscles, and tear glands. Other defects include cleft palate, hypoplasia of the external genitalia, anomalies of the internal organs, and neurodevelopmental problems (*2*).

Limb malformations are common in the upper extremities, and most individuals with upper limb malformations have normal lower limbs. Some individuals have defects in all limbs; malformations of the lower limbs with normal upper limbs are rare. The limb malformations were generally symmetrical. Upper limb malformations include amelia, phocomelia, defects in the radius and thumb, and triphalangism or hypoplasia of the thumb. Lower limb malformations include amelia, phocomelia, tibial defects, aplasia or hypoplasia of the femur, and polydactylism. Other lower-limb abnormalities include congenital dislocation of the hip and clubfoot (*2-4*).

Spinal involvement is sometimes confirmed, including congenital partial absence of the sacrum, scoliosis, and abnormalities of the disc and endplate leading to intervertebral fusion (*2,4,5*). An individual with TE in whom an anterior sacral meningocele was recognized in adulthood has also been reported (*6*).

Owing to these congenital musculoskeletal

abnormalities, children with TE had difficulty in performing activities of daily living (ADL). Physical and occupational therapies played a significant role in treating these conditions (*7,8*). In children with amelia or phocomelia in their upper limbs, various types of upper-limb prostheses, including those using electric motors or compressed gases, were used (*9,10*). However, most children discarded their prostheses for functional reasons and preferred to use their feet as they grew. Through rehabilitation with occupational therapists, most children with normal lower limbs have become independent (*11*).

The present age of survivors of TE is approximately 60 years, and additional musculoskeletal disabilities and related decline in quality of life (QOL) in adults with TE have been reported over the past 20 years (*12-15*). However, there exists no previous studies that overview the declined QOL due to musculoskeletal disabilities from the perspective of rehabilitation. This study aimed to review musculoskeletal disabilities and related rehabilitation aspects, including QOL and the rehabilitation approach.

## 2. Research design and literature search strategy

This study comprised a literature review and the authors' experience in clinical practice with Japanese individuals with TE.

### 2.1. Literature search

The authors searched PubMed for articles related to musculoskeletal disability, related QOL, and rehabilitation approaches in adults with TE. This search was conducted for literature published between January 1980 and December 2024 because most individuals with TE were born in the late 1950s or early 1960s. The search strategies included "thalidomide AND musculoskeletal", "thalidomide AND pain", "thalidomide AND quality of life", and "thalidomide AND rehabilitation". Among the identified records, studies on novel use of thalidomide, non-English literature, and duplicate records were removed, considering the titles and abstracts. The first author (NH) read the full-text articles of the screened records, and selected studies to be included in this review article. The exclusion criteria were *i*) those with no or partial relation to thalidomide, *ii*) those with no relation to secondary musculoskeletal disability, *iii*) review article, and *iv*) discussion or comment. In addition to the database search, the authors identified records from citation searching.

### 2.2. Author's experience in clinical practice

The authors provide information on the personal experiences of Japanese individuals with TE regarding secondary musculoskeletal disability and the rehabilitation approach. The provision of information on Japanese individuals with TE was approved by the ethics committees of the National Rehabilitation Center for Persons with Disabilities (approval number 2022-136), Faculty of Medicine, The University of Tokyo (approval number 2373-7), and Shiga University of Medical Science (approval number R2017-267). Written informed consent was obtained, or the opt-out method was applied to obtain consent using descriptions in the websites of the authors' affiliations.

## 3. Results of literature search and the key findings

### 3.1. Literature search results

Figure 1 displays the flow diagram for selecting studies for this review. The database search using PubMed identified a total of 1,106 records. After removing 1,025 studies on novel use of thalidomide including medication for cancer, peripheral neuropathy, psoriatic diseases,

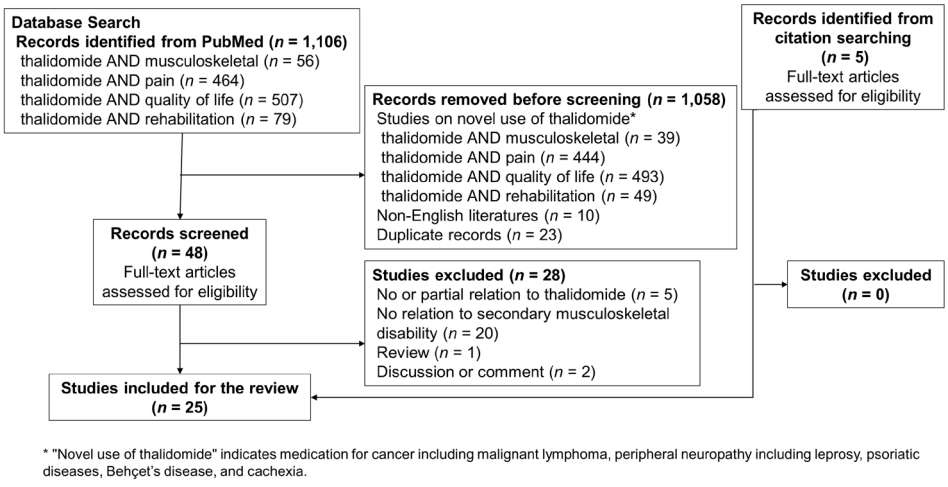


**Figure 1. Flow diagram for identifying studies.**

Behçet's disease, and cachexia, 10 non-English literature, and 23 duplicate records, 48 records were screened and full-text articles were assessed for eligibility. Among these, 28 studies were excluded according to the criteria described above, and 20 studies remained to be included in this review. In addition, 5 records were identified from citation searching, and none was excluded. Overall, 25 studies were included for this review.

Table 1 shows the subjects and design of studies included for this review. The number of studies from UK was 7, followed by Germany ($n$ = 6), Japan ($n$ = 5), and Sweden ($n$ = 4). Thirteen studies included interview and/or questionnaire, and the sample size exceeded 100 in 7 of them. Eight were report of 1 or 3 cases. There were 3 imaging studies and 2 neurophysiological studies, and each one of them was a case control study. The key findings from these studies are described based on the study subjects in the following sections.

### 3.2. Aging and musculoskeletal disability in adults with TE

Adults with TE aged 54 to 60 reported significantly greater numbers of musculoskeletal problems and nervous system symptoms, including pain, pins and needles and numbness, than the age-matched controls (*16*).

#### 3.2.1. Disabilities in upper limbs

Adults of TE with upper limb deficiency report a high prevalence of neuropathic pain in the upper limbs (*17*). Neurophysiological testing in adults complaining of numbness or tingling revealed findings of compressive neuropathy. Although many of the results revealed compression of the median nerve at the wrist, other findings (*e.g.*, suggested cervical radiculopathy) have also been observed (*18,19*). In adults with radial deficiency, including those with TE, the development of carpal tunnel syndrome and decompression surgery with good outcomes have been reported (*20,21*). They underwent surgery in their 20s or 30s, and the early development of symptoms may be due to the narrow anteroposterior diameter and small cross-sectional area of the carpal tunnel in patients with radial deficiency (*20*).

Another upper-limb disability is the pain caused by early onset osteoarthritis. Middle-aged adults undergoing shoulder joint replacement have good postoperative results, although pain and limited range of motion due to glenohumeral osteoarthritis do not respond to conservative preoperative treatments (*22,23*). An adult with TE who developed a special form of shoulder osteoarthritis has also been reported. The glenohumeral joint is formed by a convex glenoid and a concave humeral head (*24*). As for the elbow joint, though limited

**Table 1. Subjects and design of studies included for the review**

| First Author (Year) (*Ref.*) | Country | Study Subject | Study Design (Sample Size) |
|---|---|---|---|
| Bent (2007) (*12*) | UK | QOL and health status | Interview ($n$ = 28 among 70)<br>Questionnaire ($n$ = 44 aomng 88) |
| O'Carroll (2011) (*13*) | Ireland | QOL and health status | Questionnaire ($n$ = 17 among 26) |
| Ghassemi Jahani (2016) (*14*) | Sweden | QOL and function of limbs | Questionnaire ($n$ = 31 among 84) |
| Markiewicz (2023) (*17*) | UK | QOL and upper limb disability | Questionnaire ($n$ = 127 among 346) |
| Ghassemi Jahani (2014) (*25*) | Sweden | Disability in upper and lower limbs | Questionnaire for upper limbs and CT for lower limbs ($n$ = 31 among 84) |
| Imai (2020) (*27*) | Japan | QOL and pain | Questionnaire ($n$ = 51 among 67) |
| Newbronner (2019) (*32*) | UK | QOL and health status | Questionnaire ($n$ = 351 among 467) |
| Niecke (2022) (*33*) | Germany | QOL and health status | Questionnaire ($n$ = 186 among 202) |
| Hinoshita (2019) (*36*) | Japan | Life situation | Questionnaire ($n$ = 173 among 274) |
| Sagoe (2024) (*16*) | UK | Comorbid health condition | Questionnaire ($n$ = 392 among 415) |
| Ghassemi Jahani (2017) (*29*) | Sweden | Physical function and ADL with or without PFFD | Questionnaire ($n$ = 31) |
| Nippert (2002) (*34*) | Germany | QOL and health status in women | Questionnaire ($n$ = 104 among 166) |
| Samel (2019) (*35*) | Germany | QOL and health status in women | Physical examination and questionnaire ($n$ = 115 among 206) |
| Kimura (2001) (*20*) | Japan | Carpal tunnel syndrome | Case report ($n$ = 1) |
| Oshima (2006) (*21*) | Japan | Carpal tunnel syndrome | Case report ($n$ = 3) |
| Newman (1999) (*22*) | UK | Shoulder osteoarthritis | Case report ($n$ = 1) |
| Merkle (2016) (*23*) | Germany | Shoulder osteoarthritis | Case report ($n$ = 3) |
| Kimmeyer (2021) (*24*) | Germany | Shoulder osteoarthritis | Case report ($n$ = 1) |
| Fahlbusch (2023) (*30*) | Germany | Knee osteoarthritis | Case report ($n$ = 1) |
| Morrison (2020) (*37*) | UK | Intervention for fall prevention | Case report ($n$ = 1) |
| Hodo (2017) (*31*) | USA | Anatomy of lower limb | Case report ($n$ = 1) |
| Kamimura (2024) (*26*) | Japan | Imaging of upper limbs | CT for upper limbs ($n$ = 5) |
| Ghassemi Jahani (2016) (*28*) | Sweden | Degenerative changes in cervical spine | Case control study including cervical spine MRI ($n$ = 27) |
| Nicotra (2016) (*18*) | UK | Peripheral nerve dysfunction of upper and lower limbs | Case control study including neurophysiological testing ($n$ = 17) |
| Jankelowitz (2013) (*19*) | Australia | Neurological symptoms in upper limbs | Clinical and neurophysiological assessment ($n$ = 16) |

range of motion is reported, pain and development of osteoarthritis remain unelucidated (*25*). A Japanese study investigating computed tomography findings of the upper limbs in middle-aged adults with TE revealed abnormal elbow findings, including hypoplasia of the trochlea and/or capitulum of the humerus, coronoid fossa, olecranon, and coronoid processes (*26*). The same study revealed that the carpal bones made contact with the radius or ulna only in a limited area. These anatomical abnormalities may lead to age-related articular surface deformation, resulting in limitations in joint mobility and pain.

3.2.2. Disabilities in trunk and spine

A questionnaire survey of Japanese adults with TE showed that pain in the lower back or neck was relatively common (*27*). On cervical spine MRI, a higher degree of disc degeneration and more foraminal narrowing were observed in middle-aged individuals with TE than in age- and sex-matched healthy controls (*28*).

3.2.3. Disabilities in lower limbs

In a survey of 31 middle-aged adults with TE (*25*), five with proximal femoral focal deficiency (PFFD) and other malformations in the lower limbs showed significantly reduced ambulation, including three individuals using wheelchairs most of the time. Osteoarthritic changes in the hips, knees, and metatarsophalangeal joints have been observed in individuals with PFFD. In some of the remaining 26 adults without major lower limb anomalies, slightly deformed femoral head, knee abnormalities with a hypoplastic lateral femoral condyle, and knee instability were observed. Osteoarthritic changes were observed in the hips, knees, and feet; however most were mild. The same group reports that TE adults with PFFD need more assistive products and support, show lower physical function, and need longer time for ADL in the morning (*29*).

Reports on treatment for lower limb osteoarthritis are scarce. Total knee arthroplasty and patelloplasty was reported in a 59-year-old female with end-stage osteoarthritis of the left knee and phocomelia (*30*). A 54-year-old female experiencing recurrent bilateral foot pain showed dysmorphic and osteoarthritic changes in the ankle and foot on X-ray images, and anatomic abnormalities of tendons on MRI. This patient chose conservative treatment with immobilization of the foot (*31*).

3.3. Musculoskeletal disability and QOL in adults with TE

The health-related QOL (HRQOL), including its relationship with musculoskeletal disabilities, has been investigated in adults with TE across various nations and age groups. In a study of UK individuals aged approximately 40 years (*12*), most of them stated that their bodies were less flexible and that they were less able to carry things than in the past. Regarding HRQOL, the Physical Function scale of the 36-item Short Form Health Survey (SF-36) was below the population norms for this age group, and was lower in more severely affected individuals. In another UK study of individuals in their mid-50s (*32*), the physical health domain of the Short Form 12 Health Survey (SF-12) showed a markedly lower average aggregate score than the general population, whereas the mental health domain showed a slightly lower score. There was a strong negative correlation between lower SF-12 physical health scores and the severity of impairment, indicating that the more severe the thalidomide damage, the poorer the physical HRQOL. In a study from Ireland (*13*), the Illness-Intrusiveness Ratings Scale was used to assess the extent to which disability interferes with HRQOL for individuals with TE in their mid-40s, and the scores were high compared with other physical health conditions. A Swedish study evaluated the effect of limb malformations on HRQOL in individuals in their late 40s (*14*). The Physical Composite Summary (PCS) score of SF-36 was significantly reduced in relation to the national norm. Individuals with major limb deformities had a significantly lower PCS score of the SF-36 compared with those without any major deformities. In particular, those with PFFD reported a considerable reduction in PCS score. The PCS score was correlated with the upper extremity function and pain score for the lower extremities. A study from Germany on individuals aged approximately 50 years (*33*) showed a significantly reduced PCS score of the SF-36 in comparison to an age-adjusted German population with chronic diseases. Individuals with mild pain had higher physical and mental HRQOL than those with severe pain. A study from Germany on women aged 35 to 40 years (*34*) showed lower physical domain score compared with the control group in WHO QOL-BREF, and less satisfied with their QOL. The results of another German study on women aged 48 to 53 years (*35*) indicated ongoing decrease in the health status and QOL. In a study of Japanese individuals in their early 50s (*27*), most complained of physical pain, mainly in their shoulders, lower back, and neck. Significant correlations with pain severity were observed for the PCS scores on the SF-36.

3.4. Rehabilitation approach for secondary musculoskeletal disabilities in TE

There are a few reports on conservative management, including rehabilitation approaches, for secondary musculoskeletal disabilities in individuals with TE. In a survey on the life situations of Japanese individuals with TE (*36*), approximately 30% of those reporting symptoms and/or physical problems utilized massage, acupuncture, moxibustion, or chiropractic. Physical

therapy for a male with TE in his mid-50s has been reported (*37*). He had severe shortening of both upper limbs and an unequal leg length, and complained of low back pain, poor balance, and fear of falling. After wearing an insole for the unequal leg length and 15 physiotherapy treatment sessions, his complaints improved.

**4. Author's experience in clinical practice**

As for upper limb disability, we have encountered adults with TE who complained of finger pain due to tenosynovitis (Figure 2). Tenosynovitis may be common mechanism for finger pain in malformed upper limbs, but has not been described in previous reports. Abnormalities in carpal bones reported in a CT study (*26*) can be revealed in plain X-rays. Figure 3A shows fusion of the carpal bones and a narrow, deformed radiocarpal joint in a female adult in her early 50s. This individual also showed narrow intervertebral spaces with endplate irregularity and spondylolisthesis in the lumbar spine (Figure 3B). X-ray images sometimes reveal abnormalities in individuals without apparent lower limb malformations. Figure 3C shows inclined knee joint with the hypoplastic lateral femoral condyle, and Figure 4 shows acetabular dysplasia in both hips and narrowed joint space in the right.

Ergonomic improvements, including environmental modifications and the implementation of supportive devices, can be considered to improve and/or prevent the progression of secondary musculoskeletal disabilities from a rehabilitation engineering perspective. Two of the authors (HT and SS) treated a male office worker with TE complaining of numbness and tingling of the neck/shoulder and low back pain. They visited the office and assessed the office environment and his posture. By adjusting the height of the notebook PC display with a base that raised the PC slightly and applying a cushion for seat pressure dispersion and an additional shape-memory seat back that fits his back, he had remission of all the symptoms (Figure 5).

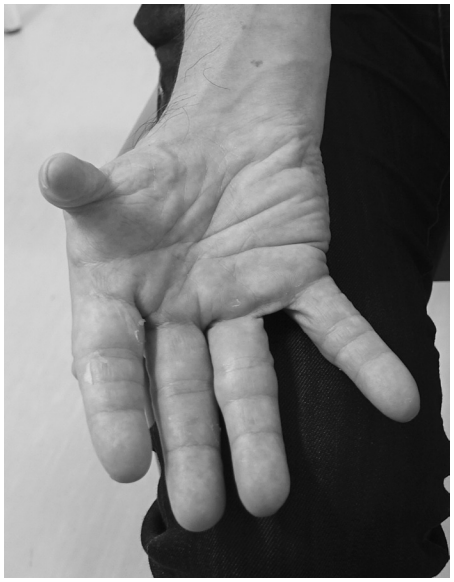

**Figure 2. Thumb and thenar hypoplasia.** This male adult with thalidomide embryopathy in his late 50s complains pain in fingers due to tenosynovitis.

**5. Discussion**

This review revealed that many adults with TE experience secondary musculoskeletal disabilities. Table 2 displays the summary of musculoskeletal disabilities, their prevalence, and interventions obtained from this study. Common symptoms include pain from neuropathy and osteoarthritis of the upper limbs, and pain in the lower back or neck. Lower limb symptoms are not

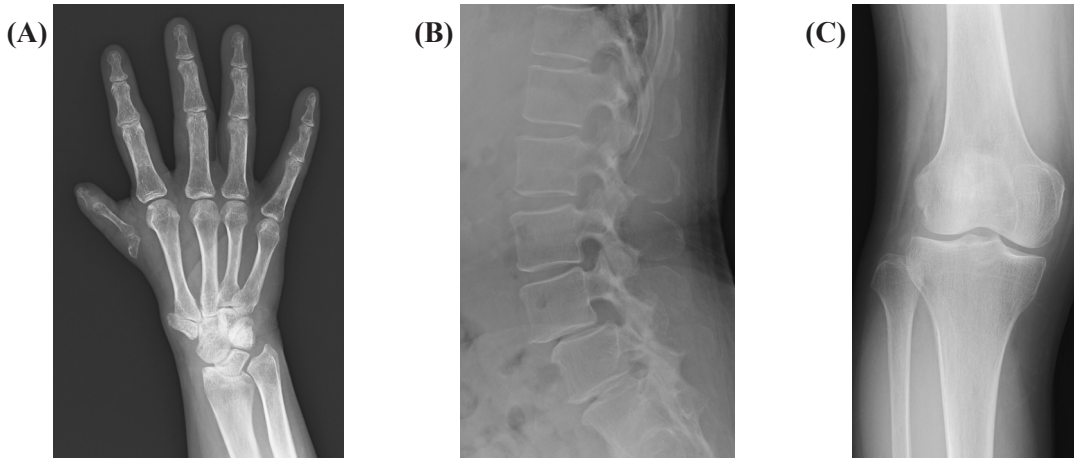


**Figure 3. X-ray images of a female adult in her early 50s.** In this female adult with thalidomide embryopathy, showing relatively mild upper-limb hypoplasia and no apparent lower-limb malformations, the right hand with thumb hypoplasia shows fusion of the carpal bones and a narrow, deformed radiocarpal joint **(A)**. The lumbar spine shows narrow intervertebral spaces with endplate irregularity and spondylolisthesis **(B)**. The right knee joint is inclined with the hypoplastic lateral femoral condyle **(C)**.

common, but include pain from osteoarthritis of the hip and knee. These disabilities are related to a decreased physical domain of HRQOL, which is particularly low in those with severe limb involvement and pain. HRQOL has been studied in various nations including UK, Sweden, and Germany (Table 1), and the decrease in physical domain was common. However, the care system and the societal support may differ among nations, and these may affect the accessibility to health care service including rehabilitation. As for available intervention, reports on rehabilitation treatment were limited, although orthopedic surgeries have been reported to resolve musculoskeletal symptoms.

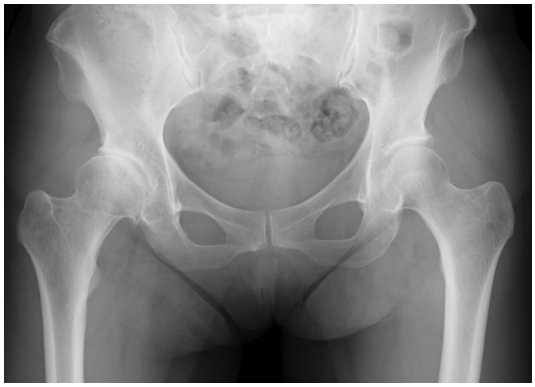

**Figure 4. Hip X-ray of a male adult in his late 50s.** This male adult with thalidomide embryopathy was affected by hearing impairment but no limb malformations. Both hips show acetabular dysplasia and the joint space in the right is narrow.

We believe that secondary musculoskeletal disabilities occur through the following mechanisms (Figure 6). Individuals with relatively mild upper limb hypoplasia normally use their upper limbs to perform ADL. As age-related changes and stress from repetitive and/or compensatory use accumulate, joint dysfunction including arthropathy, tenosynovitis, and peripheral upper limb neuropathy occur. An example of compensatory use is using index and middle fingers for pinching in an individual with TE and no thumbs. However, individuals with relatively severe upper-limb hypoplasia normally use their lower limbs to carry out their ADL. They develop spinal disorders and lower-limb arthropathy as age-related changes accumulate due to repetitive and/or compensatory use. Those who use their lower limbs to eat and wash their faces must bend their spines, which can cause spinal disorders. However, repetitive and/or compensatory use is not the only causes

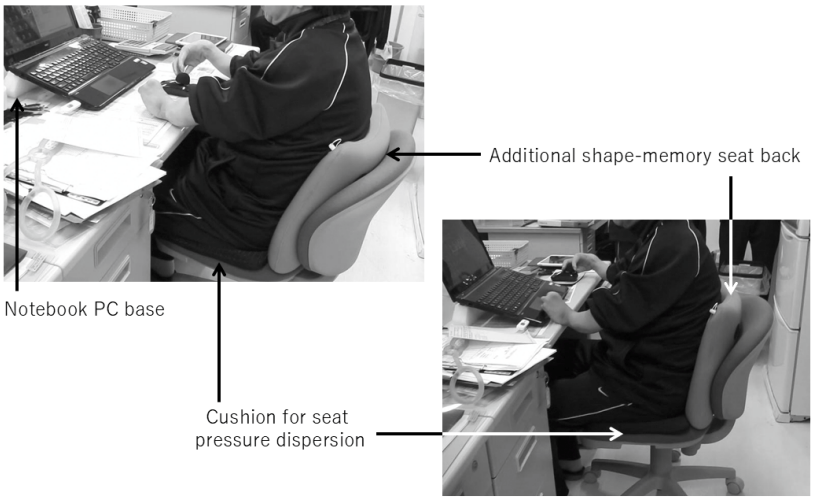


**Figure 5. Ergonomic intervention.** Sitting posture improved and the symptoms mitigated after ergonomic intervention in a male office worker with thalidomide embryopathy.

**Table 2. Summary of musculoskeletal disabilities and interventions**

| Musculoskeletal Disability | Prevalence | Available Intervention* |
|---|---|---|
| Upper Limbs | | |
| neuropathic pain in upper limbs | common | decompression surgery |
| pain from tenosynovitis | unknown | |
| pain from osteoarthritis (mainly in the shoulder) | commom | joint replacement surgery |
| Trunk and Spine | | |
| pain in the lower back or neck | common | ergonomic improvement |
| Lower Limbs | | |
| pain from osteoarthritis (mainly in the hip and the knee) | unknown | joint replacement surgery |
| reduced ambulation | common in individuals with PFFD** | physical theray wheelchair |

*Alternative medicine was applied to various symptoms in Japanese individuals. **proximal femoral focal deficiency.

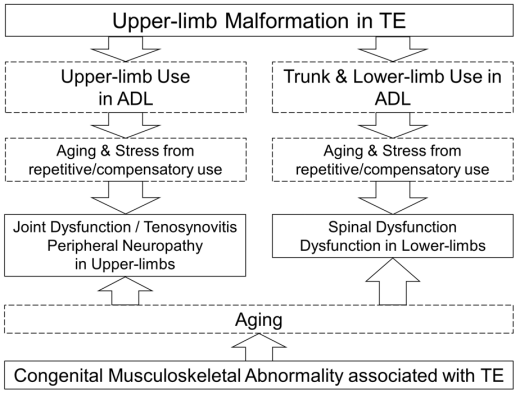


**Figure 6. Mechanism of secondary musculoskeletal disabilities related to upper-limb hypoplasia in thalidomide embryopathy.**

of these disorders. The above-mentioned congenital limb and spinal malformations may also have contributed to this finding.

Apart from TE, carpal tunnel syndrome and pain in the neck, shoulder, and elbow have been reported to occur more frequently in individuals with unilateral upper limb deficiency, both congenital and acquired (*38*). The authors regarded these symptoms as overuse problems resulting from repetitive and forceful hand-intensive tasks. As for radial deficiency unrelated to TE, carpal tunnel syndrome was reported in an adult with Holt-Oram syndrome (*39*), and grip strength and key pinch were less than the norms in adults with unilateral or bilateral radial deficiencies (*40*). These reports may partially support the mechanism model in Figure 6, though we could find no other literature on the secondary musculoskeletal problems in adults with congenital unilateral or bilateral upper limb deficiencies.

Considering the above-mentioned presumed mechanisms, various rehabilitation approaches could be useful in preventing the development and progression of secondary musculoskeletal disabilities in individuals with TE. The current review identified approaches including physical therapy, environmental modification, and alternative medicine (Table 2). Though physical therapy and environmental modification led to satisfactory outcome, these were case reports with relatively short-term observation. For adults with unilateral upper limb deficiency without TE, Burger *et al*. reported that if an occupational therapist observes and tries to teach a person with upper limb deficiency how to perform an activity without compensatory movements, this can prevent or decrease the extent of the overuse problems (*38*). In addition, we found that individuals with TE sometimes use assistive devices in their ADL, such as buttoning up their shirt, clipping nails, and twisting the plastic bottle open. Appropriate use of self-help devices to avoid stress from repetitive and/or compensatory use of the upper limbs may reduce the risk of secondary musculoskeletal disabilities.

Limitations of this study include reviewing only articles written in English obtained through a PubMed search, and the small number of Japanese individuals with TE that the authors experienced.

In conclusion, this review of musculoskeletal disabilities and QOL in adults with TE revealed that pain is common in the upper limbs and spine, and is associated with reduced physical QOL. Though reports on rehabilitation interventions are scarce and provide little evidence, rehabilitation providers are encouraged to understand the mechanism of secondary musculoskeletal disabilities and select appropriate approaches based on precise evaluation of the physical status of individuals with TE. To establish evidence to support these rehabilitation approaches, the accumulation of personal experience and further studies, preferably interventional studies with control group, are necessary.

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*Conflict of Interest*: The authors have no conflicts of interest to disclose.

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***Review***

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# Unraveling the genetic and pathophysiological mechanisms underlying disorders of sex development

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**SUMMARY**: Disorders of sex development (DSDs) encompass a spectrum of congenital conditions characterized by discordance among chromosomal, gonadal, and anatomical sex. Advances in genetic and molecular technologies have elucidated a complex landscape of underlying etiologies, including mutations in genes regulating sex determination and differentiation, copy number variations, and epigenetic alterations. These discoveries have not only enhanced diagnostic accuracy but also deepened our understanding of the molecular mechanisms driving DSDs. This review provides a comprehensive overview of the genetic architecture in DSDs, with a focus on key regulatory genes and their network interactions. We also highlight emerging concepts in the field, such as oligogenic inheritance and regulatory genomic elements, and discuss implications for personalized diagnosis, classification, and therapeutic strategies. By integrating recent advances from both clinical and basic research, this review aims to offer a framework for future investigations and translational applications in the management of DSDs.

***Keywords***: disorders of sex development (DSD), diagnostics, genetics, pathogenesis

## 1. Introduction

Disorders of sex development (DSD) is a type of congenital disease with atypical chromosomes, gonads, or anatomical sex or abnormal development, with high heterogeneity in clinical manifestations and heredity, and a prevalence of about 1: 5500 - 1 :4500 (*1*). Its incidence and rate of diagnosis are low, and multidisciplinary comprehensive evaluation is often required. Molecular genetic technology mediates in the diagnosis and has guiding significance for the early diagnosis of DSD. According to the consensus of the Chicago Conference in 2006, DSD are divided into 46, XX DSD, 46, XY DSD, and sex chromosome DSD (*2*). 46, XY DSD has a variety of causes and clinical manifestations, is difficult to diagnose clinically, and most patients require surgery.

However, the diagnosis of DSD is primarily determined by a comprehensive evaluation encompassing a medical history, physical examination, laboratory analysis, genetic evaluation, and imaging studies, among other factors. The predominant advance during the preceding decade pertains to the evolution of genetic testing. In the event that patients undergo genetic testing, approximately one-third are found to possess mutant genes (Figure 1). For children with vague external genitalia or without secondary sexual development in adolescence, the evaluation and diagnosis should be completed with the cooperation of a multidisciplinary team (MDT), which should consist of pediatric endocrinology, pediatric (urological) surgery, obstetrics and gynecology, imaging, psychology, molecular genetics, or other related departments (*3*). At the same time, if the pathogenesis can be clarified, then it can be followed by precise treatment.

## 2. 46, XX DSD of adrenal origin

46, XX DSD is mainly related to SRY gene translocation, excessive factors related to promoting development and differentiation in the fetus and androgen excess, including 46, XX testicular DSD and congenital adrenal hyperplasia (CAH). In 46, XX cases, adrenal steroid production disorder is the cause of genital abnormalities, and patients may display an aldosterone deficiency, which may lead to life-threatening salt consumption crisis (*4*). Adrenal steroidogenic defects leading to 46, XX DSD are a 21-hydroxylase deficiency, which is by far the most prevalent, and an 11β-hydroxylase deficiency.

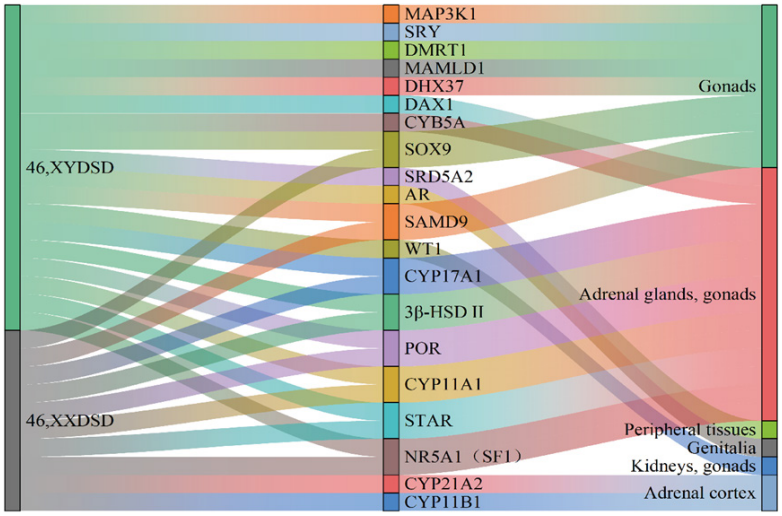


**Figure 1. Karyotype and tissue flow of representative DSD pathogenic genes to Sankey diagram.**

2.1. Pathogenesis of 46, XX DSD

2.1.1. 21- hydroxylase deficiency

The enzyme 21OH (P450c21) catalyzes the conversion of 17- hydroxyprogesterone to 11-deoxycortisol in the fascicular zone and progesterone to 11-deoxycorticosterone (DOC) in the adrenal cortical zone. 21OHD (MIM 201910) caused by a CYP21A2 (MIM 613815) mutation is the most common form, accounting for about 95% (*5*) of CAH. According to neonatal screening, the incidence of a 21- hydroxylase deficiency is estimated to be between 1/14 000 and 18 000 live births (*6*). Life-threatening forms of salt consumption, accounting for about 75% of classical CAH, are usually due to gene deletion or transformation or a stop codon or frameshift mutation, which seriously affects the activity of 21OH, thus hampering the synthesis of glucocorticoid and mineralocorticoid. Although the genetic test for a CYP21A2 mutation is not a first-line diagnostic test at present, genotyping is the key to determining affected carriers in the family (*7*). At the same time, variants in more genes involved in glucocorticoid biosynthesis, such as STAR, CYP11A1, 3β-HSD II, CYPB11B1, CYP17A1, and POR, have been identified as the cause of CAH (*8*).The p.A218V mutation in the acute regulatory gene (StAR) of steroid synthesis, which regulates ovarian steroid production and aldosterone and cortisol synthesis and secretion pathways, limits its binding activity to cholesterol and is a pathogenic variant (*9*). An increasing number of pathogenic variants are being found to be associated with 46, XX DSD.

2.1.2. 11β-hydroxylase deficiency

Microsomal cytochrome P450c11β with 11β-hydroxylase activity is coded as CYP11B1 (MIM 610613), which catalyzes the last step of cortisol biosynthesis. Mutation of the CYP11B1 gene leads to 11βOHD (MIM 202010), which is the second most common form of CAH, accounting for 0.2-8% of all cases. The prevalence of this disease is estimated to be 1 in 100,000, and the prevalence is higher among Muslims and Moroccan Jews in the Middle East (*10*). Compared to women with 21OHD, women with 11βOHD are more masculine; interestingly, however, the degree of masculinity is not related to the degree of hyperandrogenism (*11*). The patient's fertility rate is low. Simm *et al*. reported the first successful pregnancy of a 26-year-old woman who was seriously deficient in 11βOHD (*12*). The diagnosis of 11βOHD is based on an increase in the basal concentration of DOC and the high reactivity of 11-deoxycortisol (> 3 times the upper limit of the normal value) in an ACTH test. There is also low cortisol and normal or inhibited plasma renin activity (*6*). Diagnosis is difficult because neonates are usually free of hypertension and renin suppression, but molecular genetic testing can confirm the diagnosis of 11β OHD when CYP11B1 gene mutations are identified.

The advent of gene sequencing technologies, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), has precipitated a paradigm shift in the field of genetic analysis. These technologies are anticipated to facilitate the expeditious and precise identification of genetic mutations associated with 46, XX DSD, thereby enabling earlier diagnosis, particularly during the neonatal and even prenatal period. This will assist in the timely interventions required to mitigate the occurrence of severe complications, including salt depletion crises. The integration of multi-omics techniques (*e.g.* proteomics and metabolomics) may reveal a greater number of biomarkers associated with adrenal steroid synthesis disorders and provide a more comprehensive basis for diagnosis.

2.2. DSD and female reproductive capacity

In patients with DSD, fertility problems are caused by endocrine, gonad, or anatomical abnormalities inherent in the disease (*5*). In addition, medical and surgical treatment will affect the fertility of these patients. Age at diagnosis of DSD is another factor related to fertility (*13*). Because the fertility problem affects quality of life to a great extent, the fertility potential of patients with DSD needs to be considered in other medical management (*14*).

2.2.1. Excessive androgen

CAH leads to a higher adrenal androgen or progesterone level, interferes with gonadotropin secretion, and produces a series of pathophysiological consequences, leading to different degrees of chronic anovulation (*15*). Gender role reversal is relatively common among affected adult women. In addition, pre-adolescent girls with CAH may exhibit masculine and slightly feminine interests and preferences (*16*).

A wide range of pathophysiological symptoms and varying fertility rates were reported in 46,XX patients with DSD, with the most severe classic type of CAH, 21-OHD, exhibiting the lowest pregnancy and success rates (*15*). In contrast, the pregnancy rate of patients with mild CAH is closer to the normal rate (*17*). One of the less common causes of CAH is a 17- hydroxylase deficiency (17-OHD), which occurs in less than 1% (*18*). This condition could be resulted from biallelic mutations in the *CYP17A1* gene (*19*). Women with complete defects develop amenorrhea, sexual infantile syndrome, impaired secondary sexual development, and primary infertility, while some defects may manifest as female infertility in adulthood (*20*). Successful pregnancy has been reported with the help of *in vitro* fertilization cycle and frozen embryo transfer (*21*). However, there is no information about pregnancy in women with a 3β-hydroxysteroid dehydrogenase type II deficiency (3β-HSD II). Preimplantation genetic diagnosis (PGD) technology has been utilized to detect affected embryos prior to their transfer with assisted reproductive technology. Moreover, PGD necessitates the timely identification of pertinent CAH mutations in order to detect this autosomal recessive disorder. Women with CAH are vulnerable to age-related decline in oocyte quality and fertility, but few studies have reported that patients with CAH retain fertility (*22*).

2.2.2. Disorders of ovarian development

Normal ovarian tissue determines the final phenotype of external genitalia and internal genitalia. Ovotesticular DSD, also known as true hermaphroditism, is related to different karyotypes, including 46, XX (60% of cases), chimera 46, XX/XY (33% of cases) and 46, XY (7% of cases) (*23*). This DSD is characterized by bilateral ovular testes or a healthy ovary/testis and contra-lateral ovular testis; the ovular testis may contain many primordial follicles. Excision of all inconsistent male testicles and Wolffian tissues can maximize the fertility potential of patients with ovular testicular DSD as women with complete Mullerian duct structure. At the same time, it helps to reduce the level of androgen and increase the chance of ovulation. Because of the high rate of premature delivery, neonatal death, or delivery problems reported (*24*), it should be closely monitored after pregnancy. In 46, XX gonadal dysgenesis (GD) cases, most successful pregnancies were the result of assisted reproductive technology (*24,25*). A 24-year-old woman successfully became pregnant and delivered after receiving controlled ovarian stimulation and *in vitro* fertilization (*26*). However, these pregnancies are accompanied by obvious complications, including oligohydramnios, pregnancy-induced hypertension, preeclampsia, premature delivery, premature rupture of membranes, and spontaneous abortion (*14*).

2.2.3. Mullerian agenesis

The secondary sexual characteristics of patients with MRKH syndrome seem normal, but the lack of a vagina and uterus is the second most common cause of primary amenorrhea (*27*). Uterine transplantation is an innovative method in reproductive medicine that is used to treat infertility caused by an abnormal uterus. However, there are few reported cases of human uterine transplantation worldwide, and Brännström *et al*. reported the first live birth as a result of IVF after uterine transplantation (*28*). Correct and comprehensive diagnosis and psychological consultation are necessary to determine the best treatment for patients with Mullerian duct hypoplasia. (The effects of 46,XX DSD on fertility are shown in Table 1)

**3. 46, XY DSD of adrenal origin**

In 46, XY patients, DSD is caused by related testicular dysfunction, and the most common is primary adrenal insufficiency characterized by decreased cortisol secretion and excessive adrenocorticotropic hormone secretion. The nutritional function of ACTH causes CAH. The etiology and pathogenesis of 46, XY DSD are complex and diverse, and any factor that affects testicular differentiation or testosterone synthesis or action can lead to 46, XY DSD (*29*). There are many genes involved, and different pathogenic genes will cause different accompanying symptoms. The level of miRNA210 expression in 46, XY DSD patients is higher than in normal patients, which may be related to the development of cryptorchidism, confirming that RNA is one of the causative causes of 46, XY DSD (*30*). Abnormal gonadal differentiation and development have been found to be related to SRY, WT1, SF1,

**Table 1. Summary of the different types of 46, XX DSD and their effects on fertility**

| Category | Specific type | Karyotype | Pathogenesis | Clinical manifestations | Impact on fertility | Ref. |
|---|---|---|---|---|---|---|
| 46, XX DSD | 46, XX DSD | 46, XX | SRY gene translocation; excess fetal development factors; androgen excess | Ambiguous external genitalia; possible salt-wasting crisis | Fertility affected by endocrine, gonadal, or anatomical abnormalities; some patients may become pregnant with assisted reproductive technology | *4* |
| | 21-hydroxylase deficiency | 46, XX | CYP21A2 gene mutation | Salt-wasting crisis; masculinized external genitalia | Low fertility in classic 21-hydroxylase deficiency; near-normal fertility in mild cases | *5-7* |
| | 11β-hydroxylase deficiency | 46, XX | CYP11B1 gene mutation | Masculinized external genitalia; hypertension (in adults) | Low fertility in females; successful pregnancies reported | *11-12* |
| | 17- hydroxylase deficiency | 46, XX | CYP17A1 gene mutation | Amenorrhea, sexual infantile syndrome, impaired secondary sexual development, and primary infertility | Successful pregnancies reported | *15-21* |
| | MRKH syndrome | 46, XX | Mullerian duct hypoplasia | Lack of vagina and uterus | Live birth as a result of IVF after uterine transplantation | *27-28* |

SOX9, DAX-1, DMRT1, and other genes(*31*). DAX1-/Y mice displayed a female phenotype, and mating with DAX1/Y male mice produced singleton offspring, while DAX1-/Y mating with DAX1/female mice did not produce viable offspring (*32*). As shown in mice, a comprehensive evaluation of fertility following sexual reversal is imperative. A mutation in the DHX37 gene upregulates the β-catenin protein and activates the Wnt/β-catenin pathway, which may be the cause of DSD (*33*). Mutations in CYP17A1, SRD5A2, and other genes can cause abnormal development of enzymes involved in androgen synthesis, thus leading to androgen synthesis disorder. Androgen dysfunction is mainly related to the androgen receptor (AR) gene. Compared to these single-gene inheritance patterns, patients with Mastermind-like domain-containing 1(MAMLD1) associated 46,XY DSD may carry variants in other DSD-related genes, and the phenotypic outcome of affected individuals might be determined by multiple genes. A study has indicated that male mice with deletion of the causative gene MAMLD of DSD have normal reproductive organs and reproductive capacity (*34*). Recent studies have further demonstrated that DSDs caused by MAMLD1 follow a pattern of oligogenic inheritance (*35,36*).

### 3.1. Pathogenesis

An astrocyte deficiency or a cytochrome P450scc and P450c17 deficiency can lead to CAH in 46, XY newborns. The mutation of SF1 may also lead to the combined failure of adrenal glands and testes, and the detection of DSD and NR5A1 mutations in 46, XY individuals can confirm the diagnosis (*37*). A 17,20-lyase deficiency (MIM 202110) is a rare cause of CAH, which is caused by any mutation of three different genes: CYP17A1, POR, or CYB5A (*13*). 46, XY patients with a 17,20-lyase deficiency had ambiguous genitalia at birth. 3β HSD 2 (*38*) or impaired POR activity (*39*) may lead to DSD in 46, XX and 46, XY individuals, which can be confirmed by detection of a gene mutation. The biological activity in the gonads is dependent on glycosylation of gonadotropins and their receptors. Glycosylation processes are essential for the correct gonad migration and genitalia morphogenesis. Conserved oligomeric Golgi complex 6-congenital disorder of glycosylation (COG6-CDG) is a type of metabolic disorder with abnormal protein glycosylation. A patient with COG exome deletion presents with a normal male karyotype, though the patient has an underdeveloped scrotum with no palpable testes and a micropenis (*40*). A study has found that COG6-CDG can manifest as sex differentiation disorder with chromosome karyotype 46, XY and external female genitalia (*41*). Other studies have indicated a relationship between COG6 impairment and DSD, glycoprotein metabolism, and sex development; however the mechanism of action is unclear. Some deleterious variants of the COG gene are associated with

46, XY DSD because of gonadal dysgenesis.

3.2. DSD and female reproductive capacity

3.2.1. Disorders of androgen-dependent target tissues

Androgen sensitivity syndrome (AIS) phenotypes range from the appearance of infertile men to women with typical external genitalia (*42*). The degree of insufficient masculinization of external genitalia at birth and adolescence depends on the level of androgen insensitivity in the target tissue. Because the risk of premature germ cell tumors is extremely low, it is reasonable to recommend that gonadectomy be postponed until adulthood (*43*). At present, patients with complete AIS (CAIS) are considered infertile because they have no ovaries or uterus. However, a study has detected germ cells in the abdominal gonads (*42*). The existence of germ cells improves the possibility of future fertility through preservation, but this option is only experimental at this stage.

3.2.2. Disorders of androgen synthesis or action

Patients with a 5α-reductase -2 (5α-RD-2) deficiency exhibit normal female genitalia with male internal ducts. After birth, under the influence of testosterone, somatic cells are masculinized. During sexual maturity, testosterone can also induce muscle enlargement, penis growth, and testicular decline (*14*). Li *et al*. demonstrated that an SRD5A2 mutation decreased the catalytic efficiency of the 5α-reductase type 2 enzyme and dihydrotestosterone (DHT) production (*44*). Similar to CAIS cases, the impaired function of 17β-HSD III can lead to clinical manifestations of female external genitalia before puberty(*42*). With the testes in place, masculinization occurs in adolescence, similar to what happens with a 5α-RD-2 deficiency(*42*).

3.2.3. Disorders of testicular development

46, XY gonadal dysplasia (GD) is caused by any gene mutation involved in gonadal formation. NR5A1, MAP3K1, and SRY are the genes often reported to be related to 46, XY GD . Complete 46, XY GD, also known as Swyer syndrome, is characterized by bilateral GD and physiologically effective uterine and normal endometrial reactions (*45*). These individuals have streak gonads, fallopian tubes, a small uterus, and female external genitalia. Striped gonads cannot produce normal amounts of sex hormones, so secondary sexual characteristics do not all develop. Although the gonads are poorly developed, a successful pregnancy can result from oocyte donation (*45*). However, there are very few live births among such patients (*45*). Taneja *et al*. reported that a patient with Swyer syndrome had a normal pregnancy and delivery as a result of donor oocytes (*45*). Winkler *et al*. reported a successful twin pregnancy in a patient with Swyer syndrome after oocyte donation and an *in vitro* fertilization cycle (*46*).

Partial 46, XY GD is an uncommon disease that is characterized by ambiguous genitalia and different degrees of testicular dysplasia, with or without a Mullerian duct structure. Hormone therapy includes administering estrogen and progesterone to individuals with a uterus to induce menstruation and administering estrogen to individuals without a uterus at the age of 10 to avoid excessive bone maturation (*47*).A recent report described how MIRAGE syndrome caused by the sterile alpha motif domain-containing protein-9 (SAMD9) gene was responsible for an 46, XY sexual developmental disorder and adrenal insufficiency (*48*). MIRAGE syndrome is a multisystem and multiphenotypic genetic disorder. SAMD9 is expressed in a variety of tissues, and its role in the adrenal glands is often overlooked. SAMD9 mutations can directly limit testicular development while affecting placental development and HCG levels (*49*). However, reports of female patients with karyotype 46, XX are even rarer. (The effects of 46,XY DSD on fertility are shown in Table 2)

**4. Sex chromosome in DSD**

4.1. Turner syndrome

Partial or complete deletion of the X chromosome or a structural change in the sex chromosome will lead to a female phenotype, which is called Turner syndrome (TS). The complete deletion of the sex chromosome can be defined as 45, X/46, XX chimera or 45, XO. The infertility of women with X haploid TS is mainly due to premature ovarian failure (POF) with few or no oocytes (*50*). However, individuals with 45, X haploid or 45, X/46, XX chimera have normal puberty and regular menstruation, and have a natural pregnancy, giving birth to a healthy baby (*51*). TS cases experiencing natural pregnancy usually have mosaic genotype (*50*). Assisted reproductive technology has increased the probability of successful pregnancy of TS women using their own fresh or donor oocytes (*52,53*). In these cases, however, the risk of various complications increases, including pregnancy-induced hypertension, pre-eclampsia, gestational diabetes, premature delivery, multiple pregnancies, low birth weight, spontaneous abortion, inherent sex chromosome or endometrial abnormalities, and even death due to complications of aortic dissection or rupture (*54*). The uterus of TS women is smaller than a normal uterus, so single embryo transfer is performed (*51*).

4.2. Mixed gonadal dysgenesis

The main characteristic of mixed gonadal hypoplasia (MGD) is a 45, X/46, XY karyotype. The affected

**Table 2. Summary of the different types of 46, XYDSD and their effects on fertility**

| Category | Specific type | Karyotype | Pathogenesis | Clinical manifestations | Impact on fertility | Ref. |
|---|---|---|---|---|---|---|
| 46, XY DSD | 46, XY DSD | 46, XY | Adrenal dysfunction; gonadal dysgenesis | Ambiguous external genitalia; possible other endocrine abnormalities | Fertility affected by gonadal development and androgen action; some patients may become pregnant with assisted reproductive technology | *29-36* |
| | 17,20-lyase deficiency | 46, XY | SF1,NR5A1,3β-HSD II,CYP17A1, POR, or CYB5A gene mutation | Ambiguous external genitalia | Low or absent fertility | *13;37-39* |
| | Complete androgen insensitivity syndrome (CAIS) | 46, XY | AR gene mutation | Female external genitalia; no uterus or ovaries | Typically infertile; experimental germ cell preservation studies | *31;42-43* |
| | 5α-reductase-2 deficiency | 46, XY | SRD5A2 gene mutation | Female external genitalia; masculinization at puberty | Low or absent fertility | *14;44* |
| | Partial 46, XY gonadal dysgenesis | 46, XY | NR5A1, MAP3K1, SRY, SAMD9 gene mutations | Ambiguous external genitalia; gonadal dysgenesis | Low or absent fertility | *45-46* |

individuals have streak ovaries and testes with ipsilateral dysplasia, which leads to structural abnormalities, such as a primitive Mullerian duct structure, incomplete Wolff duct development, and insufficient masculinization of external genitalia (*55,56*). Despite the lower natural fertility seen in MGD patients, some may be able to conceive through the use of assisted reproductive technologies, such as egg donation and *in vitro* fertilization (*55*).

4.3. Klinefelter syndrome (KS)

The karyotypes of KS are 47, XXY, 47, XXY/46, XY, 47, XXY/46, XX and 47, XXY/48, XXXY/49, XXXXY. The karyotype of patients is mainly 47, XXY, and the phenotype of patients with KS gradually deviates from normal due to the escape and inactivation of multiple genes on the redundant X chromosome. Some patients with KS have no obvious clinical manifestations themselves, and about 64% patients have never been diagnosed throughout their lives (*57*). KS accounts for 3-4% of patients with infertility and 10-12% with azoospermia (*58*). In some patients, the clinical manifestations are being tall or having small testicles, a sparse beard, or an inconspicuous Adam's apple. There are also KS patients with psychological, behavioral, learning, and mental disorders, including impaired language ability. The specific mechanism is not clear, though it may be directly related to chromosomal abnormalities or may be caused by hypogonadism. Aksglaede *et al*. (*59*) reported that only 10% of patients were diagnosed before puberty. A study has shown that patients with KS have an increased risk of male breast cancer and extragonadal germ cell tumors (*60*). Therefore, early accurate diagnosis and close clinical monitoring of KS patients are crucial to preventing the development of tumors. (The effects of Sex chromosome DSD on fertility are shown in Table 3)

## 5. Conclusion

The diagnosis and treatment of DSD is very complicated, and individualized treatment is particularly important. At present, surgery is still the main treatment, and gender psychological determination and gender distribution are the most critical links in the treatment of patients with 46, XY DSD. The opinions of multidisciplinary teams, family members, and/or children themselves should be integrated, along with factors such as the patient's sexual psychology, sexual role, and sexual orientation, the risk of gonadal cancer, fertility potential, follow-up treatment, and the social and cultural environment so as to avoid a change in gender in adulthood.

In addition, other treatments mainly include correct identification of gender and upbringing, hormone replacement therapy, and preservation of fertility. The improper identification of DSD and gender can lead

**Table 3. Summary of the different types of sex chromosome DSD and their effects on fertility**

| Category | Specific type | Karyotype | Pathogenesis | Clinical manifestations | Impact on fertility | *Ref.* |
|---|---|---|---|---|---|---|
| Sex chromosome DSD | Turner syndrome | 45, X/46, XX | Partial or complete X chromosome deletion | Female phenotype: short stature, underdeveloped secondary sexual characteristics | Most patients are infertile due to premature ovarian failure; some patients may become pregnant with assisted reproductive technology | *50-53* |
| | Mixed gonadal dysgenesis | 45, X/46, XY | Sex chromosome mosaicism | Ambiguous external genitalia: Gonadal dysgenesis | Low or absent fertility | *55-56* |
| | Klinefelter syndrome | 47, XXY | Inactivation of multiple genes on the extra X chromosome | Tall stature, small testes, underdeveloped male secondary sexual characteristics | Azoospermia or oligospermia; some patients may become pregnant with assisted reproductive technology | *57-60* |

to an inconsistency between the patient's physical and psychological gender, resulting in profound mental stress and psychological obstacles, so attention should be paid to social and psychological support for and long-term follow-up of patients.

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***Review***

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# Towards an Asian paradigm of inflammatory bowel disease management: A comparative review of China and Japan

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**SUMMARY**: This systematic review compares inflammatory bowel disease (IBD) management between China and Japan across epidemiology, clinical strategies, health insurance, and social security policies. Epidemiologically, the incidence of IBD is rapidly increasing in China, contributing to a growing disease burden. In contrast, Japan has a stabilized incidence but a rising prevalence, driven by an aging patient population. Clinically, step-up therapy remains the mainstream approach in China, limited by regional and financial disparities in biologic access. In contrast, Japan, benefiting from the "Designated Intractable Diseases" program, favors early intensive therapy with a focus on mucosal healing. In the area of precision medicine, China is advancing rapidly in therapeutic drug monitoring (TDM) for anti-TNF agents. In contrast, Japan leads in AI-assisted endoscopic assessment, despite slower adoption of TDM. Japan's comprehensive insurance covers most costs of IBD; China has significantly reduced drug prices *via* national negotiations, and yet reimbursement rates vary regionally. China has made progress in telemedicine and standardized fecal microbiota transplantation (FMT); Japan excels in AI endoscopy and use of an elemental diet. To optimize IBD care in the Asia-Pacific, China should enhance access to advanced therapies, implement hierarchical diagnosis/treatment, and develop multi-tiered insurance. Japan must address aging-related challenges and insurance sustainability while expanding use of TDM. Sino-Japanese collaboration in genetics, microbiome research, and AI-driven diagnostics, supported by sustained policy dialogue, is key to advancing precision IBD care and shaping a scalable "Asian model" for chronic disease management.

***Keywords***: inflammatory bowel disease, ulcerative colitis, Crohn's disease, epidemiology, precision medicine, health insurance policy

## 1. Introduction

Inflammatory bowel disease (IBD) — consisting of ulcerative colitis (UC) and Crohn's disease (CD) — is marked by chronic, relapsing gastrointestinal inflammation and a high risk of complications (*1-3*). The global burden of IBD continues to grow, with its incidence rising most rapidly in the Asia–Pacific region (*4,5*). Within Asia, China and Japan offer two contrasting but complementary scenarios: China, a newly industrialized economy, is experiencing one of the world's steepest increases in IBD incidence, whereas Japan, which industrialized earlier, is now home to a substantial population in which IBD is prevalent (*5-7*). Despite similarities in ethnicity, diet, and culture, the two countries are in different epidemiological stages, offering a natural comparator with which to study the impact of industrialization and demographic transition on IBD. Their health-care financing models likewise diverge. Japan's Specified Intractable Diseases subsidy virtually eliminates out-of-pocket costs and facilitates early intensive therapy, whereas China's national price-negotiation program has markedly lowered biologic prices but regional reimbursement disparities persist — an ideal setting in which to study how distinct funding strategies affect treatment effectiveness and adherence (*8-10*). Technologically, China is rapidly expanding therapeutic drug monitoring (TDM) and telemedicine, while Japan leads in artificial intelligence (AI)-assisted endoscopy and elemental diet therapy (*11-17*); these complementary strengths could catalyze a new Asia-Pacific paradigm for IBD management

Accordingly, a systematic comparison of IBD in China and Japan could not only highlight practice gaps but also inform evidence-based prevention, management, and reimbursement policies for countries across the resource spectrum. Here, we juxtapose the two nations in terms of epidemiology, clinical management, health insurance structures, and adoption of advanced technologies in order to help optimize comprehensive IBD management and to foster regional collaboration in the Asia–Pacific (Table 1).

**Table 1. Comparison of IBD epidemiology, clinical practice, health insurance policies, and use of new technology in China and Japan**

| Domain of comparison | China | Japan | *Ref.* |
|---|---|---|---|
| Epidemiological stage | In the "rapid increase in incidence" phase: Age-standardized incidence rose by about 2.9% annually (1990–2021); prevalence is accelerating. | In the "increasing prevalence" phase: Incidence has plateaued over the past decade; prevalence continues to rise due to prolonged survival. | (*1,5,6*) |
| Overall clinical strategy | From the traditional Step-up approach to the emerging Top-down approach, but the usage of advanced therapies such as biological agents in practice remains relatively low. | Prefers "early aggressive" strategy: Early introduction of biologics, JAK inhibitors, and other advanced therapies. | (*13,14,35,36*) |
| TDM | TDM is widely practiced. In 2018, the first "Expert Consensus on TDM for IBD Biologics" was issued; the 2023 national guideline re-emphasizes reactive TDM for IFX and other anti-TNF agents. First-tier centers are standardizing routine TDM. | Adoption of TDM is relatively slow; physicians more commonly rely on empirical dose escalation or switching therapies in cases of anti-TNF loss of response. | (*35,39*) |
| Disease monitoring | Emphasis on fecal calprotectin and imaging assessments; endoscopy mainly used for diagnosis and mucosal reassessment. | Emphasis on regular endoscopic evaluation for mucosal healing; non-invasive biomarkers are used as adjuncts. | (*27,44,46*) |
| Patient management | Medical care is mainly concentrated in large tertiary hospitals; primary care capacity remains limited. | A well-developed tiered care system: management has shifted from tertiary hospitals to community facilities; many non-IBD specialists manage common cases. | (*28,33,34,47*) |
| Insurance & economic burden | Based on basic health insurance plus critical illness insurance; biologics have been included in the NRDL, but reimbursement ratios vary widely across provinces, and patients still bear considerable out-of-pocket costs. | Universal health insurance plus "Designated Intractable Disease" subsidy covers > 90% of costs; out-of-pocket expense for high-cost biologics is nearly zero. | (*8-10,36,50*) |
| Social security policies | Disability assessment and employment support systems are still being developed; outpatient reimbursement for chronic diseases varies significantly by region. | Severely affected patients can apply for disability allowances, sick leave subsidies, *etc.*; employment is legally protected. | (*18,48,49*) |
| AI & digital medicine | Internet hospitals, AI-based consultation, and imaging-assisted diagnosis are in their pilot stages; large-scale use is still in its infancy. | Global leader in AI-assisted endoscopic analysis; multicenter prospective studies have been conducted for real-time mucosal scoring and histological prediction. | (*11,12,15*) |
| FMT | Early adoption; established fecal microbiota banks and FMT guidelines; routine use in refractory UC in some tertiary hospitals. | Still mainly in the clinical research stage; guidelines advise caution; probiotics are commonly used as adjunctive supplements. | (*40,42,44,45*) |
| Dietary therapy | Specialized formulas such as elemental/low-FODMAP diets are beginning to be incorporated into personalized management at some centers, but evidence and implementation remain limited. | EEN is the first-line induction therapy for pediatric CD; extensive clinical experience, with remission rates of up to 80%. | (*16,17,45*) |

CD, Crohn's disease; EEN, exclusive enteral nutrition; FMT, fetal microbiota transplant; IBD, inflammatory bowel disease; TDM, therapeutic drug monitoring; UC, ulcerative colitis.

## 2. Epidemiological comparison

### 2.1. Trends in prevalence and incidence

Before the latter half of the 20th century, IBD was rarely reported in China and remained an uncommon disease in Japan. Since the beginning of the 21st century, both countries have witnessed a marked increase in the incidence and prevalence of IBD, albeit in different epidemiological stages (*5,6*) (Figure 1, A and B). According to nationwide Japanese data, the annual incidence of UC surged over 20-fold, from 0.6 per 100,000 in 2010 to 12.7 per 100,000 in 2019 (*18*). Overall, the prevalence of IBD increased from ~133.2 per 100,000 (2014) to ~368 per 100,000 (2022), and it is projected to exceed 600 per 100,000 by 2030 (*19,20*). Modeling indicates Japan's prevalence rose from 187.8 per 100,000 (2010) to 368.3 per 100,000 (2022), potentially surpassing projected figures for the US (645.8 *vs.* 629.9 per 100,000) by 2032 (*20*).

In contrast, China remains in the "second stage", exhibiting rapidly increasing incidence but lower overall rates (*5,7*) (Figure 1A). The age-standardized annual incidence of IBD in China rose from near zero (1990) to ~3.0 per 100,000 (2019), while the total prevalence increased from < 1 per 100,000 (1990) to ~47 per 100,000 (2019) (*1*). Although significantly below rates in Japan and South Korea, the annual growth rate in China is one of the world's highest (*1*). Projections suggest substantial increases in Chinese patients with IBD by 2030 (*21*). Thus, China's epidemic is accelerating, while Japan's is growing; both anticipate rising disease burdens (*5*) (Figure 1, A and B).

### 2.2. Disease spectrum and population characteristics

#### 2.2.1. Population characteristics and age distribution

The prevalence of IBD in Asia, and especially China and Japan, exhibits distinct features in population composition, patterns, and spectrum. Japan's growing cases tend to indicate a rising incidence of IBD among pediatric and elderly patients (*5*) (Figure 1, C and D). Studies project Japan's annual incidence of IBD will increase by 2.88%, driven primarily by the < 18 age group, while the 18–65 cohort remains stable (*19*). This necessitates healthcare adaptations for aging patients and increasing pediatric cases. Conversely, Chinese patients with IBD are predominantly young and middle-aged (peak incidence: 20–40 years) (*1*), implying greater impacts on potential workforce productivity (*5,22*). Despite lower total numbers than Japan, China's rapidly accelerating incidence signifies substantial future burdens (*1*) (Figure 1A).

#### 2.2.2. Distribution of disease subtype

The distribution of disease subtype also differs markedly. While UC remains designated intractable and historically predominant in Japan, the growth of CD has been

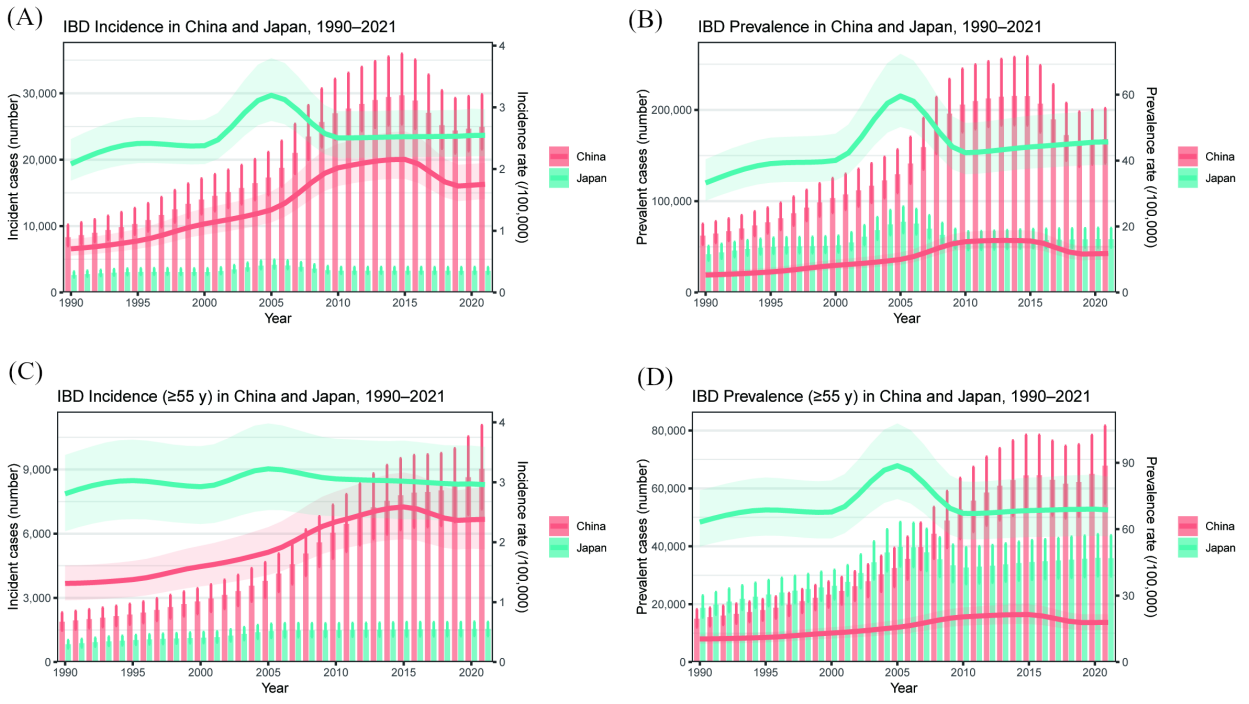


**Figure 1. IBD Burden in China and Japan (1990–2021). (A, B)** Incidence and prevalence among the total population; **(C, D)** Incidence and prevalence among the elderly population. Bars: Annual cases (left axis); lines ± 95 % UI: corresponding rate per 100,000 (right axis). Red: China; Blue: Japan. All data are from the Global Burden of Disease 2021 database.

significant recently (*18*). Early Chinese data indicated the predominance of UC, but the growth of CD now surpasses UC in some regions (*23-25*). Overall, Japan exhibits a "mature" epidemic with a large, diverse patient base, whereas China exhibits an "emerging" phase with rapid growth, necessitating vigilance with regard to future healthcare challenges (*1*).

2.2.3. Clinical and genetic characteristics

Clinical subtypes further demonstrate national variations. In China, the ratio of UC to CD is approximately 2:1, with the ileocolonic (L3) type accounting for about 48% of all CD cases (*26*). The male-to-female ratio of CD patients is about 1.5:1, whereas UC has a nearly equal gender distribution (*26*). In Japan, the UC to CD ratio is approximately 3:1, with L3 CD accounting for about 55%, and a similarly higher proportion of males among CD patients (*6,27*). A meta-analysis reported that 65% of Asian CD patients are male, in contrast to 49% in Caucasians, highlighting a unique regional gender distribution (*28*).

Genetic studies have revealed significant differences in IBD susceptibility loci between East Asian and Western populations. NOD2 mutations, which are closely associated with CD in Western populations, are rare in Japan (*29*). Conversely, TNFSF15 variants are closely associated with IBD in Asians, while high-risk Western loci like ATG16L1 are less frequent in East Asians (*20*). These findings underscore substantial genetic divergence in IBD susceptibility among Chinese, Japanese, and Western populations.

2.2.4. Contrast with Western epidemiology and phenotype

In North America and Western Europe, IBD has reached a late-plateau stage: incidence has stabilized, and yet prevalence now exceeds 600–700 per 100 000 (*5,30*). In contrast, China remains in a rapid-growth phase, whereas Japan is in an growing phase with an aging patient population. Consequently, Western IBD cohorts are more likely to be overweight or obese and to present with metabolic comorbidities such as non-alcoholic fatty-liver disease or type 2 diabetes. In China — and, to a lesser extent, Japan — under-nutrition and low body mass index are still relatively common (*31*). These contrasting phenotypes mirror dietary and lifestyle differences (higher intake of ultra-processed, high-fat foods and earlier widespread use of antibiotics in the West versus more fiber-rich diets and later industrialization in East Asia) and reflect disparities in healthcare system maturity: Western countries have decades-old multidisciplinary IBD services with integrated dietetic support, while China is still building specialist capacity (*32,33*). Collectively, differences in body habitus, environmental exposure, and healthcare infrastructure highlight the need for region-specific prevention and management strategies.

**3. Clinical management and precision medicine**

3.1. Overall therapeutic strategies

3.1.1. China: From traditional step-up to emerging top-down strategies

While both countries follow international IBD guidelines, real-world practices diverge due to variations in healthcare infrastructure and physician decision-making. Historically, IBD management in China has centered around a step-up therapeutic strategy, beginning with 5-aminosalicylic acid (5-ASA) and corticosteroids, progressing to immunomodulators and biologics in refractory cases. This approach was driven by factors such as limited availability of biologics, insufficient availability of specialists, and a high patient out-of-pocket burden. In recent years, however, treatment paradigms have evolved. The 2023 Chinese Consensus on the Diagnosis and Treatment of IBD explicitly advocates for early introduction of biologics in high-risk patients, supporting an "accelerated step-up" or even top-down strategy (*13,14*). The guideline also recommends proactive use of TDM to help optimize anti-TNF therapy and proposes de-escalation protocols for cases of stable remission (*13,14*).

Real-world implementation is increasing but on an uneven basis. One large-scale survey reported that only 13.7% of Chinese UC patients received biologics within the first year of diagnosis, and mucosal healing rates remained below 15% (*34*). Nonetheless, major IBD centers in cities like Nanjing and Shanghai are increasingly adopting early biologic strategies, often guided by risk-based stratification models. Expanded physician training, policy support, and reimbursement reforms will be key to scaling these practices nationally.

3.1.2. Japan: Early biologic era

Conversely, Japan entered the biologic era earlier (with post-infliximab approval in the early 2000s), shifting toward proactive treatment. Current guidelines emphasize early mucosal healing and prevention of complications (*18*). Biologics and targeted small molecules are widely used for moderate to severe disease. Second-line therapies (intravenous cyclosporine/tacrolimus for steroid-refractory UC) and early biologics are more common (*35*). Japanese physicians traditionally favor tacrolimus and leukocyte apheresis for steroid-refractory UC, in contrast to China's earlier switch to biologics (*35*). While therapeutic concepts converge, China's utilization of advanced therapy lags due to historical limitations on drug access and economic factors (*36,37*). Bridging this gap requires enhanced physician training and improved

reimbursement.

### 3.2. Use of biologic therapies

Biologics (TNF, integrin, IL-12/23, and JAK inhibitors) have transformed IBD management. Japan's comprehensive insurance facilitates access, with > 50% of UC and ~75% of CD patients receiving biologics (*36*). Anti-TNF agents became standard for severe cases post-2002; newer agents (ustekinumab, vedolizumab, and tofacitinib) expanded options, enabling mechanism-based selection (*36*). Critically, Japan's intractable disease subsidy system minimizes the financial impact on drug selection (*36*).

China faces greater challenges: biologics were incorporated into reimbursement schemes only recently (*e.g.*, adalimumab was included nationally in 2019) (*10*). Consequently, biologic utilization nationwide remains substantially lower than in developed countries, hindered by cost and limited physician/patient awareness (*38*). Localized production, greater reimbursement, and enhanced medical education are expected to improve future adoption.

### 3.3. TDM

#### 3.3.1. China: Growing emphasis on TDM

TDM is a key component of precision medicine. By measuring drug concentrations and anti-drug antibodies in patients' blood, TDM can optimize dosing and guide therapeutic adjustments (*39*). Here, practices diverge significantly between China and Japan. According to a 2020 survey of Asian IBD specialists, when selecting management options for patients who do not respond to anti-TNF therapy, more than 90% of Chinese clinicians would consider, among other possibilities, measuring serum trough concentrations of anti-TNF agents and anti-drug antibodies. The corresponding proportions were approximately 32% in South Korea and less than 15% in Japan, suggesting that the adoption of TDM in China already surpasses the regional average across Asia (*35*). This may be attributed to China's growing emphasis on precision IBD care in recent years, with multiple centers establishing drug concentration monitoring platforms and clinically utilizing locally produced reagents and laboratory services (*35*).

#### 3.3.2. Japan: Adoption of TDM is relatively slow

In contrast, the uptake of TDM in Japan has been relatively slow. Most Japanese clinicians still prefer empirical dose escalation or interval shortening when confronted with a poor response to anti-TNF therapy, rather than routinely performing drug concentration testing (*35*). Potential reasons include the previous lack of commercial assays in Japan and the fact that biologic therapy is covered by insurance, while TDM testing has typically been paid for out-of-pocket by patients. However, with mounting supporting evidence, awareness of TDM's value is rising in Japan, and some centers have begun to offer these services, with broader implementation expected in the coming years. In China, efforts should focus on ensuring the quality and standardization of testing and on using TDM results to guide clinical decision-making — for example, distinguishing between secondary loss of response due to low drug levels and immunogenicity — to inform whether to switch drugs or intensify therapy (*39*). In summary, TDM is a pivotal tool for personalized IBD management, and there are differences in both awareness and practice in China and Japan, which may provide opportunities for mutual learning.

### 3.4. Microbiome-based interventions

Beyond TDM, gut-microbiota-targeted interventions offer a complementary avenue for precision care. Fecal microbiota transplantation (FMT), which is intended to re-establish microbial homeostasis, has shown induction potential in refractory UC (*40*). China adopted this approach early: national stool banks and an Expert Consensus on the Clinical Practice of FMT have been established, and several tertiary centers now provide washed microbiota transplantation (WMT) as an adjunct, lowering adverse event rates from 38% with conventional FMT to 12% (*41-43*). Japan, in contrast, remains cautious, limiting FMT to research protocols without routine clinical use in IBD (*44*).

Probiotic strategies also diverge. Japan prescribes formulations such as Clostridium butyricum as adjunct therapy, whereas most Chinese patients self-administer over-the-counter probiotics whose efficacy still needs to be confirmed in high-quality RCTs (*45,46*). Nutritional modulation follows a similar pattern: elemental diets are widely used in Japan as first-line induction for CD — achieving pediatric remission rates approaching 80% — and are now being incorporated into personalized regimens at selected Chinese centers (*16,17*).

### 3.5. Monitoring strategies and care delivery models

China and Japan also differ in their approaches to patient management. In Japan, the provision of IBD care has progressively shifted from tertiary hospitals to community hospitals, and an increasing number of non-IBD specialists now manage clinically stable cases (*36*). This has enabled Japan to develop an extensive tiered care network, but also presents challenges for consistency in care, prompting the country to enhance IBD training for non-specialists (*47*). In China, most IBD patients are still managed at large tertiary hospitals, while the diagnostic and treatment capabilities of primary care facilities remain limited (*48*) (Table 2). As a result,

**Table 2. Comparison of IBD diagnosis and support systems in China, Japan, Europe, and the US**

| Comparison domain | China | Japan | Europe and the US | *Ref.* |
|---|---|---|---|---|
| Initial point-of-care facilities and their diagnostic capacity | Gastroenterology departments in county-level hospitals possess colonoscopy capability but have limited diagnostic experience; a hierarchical referral system is being expanded. | Community gastroenterology clinics predominate; about 80% are equipped with portable colonoscopes, enabling same-day screening; fully covered by universal health insurance. | Predominantly managed by family physicians who provide symptomatic care; no endoscopic accreditation; dependent on a mandatory referral system. | (*22,28,43*) |
| Nursing infrastructure | Study nurses double as follow-up coordinators (pilot phase); follow-up is predominantly outpatient. | Comprehensive nursing teams with training programs for specialized nurses; IBD outpatient nurses are included in routine practice. | Dedicated IBD nursing teams responsible for patient education and follow-up, with telephone and e-mail support. | (*26,27,42*) |
| Follow-up frequency and assessment tools | Endoscopy every 1–2 years with variable adherence — many patients present only upon relapse; biomarkers: CRP/ESR widely available, fecal calprotectin limited to tertiary centers. | High-frequency endoscopic surveillance (particularly post-operatively); biomarkers: CRP, fecal calprotectin plus immunochemical fecal occult blood testing. | Endoscopy every 3–6 months; biomarkers (CRP, fecal calprotectin) every 3–6 months; high-resolution endoscopy or MRI is routinely used. | (*27,44,46*) |
| Patient education and proactive management | Public-interest initiatives (*e.g.*, IBD Care Center) and WeChat-based guidance enhance interaction, but a systematic framework is still in its infancy. | Classes for specialized nurses emphasizing adolescent transition care and healthy lifestyle. | Structured education programs on diet, pharmacotherapy, and psychosocial health, supported by mHealth platforms; patient-centered shared decision-making. | (*27,55,56*) |
| Patient organizations and community support | Hospital-led support platforms; nascent local patient groups and WeChat communities remain small-scale. | National IBD Network and regional associations hold regular meetings and offer employment support. | Well-established non-profit organizations (CCFA/EFCCA) provide peer-support groups and online resources. | (*28,34,49*) |
| Mechanisms for responding to relapse | WeChat/telephone emergency contacts plus pilot follow-up apps; post-relapse response remains slow. | Telephone-booking rapid clinics with systematic recall reminders; endoscopy-guided therapeutic decisions. | Rapid-access IBD clinics, coupled with electronic medical-record alerts, facilitate urgent follow-up and remote therapeutic adjustments. | (*27,28,46*) |

IBD, inflammatory bowel disease.



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China has promoted the development of IBD centers and pilot programs for tiered care, encouraged the formation of provincial and municipal IBD specialist alliances, established referral standards, and enhanced recognition and management at the primary care level. To mitigate urban–rural disparities and relieve the caseload at academic centers, the National Health Commission has introduced a tiered-care reform strategy centered on IBD-specific regional medical consortia that link services across the province–city–county hierarchy. Under this framework, provincial IBD centers function as referral hubs for complex and refractory cases, municipal hospitals deliver standardized maintenance therapy, and county-level facilities focus on early screening and triage. Collectively, these reforms aim to decentralize care, harmonize treatment pathways, and narrow geographic inequities in IBD management.

There are also differences in disease monitoring preferences. Japanese clinicians tend to favor direct endoscopic assessment: in addition to standard colonoscopy, Japan is a global leader in small bowel endoscopy (capsule endoscopy and double-balloon enteroscopy), which is routinely used to assess small bowel involvement in CD. Japan has also pioneered research on AI-assisted endoscopic evaluation of mucosal inflammation. In contrast, Chinese clinicians more often combine noninvasive markers and imaging: fecal calprotectin, MRI/CT enterography, and other modalities are increasingly utilized (*35*). These differences reflect variations in resource allocation and patient preferences: capsule endoscopy is reimbursed in Japan but remains an out-of-pocket, high-cost option in China, making laboratory tests more attractive to patients. As such, IBD monitoring in the two countries reflects a contrast between "invasive" and "noninvasive" strategies. Nevertheless, the overall trend is toward more precise evaluation and rigorous follow-up to detect disease changes and adjust treatment in a timely manner.

In the quest for more precise disease assessment, AI is assuming an increasingly prominent role. Japan leads AI-assisted endoscopy, where deep-learning models autonomously interpret UC images, quantify mucosal healing, and assign Mayo endoscopic subscores with > 90% accuracy, thereby standardizing evaluation and limiting observer bias (*11,12*). China, in contrast, is expanding AI deployment across clinical services: big-data and natural-language–driven IBD consultation platforms support decision-making, while a nationwide "Internet hospital" network (> 3,000 sites by the end of 2023) integrates teleconsultation, e-prescriptions, and coordinated offline care, facilitating remote symptom monitoring and medication resupply.

## 4. Differences in health insurance and social security policies

### 4.1. Japan's multitiered patient support system

Since the 1970s, the Japanese Government has classified UC and CD as "designated intractable diseases" ("Nanbyo"), granting affected patients access to special medical subsidies (*8,9*). Currently, Japan operates a universal health insurance system, under which IBD patients receive reimbursement for medical expenses according to statutory provisions. In addition, the intractable disease subsidy further alleviates out-of-pocket costs for high medical expenses (*36*). For example, Japanese Government policy covers 70–80% of costs for designated intractable diseases, leaving patients to pay only 20–30%. There is also a monthly payment ceiling based on household income (*8*). This means that even with the use of expensive biologics, the patient's personal financial burden is relatively low, with most costs borne by the government and insurers (*36*). This system has greatly promoted the use of biologics in Japan and ensured long-term disease management. Nevertheless, studies have found that low-income patients still face a monthly co-payment of 10,000–20,000 yen, which can impact their work (*18*). To address this, patients may apply for additional welfare benefits such as a chronic disease certificate, and those with severe illness can receive nursing care subsidies. Moreover, Japan has active patient advocacy groups and social security support systems that provide psychological counseling and employment protection for IBD patients (*49*). These measures result in a higher overall quality of life for Japanese IBD patients compared to those in countries with heavier economic burdens.

### 4.2. Improved insurance coverage for IBD in China

China currently has no intractable disease subsidy specifically for IBD. However, the three-tier payment structure of the national social health-insurance system — the pooled fund of Basic Medical Insurance, Catastrophic Medical Insurance, and means-tested Medical Assistance — has begun to cushion the economic burden on patients. In the past, the high cost of biologics — such as several thousand RMB per injection for infliximab — made lifelong treatment unaffordable for many. Since the late 2010s, several IBD-related drugs have been included in China's National Reimbursement Drug List (NRDL). For example, adalimumab (Humira) was included in the reimbursement list in 2019 after price negotiations, leading to a substantial price reduction. According to a single-center study, the annual out-of-pocket cost for biologics dropped from an average of 20,000 RMB to about 8,800 RMB per year, a reduction of more than 50% after insurance coverage (*50*). This has greatly improved access and adherence to biologic therapy. Currently, infliximab, adalimumab, ustekinumab, vedolizumab, and tofacitinib are all available in China and are gradually being included in reimbursement

programs. However, reimbursement proportion and policies vary by region: most areas cover about 70% of costs, with patients still paying around 30% out of pocket, while less developed regions provide less coverage (often < 60%).

Twenty-five of 31 provinces now classify IBD as a "special disease, outpatient care" , activating a mechanism for reimbursement of outpatient care for special diseases that allows patients to claim outpatient drug costs at the same reimbursement rate as inpatient care, thereby avoiding unnecessary hospital admission. In provinces where this mechanism is absent, patients must still be hospitalized to be reimbursed for high-cost drugs, and out-of-pocket spending remains substantial. To fill the gap in formal insurance, China has recently introduced patient assistance programs led by charitable organizations. For example, the China Charity Federation has collaborated with pharmaceutical companies to offer programs where patients purchasing a certain course of medication can receive additional doses free of charge, further reducing overall costs. The Chinese Red Cross Foundation has also established a dedicated fund for IBD care to assist financially disadvantaged patients. Overall, health insurance coverage for IBD in China is improving rapidly, but there remains a clear gap compared to Japan. Out-of-pocket payments remain relatively high and regional disparities persist, with some families facing poverty due to illness. Potential solutions include expanding outpatient reimbursement for IBD in more provinces, increasing the reimbursement rate for biologics, and developing supplementary commercial insurance. Additionally, increasing public awareness and advocating for the inclusion of IBD in major chronic disease management would be beneficial.

### 4.3. Social support and disability protection

IBD often affects patients' quality of life and ability to work, making appropriate social security measures essential. In Japan, the disability certificate system provides benefits for patients with severe IBD, including employment leave subsidies and nursing care services. UC is recognized as a condition eligible for special medical subsidies, and patients' employment rights are protected by law, requiring employers to provide reasonable accommodations. China has lagged behind in this regard, with IBD not currently recognized as a disability and most patients not entitled to disability benefits. However, as the disease burden increases, there is growing advocacy for improved employment protection and livelihood support for IBD patients (*48*). This includes policies such as medical leave, tax reductions, and exemptions. Patient education and public awareness are also critical: due to the private nature of symptoms such as diarrhea and abdominal pain, many patients face misunderstanding or even discrimination. In recent years, China has organized annual "World IBD Day" activities to raise public awareness, and campaigns such as "IBD without Borders — Breaking Taboos" are fostering a more inclusive social environment. In summary, health insurance and social security are essential components of comprehensive IBD management. The Japanese experience demonstrates that robust policy support can significantly improve patient outcomes and quality of life (*49*). China is moving in this direction, but further progress is needed in insurance reimbursement, charitable assistance, and legal protection to establish a comprehensive IBD support network that integrates healthcare and social services.

### 4.4. Psychosocial support and societal engagement strategies

IBD significantly impairs patients' psychological well-being and social functioning (*51-53*). Enhancing public awareness and mitigating disease stigma constitute critical challenges in both nations. Establishing regular exchanges between Chinese and Japanese IBD patient organizations is essential to facilitating the sharing of educational resources and rehabilitation experiences. Organizing joint annual online patient forums, featuring bilingual presentations by experts, could increase patient confidence and improve disease literacy. In terms of psychological support, Japan possesses expertise in training professional IBD counselors (*54*); collaborative Sino-Japanese efforts should focus on developing, implementing, and evaluating culturally adapted psychological assessment and intervention guidelines. Social media constitutes a critical platform; implementing joint public campaigns — such as photo exhibitions, essay contests, and charity runs — can effectively raise awareness, advocate for policy support, and foster inclusive societal attitudes toward IBD patients (*48,55,56*). As part of policy advocacy, Chinese and Japanese researchers and patient groups should jointly petition international health-related organizations to incorporate IBD in global chronic disease prevention frameworks. They must concurrently push for enhanced legislative protections within domestic jurisdictions.

## 5. Conclusion and Outlook

China and Japan face distinct IBD challenges shaped by divergent epidemiological stages: China is contending with a rapidly rising incidence, while Japan is managing growing prevalence within an aging population. Clinically, China is bridging gaps in access to biologics and adoption of precision medicine, while Japan is capitalizing on innovations like AI to enhance the quality of care. Policymaking reveals core contrasts: Japan substantially subsidizes patient costs, while China prioritizes drug price negotiations and multi-tiered

insurance frameworks. Critical collaborative priorities must address: *i*) Cost sustainability (Japan: optimizing efficiency, China: expanding reimbursement); and *ii*) Joint research (shared data, examination of pathogenesis, and optimization of therapy). Harnessing complementary strengths — China's scale and Japan's advanced systems — offers a unique pathway to developing an effective "Asian paradigm" for chronic disease management in response to this shared burden.

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***Brief Report***

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# The effects of mindfulness-based cognitive behavioral group program for patients with intractable disease and high depression

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**SUMMARY**: This study examined the efficacy of a Mindfulness-Based Cognitive Behavioral Group Program (MCBGP) designed to improve the mental health of patients with intractable diseases. Adults ($n$ = 35) with such diseases participated in the study. They were categorized into a high- or low-depression group based on the Profile of Mood States (POMS) depression subscale score of 60 as the cutoff score. MCBGP was conducted monthly over three sessions, each session lasting 120 minutes. Each session consisted of psychoeducation, self-disclosure, and mindfulness meditation. The program outcomes were evaluated using the Stanford University Chronic Disease Self-Management Questionnaire, the POMS, and the World Health Organization Quality of Life instruments. The results showed that in the high-depression group ($n$ = 11), health distress ($p$ = 0.013), activity limitations ($p$ = 0.022), depression ($p <$ 0.001), anxiety/tension ($p$ = 0.002), anger/irritability ($p$ = 0.004), fatigue ($p$ = 0.023), and confusion ($p$ = 0.033) were significantly reduced. The total quality of life scores were significantly improved ($p$ = 0.028) after the program, whereas no significant improvements were observed in the low-depression group ($n$ = 24). It was concluded that the MCBGP was effective in improving mental health outcomes and enhanced the quality of life in patients with intractable diseases and comorbid depression.

***Keywords***: intractable disease, mindfulness meditation, depression, QOL, cognitive behavioral group therapy

## 1. Introduction

Unclear pathophysiological mechanisms and a lack of established treatments are characteristics of intractable diseases. Patients with such diseases typically require lifelong medical care. Intractable diseases, which are chronic illnesses, cause persistent physical pain, emotional distress, and burdens, including reduced income and increased medical expenses (*1,2*). These conditions also disrupt family relationships and roles (*3*), reduce social functioning, and diminish overall well-being (*4*). People with chronic physical illnesses also have a high prevalence of comorbid depression, which aggravates their mental health decline (*5*). Optimal healthcare maintenance becomes increasingly complex because of these numerous stressors. Stress responses also negatively affect patients' quality of life (QOL) (*6*). Therefore, effective stress management interventions are crucial for improving the mental health of patients with intractable diseases.

Psychosocial interventions for improving the mental health of this population have focused on specific diseases. Luo *et al*. (*7*) performed a meta-analysis of 14 studies involving 507 patients with Parkinson's disease and reported that Cognitive Behavioral Therapy (CBT) was effective in improving symptoms of depression, anxiety, and sleep disturbances but not fatigue or QOL. The CBT provided in these research included relaxation training, thought restructuring, sleep hygiene, and worry control, and others. Sessions lasted 60–120 minutes once a week for 6–12 weeks. The CBT was delivered by group or by telephone.

Similarly, Shi *et al*. (*8*) conducted a systematic review of CBT interventions for individuals living with HIV and reported that CBT led to short-term improvements in depression and long-term reductions in viral load. The CBT included psychoeducation about HIV and depression, motivational interview, behavioral activation, cognitive restructuring, problem-solving, and relaxation. The CBT was delivered individually, once a week for 45–60 minutes, for 9 to 14 weeks, and were conducted by clinical psychologists with a master's or doctoral degree.

On the contrary, a review of psychosocial interventions' impact on adults with muscular dystrophy by Walklet *et al*. (*9*) reported that only 7 of the 10 studies meeting the inclusion criteria demonstrated short-term effects of the interventions. Moreover, the evidence

supporting improvements in QOL and well-being was limited. The psychosocial interventions carried out here included expressive disclosure, CBT to fatigue, Hypnosis, and others. These interventions were delivered by psychologists, social workers, or occupational therapists.

The current study implemented a cognitive behavioral group therapy program incorporating mindfulness meditation named the Mindfulness-Based Cognitive Behavioral Group Program (MCBGP). The MCBGP was designed to reduce psychological stress and improve QOL in individuals with various intractable diseases. This study evaluated the MCBGP to determine its efficacy in enhancing mental health outcomes and the overall well-being of this population.

## 2. Patients and Methods

### 2.1. Participants

Patients diagnosed with 27 intractable diseases ($n$ = 35, mean age = 48 years, SD = 17.1; mean illness duration = 13.9 years, range = 1–45 years) voluntarily participated in the stress reduction program organized by the Okinawa Intractable Diseases Support Center (OIDSC) between 2017 and 2023. Eligibility criteria for this study required participants to have a medically diagnosed intractable disease and the ability to attend all the program sessions. Table 1 summarizes the patient characteristics. Their diagnoses included Behcet's disease, Castleman Disease, Collagen disease, Congenital adrenal enzyme deficiency, Crohn's disease, Dermatomyositis, Eosinophilic chronic rhinosinusitis, Eosinophilic polyangiitis granulomatosis, Generalized dystonia, Hypoparathyroidism, Ichthyosis, Idiopathic osteonecrosis of the femoral head, Juvenile Idiopathic Arthritis, Mixed connective tissue disease, Multiple sclerosis, Multiple system atrophy, Neurofibromatosis type 1, Neuromyelitis optica, Parkinson's disease, Primary biliary cholangitis, Retinitis Pigmentosa, Scleroderma, Sjogren syndrome, Systemic lupus erythematosus, Takayasu arteritis, and Ulcerative colitis. Participation in the program was free of charge.

**Table 1. Demographics and characteristics of participants**

| Characteristics | Data |
|---|---|
| Participants ($n$ = 35, adults) | |
| Sex | |
| Men | 7 (20.0%) |
| Women | 28 (80.0%) |
| Age (years) | Mean = 48.0 (SD = 17.1) Range = 20–82 |
| Duration of illness (years) | Mean = 13.9 (SD = 13.1) Range = 1–45 |
| Disease | $n$ (%) |
| Behcet's disease | 1 (2.9%) |
| Castleman Disease | 1 (2.9%) |
| Collagen disease | 1 (2.9%) |
| Congenital adrenal enzyme deficiency | 1 (2.9%) |
| Crohn's disease | 1 (2.9%) |
| Dermatomyositis | 1 (2.9%) |
| Eosinophilic chronic rhinosinusitis | 1 (2.9%) |
| Eosinophilic polyangiitis granulomatosis | 1 (2.9%) |
| Generalized dystonia | 1 (2.9%) |
| Hypoparathyroidism | 1 (2.9%) |
| Ichthyosis | 1 (2.9%) |
| Idiopathic osteonecrosis of the femoral head | 1 (2.9%) |
| Juvenile Idiopathic Arthritis | 1 (2.9%) |
| Mixed connective tissue disease | 1 (2.9%) |
| Multiple sclerosis | 3 (8.6%) |
| Multiple system atrophy | 2 (5.7%) |
| Neurofibromatosis type 1 | 1 (2.9%) |
| Neuromyelitis optica | 1 (2.9%) |
| Parkinson's disease | 3 (8.6%) |
| Primary biliary cholangitis | 2 (5.7%) |
| Retinitis Pigmentosa | 3 (8.6%) |
| Scleroderma | 1 (2.9%) |
| Sjogren syndrome | 2 (5.7%) |
| Systemic lupus erythematosus | 1 (2.9%) |
| Takayasu arteritis | 1 (2.9%) |
| Ulcerative colitis | 1 (2.9%) |

### 2.2. The MCBGP

The program was conducted monthly for three sessions (3 months), each lasting 120 minutes. It was supervised by a clinical psychologist (CP) with a doctoral degree who had completed a 7-day professional training in Mindfulness-Based Stress Reduction in 1999 and had maintained a regular mindfulness meditation practice for 27 years. Figure 1 illustrates the program's structure and content. The fundamental elements of each session consisted of psychoeducation, self-disclosure, and stress reduction strategies.

The psychoeducation module of the intervention taught participants about stress mechanisms and coping methods, the association between cognition, emotions, and behavior, automatic thought identification, problem-solving therapy, interpersonal relationships, the effects of the illness on interpersonal relationships, and communication with healthcare providers. During psychoeducation, participants were informed that mindfulness would not eliminate all suffering related to their illness but could serve as a tool for managing stress, which is one of the many challenges encountered in daily life.

The self-disclosure component requested the participants to share their experiences related to the illness, sources of stress, coping strategies, emotional reactions, current problems, and changes in interpersonal relationships after the illness diagnosis. The participants were free to choose whether they wanted to participate in self-disclosure activities and retained the right to avoid discussing any information they felt uncomfortable sharing. Each session included two 10-minute mindfulness meditation practices as a stress reduction strategy.

The homework component assigned participants daily

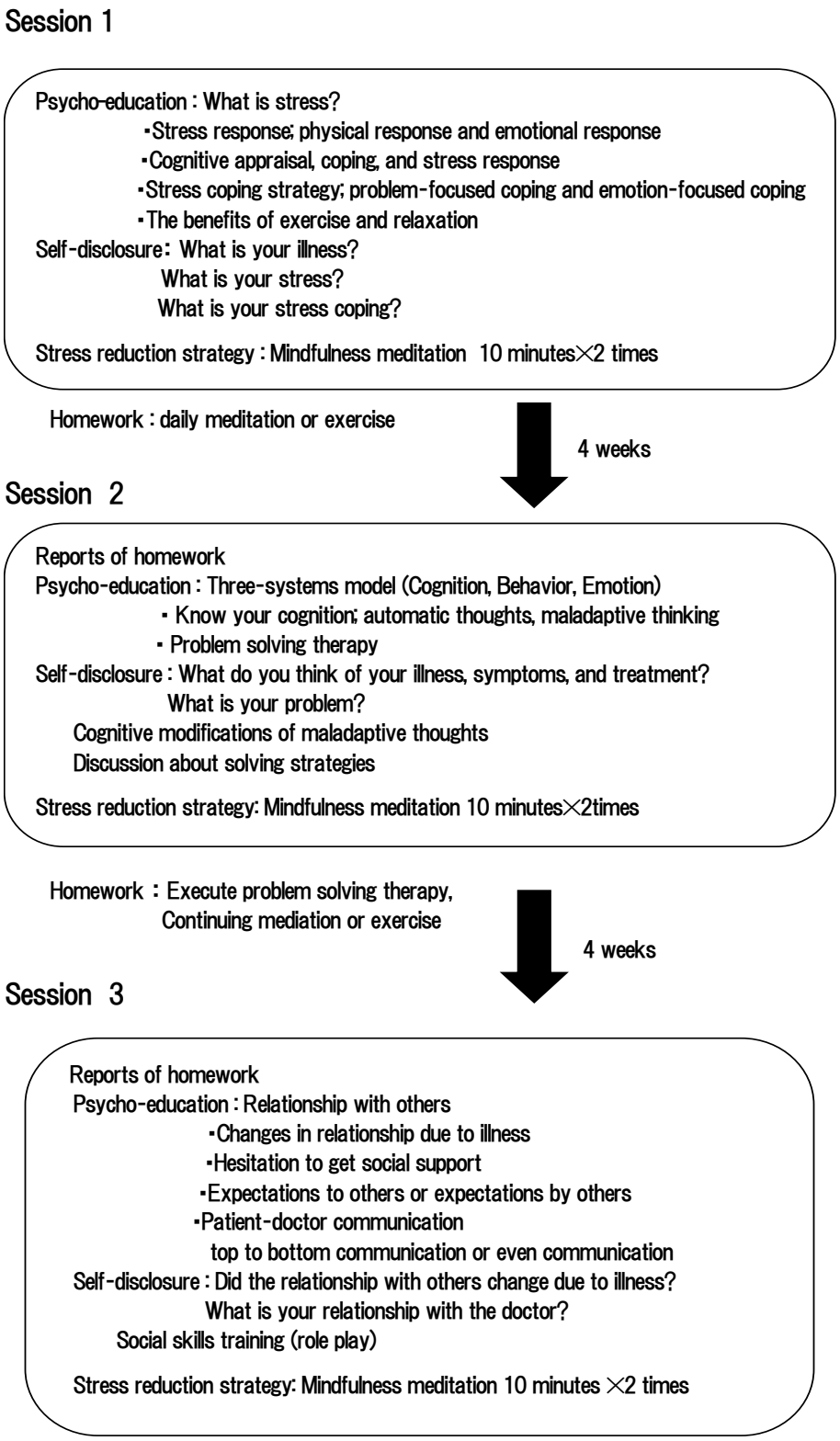


**Figure 1. Contents of the Mindfulness-Based Cognitive Behavioral Group Program (MCBGP).**

homework between sessions, which included practicing and recording stress management activities, such as mindfulness meditation, or physical exercise, such as walking. The CP made phone calls between sessions to follow up on the participant's adherence to homework. If the participants were not completing their assigned tasks, the CP helped identify barriers and explored solutions to improve compliance.

To ensure fidelity of the intervention and prevent therapist bias, three staff of OIDSC attended each group as observers and, with participants' permission, recorded each session verbatim and on videotape.

2.3. Instruments for evaluating the program's efficacy

2.3.1. Symptoms evaluation

The Stanford University Chronic Disease Self-Management Questionnaire assesses five symptom-related domains (*10*). These domains include Health Distress (0–5), Fatigue (0–10), Pain (0–10), Shortness of Breath (0–10), Limitations in Social/Role Activities (0–4), and Self-Efficacy for Managing Chronic Disease (0–10). Higher scores for all items except for self-efficacy indicate more disease symptoms.

2.3.2. Stress response evaluation

The Profile of Mood States (POMS) Brief Form Japanese Version (*11*) was used to evaluate Stress responses. This scale is a 30-item shortened version of the full 65-item version of the POMS (*12*). Like the full version, it assessed five items: Tension-Anxiety, Depression, Anger-Hostility, Vigor, Fatigue, and Confusion. It also assesses Total Mood Disturbance (TMD), which is the sum of tension-anxiety, depression, anger, fatigue, and confusion then subtracts vigor. In this scale, high scores indicate a more negative mood for all items except for vigor. All subscale scores were converted into T scores (20–85).

2.3.3. QOL evaluation:

The WHO-QOL 26 (*13*) assesses the overall QOL (1–5), as well as satisfaction in Physical (1–5), Psychological (1–5), Social relationship (1–5), and Environmental (1–5) subdomains of QOL. Higher scores in all areas indicate high QOL.

2.4. Procedure

The three scales were administered as a pre-test one week before starting the program and a post-test one week after the program concluded. Participants received written feedback summarizing their test results. The purpose and use of the data for research were explained to the participants in advance, and written informed consent was obtained. The Research Ethics Committee of Okinawa International University approved this study (Approval No.:66). It was conducted following the principles outlined in the Declaration of Helsinki.

2.5. Data analysis

At the pre-test, the participants were divided into high- and low-depression groups based on the Profile of Mood States depression subscale score of 60 as the cutoff score. The high- and low-depression groups' pre- and post-test means (*t*-tests) were compared using R (*14*). Effect sizes were calculated using Cohen's method (*15*).

## 3. Results and Discussion

**Table 2. Demographics and characteristics of high depression participants**

| Characteristics | Data |
|---|---|
| High depression participants ($n$ = 11, adults) | |
| Sex | |
| Men | 3 (27.3%) |
| Women | 8 (71.7%) |
| Age (years) | Mean = 42.4 |
| | (SD = 20.7) |
| | Range = 20–76 |
| Duration of illness (years) | Mean = 11.0 |
| | (SD = 10.3) |
| | Range = 1–32 |
| Disease | *n* |
| Multiple sclerosis | 1 |
| Parkinson's disease | 1 |
| Behcet's disease | 1 |
| Idiopathic osteonecrosis of the femoral head | 1 |
| Eosinophilic polyangiitis granulomatosis | 1 |
| Primary biliary cholangitis | 1 |
| Juvenile Idiopathic Arthritis | 1 |
| Ichthyosis | 1 |
| Eosinophilic chronic rhinosinusitis | 1 |
| Dermatomyositis | 1 |
| Hypoparathyroidism | 1 |

The high-depression group ($n$ = 11, mean age = 42.4 years, SD = 20.7; mean illness duration = 11.0 years, SD = 10.3) and the low-depression group ($n$ = 24, mean age = 50.6 years, SD = 15.0; mean illness duration =15.3 years, SD = 14.3) consisted of patients with Multiple sclerosis, Parkinson's disease, Behcet's disease, Idiopathic osteonecrosis of the femoral head, Eosinophilic polyangiitis granulomatosis, Primary biliary cholangitis, Juvenile Idiopathic Arthritis, Ichthyosis, Eosinophilic chronic rhinosinusitis, Dermatomyositis, and Hypoparathyroidism (Table 2). There were neither statistically significant differences between the two groups in their age distribution ($T$ = 3.33, $df$ = 14.97, $p$ = 0.255) nor illness duration ($T$ = 0.988, $df$ = 26.54, $p$ = 0.331). Moreover, there were no significant group differences in the types of illness in each group.

Table 3 shows that the post-intervention results of the high-depression group indicated a significant reduction in health distress ($T$ = 3.00, $df$ = 10, $p$ = 0.013, $d$ = 0.75) and a significant improvement in activity limitations ($T$ = 2.70, $df$ = 10, $p$ = 0.022, $d$ = 0.43). Moreover, significant reductions were observed in tension-anxiety ($T$ = 4.26, $df$ = 10, $p$ = 0.002, $d$ = 1.04), depression ($T$ = 7.31, $df$ = 10, $p$ < 0.001, $d$ = 2.30), anger-hostility ($T$ = 3.70, $df$ = 10, $p$ = 0.004, $d$ = 0.96), fatigue ($T$ = 2.68, $df$ = 10, $p$ = 0.023, $d$ = 0.73), and confusion ($T$ = 2.48, $df$ = 10, $p$ = 0.033, $d$ = 0.66), indicating a reduced stress responses. Furthermore, the TMD scores decreased significantly at post-test ($T$ = 6.87, $df$ = 10, $p$ < 0.001, $d$ = 1.59). Furthermore, significant QOL improvements were observed in the physical ($T$ = 2.47, $df$ = 10, $p$ = 0.033, $d$ = 0.59) and psychological ($T$ = 2.68, $df$ = 10, $p$ = 0.023, $d$ = 0.58) domains. The overall QOL score also showed a statistically significant increase ($T$ = 2.56, $df$ = 10, $p$ =

**Table 3. The effects of MCBGP in the high depression participants (*n* = 11)**

| Items | Pre | | Post | | *t* | *df* | *p*-value | *d* |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | | | |
| Health Distress | 3.1 | 0.89 | 2.4 | 0.98 | 3.00 | 10 | 0.013 | 0.75 |
| Fatigue | 6.5 | 2.34 | 6.0 | 2.45 | 1.05 | 10 | 0.320 | 0.21 |
| Shortness of Breath | 2.5 | 1.92 | 2.1 | 2.21 | 0.66 | 10 | 0.526 | 0.19 |
| Pain | 3.2 | 3.16 | 2.5 | 2.62 | 1.30 | 10 | 0.224 | 0.24 |
| Activities Limitations | 2.0 | 1.50 | 1.4 | 1.29 | 2.70 | 10 | 0.022 | 0.43 |
| Self-Efficacy | 5.7 | 1.74 | 6.2 | 2.00 | 1.07 | 10 | 0.308 | 0.27 |
| POMS | | | | | | | | |
| Tension-Anxiety | 66.4 | 8.72 | 57.5 | 8.45 | 4.26 | 10 | 0.002 | 1.04 |
| Depression | 71.6 | 5.63 | 56.5 | 7.37 | 7.31 | 10 | 0.000 | 2.30 |
| Anger-Hostility | 61.6 | 13.63 | 49.7 | 10.92 | 3.70 | 10 | 0.004 | 0.96 |
| Vigor | 45.3 | 8.58 | 48.6 | 8.43 | 1.28 | 10 | 0.231 | 0.39 |
| Fatigue | 61.1 | 8.80 | 53.7 | 11.33 | 2.68 | 10 | 0.023 | 0.73 |
| Confusion | 69.0 | 9.77 | 61.9 | 11.60 | 2.48 | 10 | 0.033 | 0.66 |
| TMD | 284.5 | 28.71 | 230.7 | 38.33 | 6.87 | 10 | 0.000 | 1.59 |
| QOL-26 | | | | | | | | |
| QOL | 2.9 | 0.32 | 3.1 | 0.27 | 2.56 | 10 | 0.028 | 0.69 |
| Physical | 2.9 | 0.56 | 3.2 | 0.45 | 2.47 | 10 | 0.033 | 0.59 |
| Psychological | 2.6 | 0.57 | 2.9 | 0.47 | 2.68 | 10 | 0.023 | 0.58 |
| Social | 2.8 | 0.86 | 2.9 | 0.57 | 0.50 | 10 | 0.629 | 0.14 |
| Environment | 3.1 | 0.30 | 3.3 | 0.42 | 1.51 | 10 | 0.163 | 0.55 |

Bold font shows significance in statistical tests ($p < 0.05$). MCBGP, Mindfulness-Based Cognitive Behavioral Group Program (MCBGP).

0.028, $d = 0.69$).

The significant improvement in depressive symptoms among high-depression participants may be attributed to the effects of mindfulness meditation. Mindfulness meditation has demonstrated efficacy as a component of mindfulness-based cognitive therapy for depression (*16,17*). The effective mechanism of mindfulness meditation involves interrupting negative thought cycles by promoting cognitive decentering, thereby preventing the worsening of depression (*18*). The observed reduction in health distress among participants further suggests that mindfulness meditation may have helped patients disengage from persistent illness-related rumination, contributing to improving depressive symptoms.

Crucially, the current study introduced mindfulness meditation within the framework of stress management. It is possible that presenting mindfulness in such a context enhanced participants' motivation and engagement. This framing is consistent with previous findings that mindfulness-based cognitive therapy effectively reduces various stress responses, including anxiety, tension, anger, fatigue, and confusion (*16,17*).

The group-based delivery of the program may have further contributed to psychological improvements and enhanced QOL (*19*). Yalom emphasized the therapeutic role of group settings' universality, in which individuals benefit from recognizing shared struggles among peers (*20*). The participants in this program listened to self-disclosures of others who did not necessarily have the same illness but were affected by similar, rare diseases. Sharing their experience may have helped reduce feelings of isolation and promoted a sense of relief and solidarity (*20*), which may have reduced feelings of anxiety, anger, and confusion and supported improvements in their overall well-being.

Table 4 shows the pre and post-intervention results of the low depression groups. The results of pre-intervention in the POMS showed that, compared to the average values of the normative population (*11*), there were no significant differences in tension-anxiety ($T = 1.85$, $df = 5659$, $p = 0.063$), fatigue ($T = 0.309$ , $df = 5659$ , $p = 0.757$), and confusion ($T = 0.773$, $df = 5659$, $p = 0.439$). Depression ($T = 4.332$, $df = 5659$, $p < 0.0001$), anger-hostility ($T = 7.734$, $df = 5659$, $p < 0.0001$), and vigor ($T = 6.952$, $df = 5659$, $p < 0.0001$) were significantly lower. In terms of QOL, there were no significant differences in overall QOL ($T = 0.761$ , $df = 1421$, $p = 0.473$), psychological ($T = 1.183$, $df = 273$, $p = 0.238$), social ($T = 0.542$, $df = 273$, $p = 0.592$), and environment ($T = 0.614$, $df = 273$, $p = 0.539$), but physical ($T = 3.165$ , $df = 273$, $p = 0.002$) was significantly lower than the value of normative population (*13*).

At post intervention, activity limitations shows an improving trend ($T = 2.06$, $df = 23$, $p = 0.051$, $d = 0.25$). The mean of depression was increased, but this change is not statistically significant ($T = 1.93$, $df = 23$, $p = 0.662$). There were no statistically significant changes in any other symptom domain, stress responses, or QOL measures, in the low depression group.

Low depression patients did not demonstrate significant psychological or QOL improvements. However, these patients exhibited low stress responses at pre-intervention, and their baseline QOL except physical, was similar to normative average in Japan (Mean = 3.29) (*13*). Therefore, the lack of change in this subgroup may be due to the floor effect rather than the inefficacy of the program. The lack of improvement in physical domain is likely due to that the MCBGP did not result in

**Table 4. The effects of MCBGP in the low depression participants (*n* = 24)**

| Items | *n* | Pre | | Post | | *t* | *df* | *p*-value | *d* |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | | | | |
| Health Distress | 24 | 2.2 | 1.19 | 2.0 | 1.29 | 1.17 | 23 | 0.253 | 0.16 |
| Fatigue | 24 | 4.8 | 2.66 | 4.6 | 2.87 | 0.36 | 23 | 0.724 | 0.07 |
| Shortness of Breath | 24 | 3.1 | 3.05 | 2.8 | 2.73 | 0.50 | 23 | 0.625 | 0.10 |
| Pain | 24 | 3.5 | 2.86 | 3.3 | 3.20 | 0.58 | 23 | 0.567 | 0.07 |
| Activities Limitations | 24 | 1.7 | 1.32 | 1.4 | 1.13 | 2.06 | 23 | 0.051 | 0.25 |
| Self-Efficacy | 24 | 5.4 | 2.45 | 5.6 | 2.06 | 0.34 | 23 | 0.736 | 0.09 |
| POMS | | | | | | | | | |
| Tension-Anxiety | 24 | 48.8 | 10.86 | 49.4 | 11.85 | 0.32 | 23 | 0.753 | 0.05 |
| Depression | 24 | 47.2 | 5.64 | 50.1 | 9.31 | 1.93 | 23 | 0.662 | 0.38 |
| Anger-Hostility | 24 | 45.0 | 6.54 | 45.8 | 10.33 | 0.48 | 23 | 0.638 | 0.09 |
| Vigor | 24 | 45.5 | 12.65 | 45.7 | 9.98 | 0.05 | 23 | 0.961 | 0.02 |
| Fatigue | 24 | 50.2 | 8.89 | 49.5 | 10.20 | 0.38 | 23 | 0.706 | 0.07 |
| Confusion | 24 | 50.5 | 9.11 | 52.4 | 11.84 | 0.93 | 23 | 0.365 | 0.18 |
| TMD | 24 | 196.2 | 31.97 | 201.5 | 47.17 | 0.68 | 23 | 0.503 | 0.13 |
| QOL-26 | | | | | | | | | |
| QOL | 24 | 3.2 | 0.46 | 3.2 | 0.48 | 0.07 | 23 | 0.946 | 0.00 |
| Physical | 24 | 3.1 | 0.62 | 3.1 | 0.64 | 0.23 | 23 | 0.816 | 0.00 |
| Psychological | 24 | 3.2 | 0.69 | 3.3 | 0.67 | 0.07 | 23 | 0.948 | 0.15 |
| Social | 24 | 3.4 | 0.64 | 3.4 | 0.60 | 0.10 | 23 | 0.924 | 0.00 |
| Environment | 24 | 3.3 | 0.48 | 3.3 | 0.44 | 0.50 | 23 | 0.623 | 0.00 |

MCBGP, Mindfulness-Based Cognitive Behavioral Group Program (MCBGP).

further improvement in physical symptoms. Similarly, the lack of improvement in vigor, which was lower than normative average, may be due to the fact that the program did not include any energy-boosting content, such as behavioral activation (*8*).

Future studies are expected to address several limitations of this study that constrain the generalizability of its findings. Most notably, the study had no control group, limiting the ability to attribute observed changes to the intervention. However, designing a control group of patients with a comparable mixture of rare, intractable conditions is difficult. Nevertheless, future research could overcome this issue by employing a waiting-list control design (21), allowing researchers to compare data collected before and after a non-intervention period.

This program treated 27 different intractable diseases as one group. This was both a strength and a limitation of the program. One limitation was that the number of patients with each disease was small, and it was not possible to improve symptoms specific to each disease, such as pain and fatigue. A strength was that the program was able to provide to patients with such a wide variety of intractable diseases, which helped participants to learn that there are so many rare intractable diseases. It would be difficult for a hospital to bring together patients with such a wide variety of intractable diseases, and this was made possible by the existence of OIDSC.

Another limitation is the uncertainty regarding the program's long-term effects. Follow-up data are currently being collected, and time and a sufficient sample size are needed to assess the stability and durability of the intervention's long-term outcomes.

According to the transtheoretical behavioral change model, psychotherapy patients move through five stages: pre-contemplation, contemplation, preparation, action, and maintenance (*22*). The intervention used in this study matches the action stage because the participants took direct action to change their behavior. Moreover, people who have chronic and incurable illnesses need to maintain mindfulness practice for an extended period to build psychological resilience. However, people struggle to maintain regular mindfulness practice because they need ongoing support and encouragement (*23*). Therefore, helping patients with intractable diseases integrate mindfulness into their daily lives may require establishing an accessible support system.

## 4. Conclusion

Despite these limitations, the findings of this study indicate that a cognitive behavioral group program incorporating mindfulness meditation may offer meaningful mental health and QOL for patients with intractable diseases. With access to appropriate and sustainable coping strategies, patients may be better equipped to maintain long-term psychological well-being and life satisfaction.

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***Brief Report***

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# Three-year real-world outcomes of lanadelumab prophylaxis in hereditary angioedema: Complete disease suppression and psychosocial benefits in two East Asian patients

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**SUMMARY**: Hereditary angioedema (HAE) is a rare, potentially life-threatening disorder characterized by recurrent, disabling episodes of subcutaneous or submucosal swelling. Lanadelumab, a monoclonal antibody targeting plasma kallikrein, is approved for long-term prophylaxis and has shown high efficacy in clinical trials. However, real-world data on its prolonged use, particularly from East Asia, remain scarce. This report evaluates 3-year clinical and patient-reported outcomes of lanadelumab prophylaxis in two Japanese patients with HAE type I. Both male patients (in their 30s and 70s) received subcutaneous lanadelumab, 300 mg, every 2 weeks, later extended to every 4 weeks following disease stabilization. Clinical efficacy was assessed by attack frequency. Patient-reported outcomes (PROs) included the Angioedema Control Test (AECT), Angioedema Quality of Life Questionnaire (AE-QoL), Hospital Anxiety and Depression Scale (HADS), and Treatment Satisfaction Questionnaire for Medication (TSQM-9). Safety and tolerability were also monitored. Both patients achieved complete or near-complete elimination of HAE attacks during the 156-week follow-up. AECT scores reached the maximum of 16 by week 12 and remained stable. AE-QoL scores improved by approximately 30 points, reflecting sustained quality-of-life benefits. HADS-Anxiety scores declined into the normal range, indicating reduced anticipatory anxiety. TSQM-9 global satisfaction remained above 90 out of 100, and no serious adverse events occurred; one patient experienced mild transient injection-site swelling. This case series presents the longest real-world follow-up of lanadelumab in East Asia. Findings confirm its sustained efficacy, safety, and psychosocial benefits, including enhanced quality of life and emotional recovery. These findings suggest that lanadelumab may play an important role in the long-term management of HAE in Asian clinical settings.

***Keywords***: hereditary angioedema, lanadelumab, patient-reported outcomes, quality of life, anxiety, kallikrein inhibitor, East Asian population

## 1. Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent episodes of subcutaneous or submucosal swelling, most commonly caused by C1-inhibitor (C1-INH) deficiency (HAE type I) or dysfunction (type II), resulting in excessive bradykinin generation (*1*). Attacks typically affect the face, extremities, gastrointestinal tract, or airway, with laryngeal edema being potentially life-threatening. In addition to the physical burden, HAE imposes a substantial psychosocial impact—patients often live in chronic fear of unpredictable attacks, leading to anxiety, impaired quality of life, and reduced social functioning (*2,3*).

Lanadelumab, a fully human monoclonal antibody that inhibits plasma kallikrein, was approved in 2018 for the long-term prophylaxis of HAE. The pivotal HELP study demonstrated that lanadelumab reduced attack rates by approximately 87% compared to placebo, with sustained benefits confirmed in open-label extension studies (*4,5*). The standard dosing regimen is 300 mg subcutaneously every 2 weeks, with extension to every 4 weeks possible in patients with stable disease control (*6*).

Although the efficacy of lanadelumab has been well documented in Western populations (*7-12*), clinical trials and real-world data from East Asia remain limited (*13,14*). In Japan, lanadelumab became commercially available only in 2022, and most existing reports describe follow-up durations of one year or less (*15,16*). As prophylactic options expand globally, optimal strategies — including treatment duration, monitoring approaches, and tapering decisions — remain insufficiently defined.

Beyond preventing attacks, long-term prophylaxis plays a crucial role in alleviating the psychological burden of HAE, including anticipatory anxiety and fear

of asphyxiation. In this regard, patient-reported outcomes (PROs) such as the Angioedema Control Test (AECT) (*17*), Angioedema Quality of Life Questionnaire (AE-QoL) (*18*), treatment satisfaction measures (*19,20*), and the Hospital Anxiety and Depression Scale (HADS) (*21,22*) offer valuable insights into the broader benefits of sustained therapy (*23*).

Here, we present two Japanese patients with HAE who received continuous lanadelumab prophylaxis for 156 weeks (~3 years) — to our knowledge, the longest real-world follow-up reported in East Asia. Along with clinical outcomes, we evaluated multiple PROs to assess long-term disease control, quality of life, and emotional well-being. This case series aims to inform clinical practice by illustrating how prolonged lanadelumab therapy can achieve not only physical remission but also meaningful psychosocial recovery in the management of HAE.

## 2. Patients and Methods

### 2.1. Patients and setting

This observational case series included two adult male patients with HAE type I, diagnosed based on low antigenic and functional levels of C1-INH. Both patients were managed in our dermatology department and had longstanding histories of frequent angioedema attacks prior to initiating prophylactic therapy. Patient 1, a man in his 30s, was diagnosed with HAE at age 20. Initially, he experienced infrequent attacks (approximately one facial or abdominal episode per year), but in the five years preceding prophylaxis, his attack frequency increased to monthly peripheral swellings and abdominal attacks requiring on-demand treatment, significantly impairing his daily life. Patient 2, in his 70s, had experienced HAE symptoms since adolescence and was diagnosed at age 30. He suffered multiple severe episodes, including facial and tongue edema, and was hospitalized at least six times for trauma-induced angioedema (*e.g.*, following dental procedures or spinal anesthesia). In the year before starting prophylaxis, he experienced approximately two attacks per month and lived with persistent fear of laryngeal involvement.

### 2.2. Lanadelumab prophylaxis

Both patients began lanadelumab prophylaxis between 2019 and 2020 through a compassionate use program prior to local commercial availability. The initial regimen consisted of lanadelumab 300 mg administered subcutaneously every two weeks. Patients received injection training, with initial doses administered under medical supervision. After achieving sustained attack-free status for 6–12 months, dosing was extended to every four weeks in both patients, in accordance with product labeling and through shared decision-making. Lanadelumab prophylaxis continued uninterrupted throughout the observation period (156 weeks for Patient 1; 152 weeks for Patient 2). On-demand C1-INH was used only in the event of breakthrough attacks.

### 2.3. Outcome assessments

Patients were followed regularly — every 4–8 weeks in the first year, and every 3–6 months thereafter. At each visit, the number and frequency of attacks since the previous visit were recorded based on patient interviews and medical records. The following validated PRO instruments were administered at baseline and periodically during treatment:

*i*) Angioedema Control Test (AECT): A 4-item tool assessing disease control over the prior 4 weeks (score range: 0–16; ≥ 12 indicates good control). AECT was evaluated at baseline, at 12 weeks, and annually thereafter.

*ii*) Angioedema Quality of Life Questionnaire (AE-QoL): A 17-item HAE-specific QoL measure covering four domains, with a total score range of 0 to 100 (higher scores indicate worse QoL). AE-QoL was administered at baseline and approximately at months 3, 6, 12, 24, and 36.

*iii*) Hospital Anxiety and Depression Scale (HADS): A 14-item questionnaire measuring anxiety (HADS-A) and depression (HADS-D), each scored from 0–21. Scores ≥ 11 suggest clinically significant distress. HADS was assessed at baseline and at multiple time points to track anxiety related to fear of attacks.

*iv*) Treatment Satisfaction Questionnaire for Medication (TSQM-9): A 9-item tool assessing effectiveness, convenience, and global satisfaction (scores range: 0–100). TSQM-9 was administered at follow-up visits starting from month 3 onward.

### 2.4. Ethics statement:

This case report was conducted at Saitama Medical Center, Japan, in accordance with the ethical principles of the Declaration of Helsinki (1975). Written informed consent was obtained from all patients for the publication of this report, including relevant clinical details and anonymized data. According to the institutional policy, case reports involving one or two patients that do not contain identifiable information are exempt from formal review by the institutional review board (IRB). Therefore, IRB approval was not required for this publication.

## 3. Results and Discussion

This case series provides the longest real-world follow-up to date of lanadelumab prophylaxis in East Asian patients with HAE, suggesting sustained clinical remission, improved psychosocial well-being, and favorable

safety over a 3-year period. Both patients demonstrated a rapid and lasting resolution of angioedema attacks following the initiation of lanadelumab. Patient 1 became completely attack-free after the first month of therapy, while Patient 2 experienced only one mild episode of localized swelling at the injection site — likely attributable to a transient injection-triggered response — which resolved spontaneously without recurrence. Neither patient required acute treatment or hospitalization throughout the 3-year follow-up, indicating robust long-term disease control (Figure 1A). We also conducted a PubMed-based search (terms: "lanadelumab" AND "hereditary angioedema" AND "real-world" AND "Asia"), which yielded no other reports with follow-up durations of ≥ 3 years in East Asian populations. While not exhaustive, this search supports the novelty of our observations.

Prior to treatment, Patient 1 reported an estimated 15–20 attacks annually, while Patient 2 experienced around 24 episodes. Under lanadelumab prophylaxis, Patient 1 remained entirely attack-free, and Patient 2 experienced only one mild episode in the first year, followed by complete remission — corresponding to a 100% and > 95% reduction in attack frequency, respectively. These outcomes exceed those reported in pivotal trials such as the HELP study and its extension, where lanadelumab reduced attack rates by ~87% and maintained remission for up to 33 months in some patients (*4,5*). Moreover, our findings are consistent with recent real-world data from Germany and China (*12,14*), which may further support lanadelumab's durable efficacy.

Regarding patient-reported outcomes, both individuals achieved maximum AECT scores (16/16) by Week 12, sustained through Week 156, indicating complete disease control (Figure 1B). AE-QoL scores improved markedly, with Patient 1's total score decreasing from 42 to 10 and Patient 2's from 62 to 30 (Figure 2). The largest improvements were observed in the "Fear/Shame" and "Fatigue/Mood" domains. This pattern may suggest that lanadelumab not only reduces physical symptoms but also alleviates psychosocial distress associated with unpredictability and perceived stigma. In East Asian contexts, such burdens may be differentially perceived, as suggested by prior studies (*14,16*). Notably, while our patients showed maximal improvement in "Fear/Shame", Japanese real-world data have reported "Functioning" as the most responsive domain (*16*), suggesting potential cultural variation.

Psychological recovery was further supported by reductions in HADS scores. At baseline, Patient 2 presented with moderate anxiety (HADS-A: 14), and Patient 1 with borderline abnormal anxiety (HADS-A: 8). By Week 156, both scores had fallen into the normal range (2 and 4, respectively), with no clinically significant depressive symptoms observed throughout the study period (Figure 3). These findings suggest that long-term prophylaxis with lanadelumab may contribute to improved emotional well-being, complementing the physical control of disease.

Treatment was well tolerated. No serious adverse events, hypersensitivity reactions, or abnormal laboratory findings were reported. The sole adverse event was a mild injection-site reaction in Patient 2. Notably, both patients successfully extended dosing intervals from biweekly to monthly regimens after 6–12 months of disease stability, without any resurgence of attacks. This approach aligns with product labeling and current clinical practice in Europe and China (*6,14*) and may enhance convenience and adherence, especially in older patients or those with limited healthcare access.

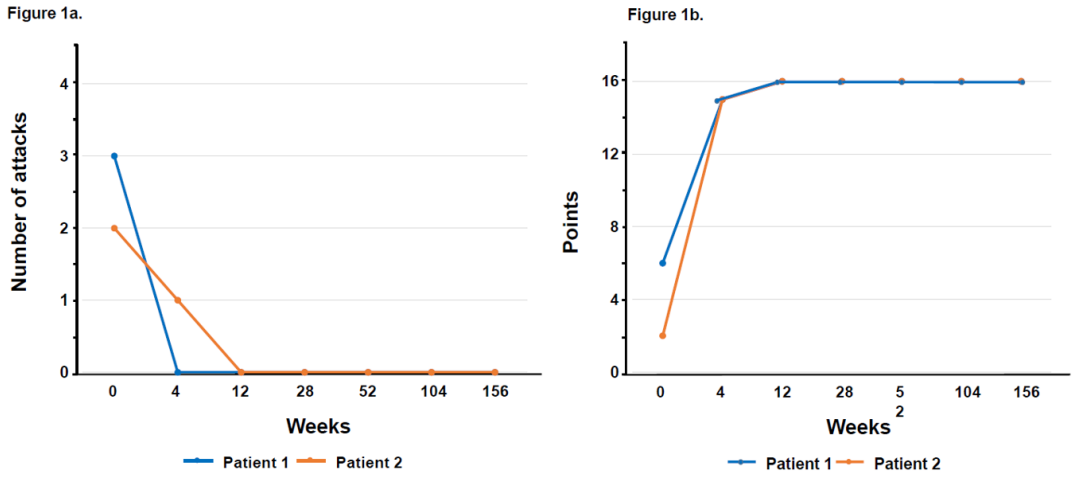


**Figure 1. (A)** Attack frequency at baseline reflects approximate yearly rates prior to treatment. Patient 1 (blue) and Patient 2 (orange) both experienced near-complete elimination of attacks over 156 weeks of lanadelumab use. Patient 2 had one mild attack in Year 1 (localized angioedema at the injection site) and remained attack-free thereafter. This illustrates the sustained, long-term efficacy of lanadelumab in preventing HAE attacks. **(B)** Angioedema Control Test (AECT) scores from baseline to Week 156. Both patients achieved the maximum score of 16 by Week 12, indicating optimal disease control, which was maintained throughout follow-up.

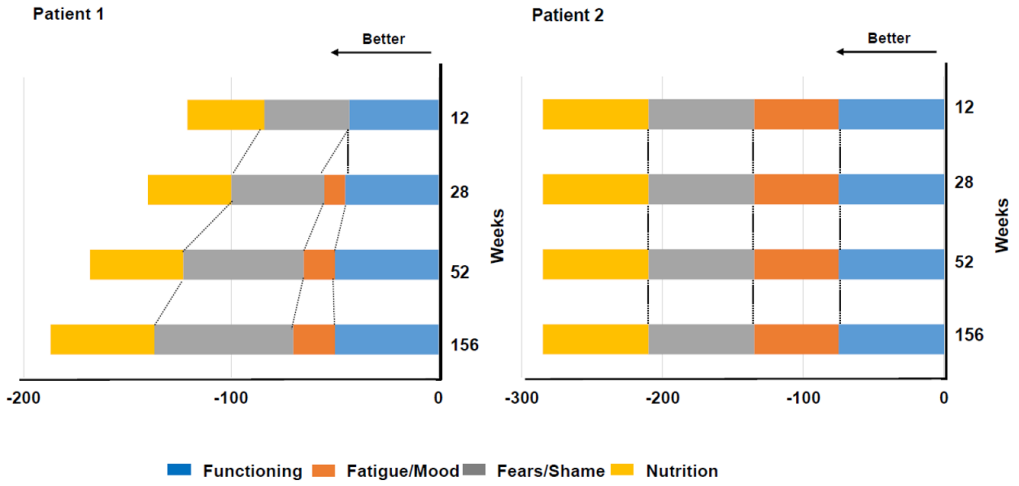


**Figure 2. Angioedema Quality of Life Questionnaire (AE-QoL) total scores over time (lower scores reflect better quality of life).** Both patients showed approximately 30-point reductions from baseline to Week 156, indicating significant and sustained improvement.

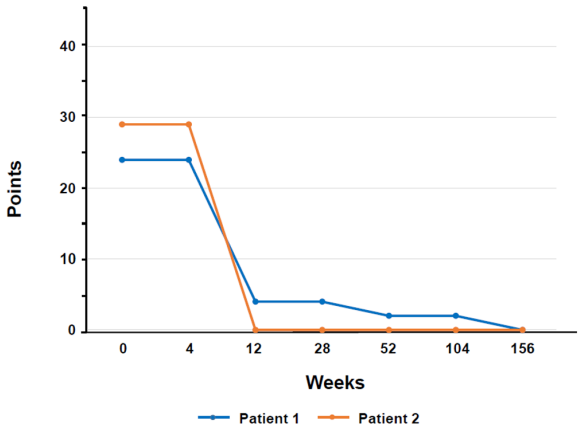


**Figure 3. Hospital Anxiety and Depression Scale (HADS) subscale scores.** Anxiety levels steadily declined during treatment; by Week 156, both patients' scores had normalized (≤ 7, indicated by shaded gray line), reflecting substantial relief from HAE-related anxiety. HADS scores are interpreted as follows: 0–7 = normal; 8–10 = borderline; 11–21 = clinically significant anxiety or depression.

Both patients expressed high satisfaction with therapy, with TSQM-9 Global Satisfaction scores exceeding 85 by Month 3 and remaining above 90 thereafter (Figure 4). Neither required dose adjustment nor discontinued therapy. These long-term outcomes indicate not only clinical efficacy but also patient acceptability and sustained adherence.

While limited by the small sample size and male-only cohort, this case series offers valuable insight into individualized trajectories of recovery and suggests a potential role for lanadelumab in East Asian clinical settings. The consistent responses observed across patients of different ages and clinical backgrounds suggest broad applicability of prophylactic treatment. However, further studies are warranted to examine long-term outcomes in female patients, where hormonal factors may influence disease dynamics.

In conclusion, this 3-year real-world experience demonstrates that lanadelumab prophylaxis offers more than just attack suppression — it may facilitate emotional recovery, restore daily functioning, and significantly improve quality of life. A comprehensive, patient-centered strategy incorporating preventive therapy, emergency preparedness, and psychological support is essential to fully leverage the long-term benefits of lanadelumab in managing HAE.

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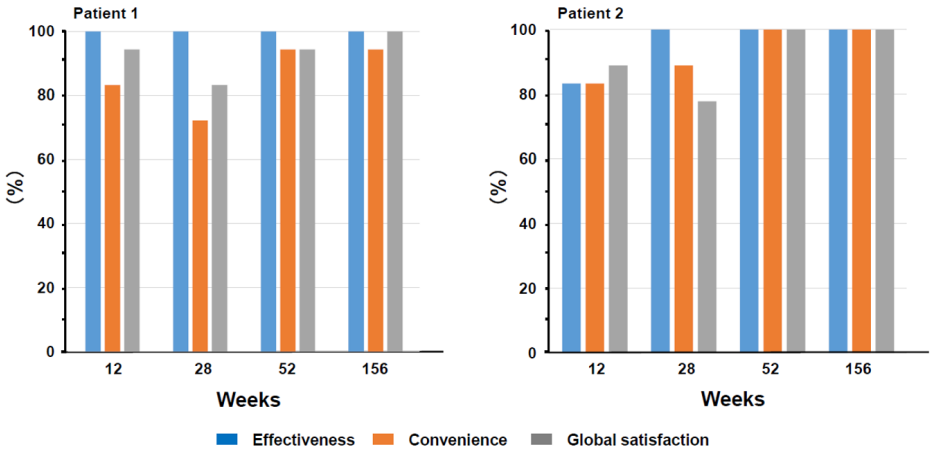


**Figure 4. Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores at Weeks 12, 28, 52, and 156 across three domains (effectiveness, convenience, and global satisfaction).** Higher scores indicate greater treatment satisfaction. Both patients reported consistently high satisfaction throughout treatment. Note: Error bars are not shown, as data reflect individual case trajectories.

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***Brief Report***

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# Clinical and genetic analysis of X-linked nephrogenic diabetes insipidus caused by a novel *AVPR2* mutation (NM_000054.6:exon3:c.245G>A (p.Cys82Tyr)) in a Chinese boy

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**SUMMARY**: X-linked nephrogenic diabetes insipidus (X-NDI) is a rare congenital disease caused by inactivating mutations of the vasopressin type-2 receptor (*AVPR2*), characterized by impaired renal concentrating ability, dramatic polyuria, polydipsia and risk of dehydration. This study aims to elucidate the pathogenic mechanisms associated with a novel variant in the *AVPR2* gene, which has been implicated in X-NDI. Whole exome sequencing (WES) was employed to identify genetic variants, complemented by bioinformatic analyses to predict the functional impact of these mutations. A male patient, aged 11.5 years, presented with polydipsia, polyuria, rapid weight gain, and associated physical anomalies, alongside hormonal imbalances and elevated serum sodium and chloride levels. Notably, WES revealed a hemi variant in the *AVPR2* gene (NM_000054.6:exon3:c.245G>A(p. Cys82Tyr)), classified as a variant of uncertain significance. The findings indicate that a combined pharmacological approach can effectively manage X-NDI symptoms without significant side effects, suggesting a favorable prognosis for the patient. After hydrochlorothiazide for one month, both serum sodium and chloride recovered a normal level. This study highlights the importance of early diagnosis and personalized treatment strategies in enhancing patient outcomes. Future research should focus on expanding genetic testing within the population to further elucidate the genetic underpinnings of X-NDI and explore the potential for targeted therapies, ultimately improving the management of this challenging condition. This newly identified mutation expands the spectrum of mutations in X-NDI.

***Keywords***: X-linked nephrogenic diabetes insipidus, *AVPR2*, hydrochlorothiazide, indomethacin

## 1. Introduction

Nephrogenic diabetes insipidus (NDI) is a rare but significant genetic disorder characterized by the inability of the kidneys to concentrate urine due to resistance to the antidiuretic hormone arginine vasopressin (AVP). This condition leads to excessive thirst and urination, resulting in risk of dehydration and electrolyte imbalances that can severely impact health and quality of life. Estimates of the incidence of congenital NDI indicate 8.8 per million male live births (*1*). 90% percent of all instances of nephrogenic diabetes insipidus (NDI) are attributed to X-linked inheritance (*AVPR2* gene mutations), while the remaining approximately 10% result from loss-of-function mutations in the aquaporin 2 (*AQP2*) gene (*2-6*). The significant expression of the receptor in the thick ascending limb (TAL), distal convoluted tubule (DCT), collecting duct (CNT), and collecting duct (CD), which play crucial roles in the reabsorption of water and solutes from glomerular filtrate, leads to a renal phenotype in X-linked (X-NDI) that is characterized by pronounced polyuria, hyposthenuria, compensatory polydipsia, hypernatremia, and elevated plasma osmolarity. This condition severely diminishes quality of life due to the constant need to urinate, even during sleep, the frequent requirement to consume water, and the necessity to adjust daily activities to accommodate these demands (*7-9*).

Current treatment options for X-NDI remain limited, primarily focusing on symptomatic management through fluid replacement and pharmacological interventions. Thiazide diuretics and nonsteroidal anti-inflammatory drugs have been utilized with varying degrees of success (*3*). Despite these approaches, many patients experience persistent symptoms, indicating an urgent need for further research into the underlying genetic mechanisms of X-NDI and the development of targeted therapies. Advances in genetic testing and whole exome sequencing (WES) have opened new avenues for identifying pathogenic variants associated with the

disorder, thereby enhancing our understanding of its molecular underpinnings (*10*).

Recent studies have identified numerous mutations within the *AVPR2* and *AQP2* genes, elucidating the complex relationship between genetic alterations and clinical manifestations of NDI (*11*). However, there remains a significant gap in our knowledge regarding the full spectrum of genetic variations contributing to X-NDI and their functional implications. This highlights the necessity for comprehensive genetic analyses in affected individuals, which can inform clinical management and facilitate personalized treatment approaches (*12*).

In this study, we employ whole exome sequencing to identify novel genetic variants in the *AVPR2* gene associated with nephrogenic diabetes insipidus. This approach allows for an in-depth investigation of the genetic landscape, aiming to elucidate pathogenic mechanisms underlying identified variants. By integrating genetic analysis with clinical evaluations, we seek to provide valuable insights that could enhance diagnostic accuracy and therapeutic strategies for individuals affected by X-NDI.

Our primary objective is to characterize the novel *AVPR2* variant identified in a patient with nephrogenic diabetes insipidus, exploring its potential clinical implications. We anticipate that our findings will contribute to a better understanding of the genetic basis of X-NDI and pave the way for future research aimed at developing targeted therapies that address underlying causes of this challenging condition. Ultimately, this research aims to improve patient outcomes through enhanced diagnostics and personalized treatment options based on genetic insights.

## 2. Materials and Methods

### 2.1. Patient

In 2025, an 11.5-year-old male patient visited the outpatient department of Paediatric Endocrinology, Shandong Provincial Hospital, for polydipsia, polyuria, and rapid weight gain. The parents of this patient are physically healthy, nonconsanguineous, and the maternal uncle of this patient has similar clinical manifestations. The clinical evaluation, baseline and dynamic hormonal levels, and genetic analyses were obtained from the patient with signed consent from the parents.

### 2.2. Clinical observations

The following hormones were measured in the serum samples: Insulin, luteinizing hormone (LH), C-peptide, progesterone, oestrogen, testosterone, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and insulin-like growth factor-1 (IGF-1). Water deprivation vasopressin test and oral glucose tolerance test (those involving oral glucose, insulin, glucose, and C-peptide at baseline and +30', +60', +120', +180' after glucose oral) were conducted with standard procedures. All hormones were measured by chemiluminescent methods (Roche, Basel, Switzerland) following the manufacturer's instructions. Blood electrolyte levels, routine blood tests, urinalysis and urine osmolality were measured in the hospital laboratory. Additionally, pituitary magnetic resonance imaging (MRI), and bone age were also carried out in the hospital.

### 2.3. Genome sequencing

Peripheral venous blood (3-5 mL) was obtained from the proband and his parents. The DNA extracted from the peripheral blood was subjected to WES. The exonic regions of the genomic DNA from the patient were fragmented, ligated, amplified, and purified in accordance with the manufacturer's instructions, and subsequently analyzed utilizing the SeqCap EZ Med Exome Enrichment Kit (Roche NimbleGen) as per the provided guidelines. This process enabled capture of all known genes' exons and their adjacent regions. Following post-capture amplification and purification, the DNA library was constructed using the Illumina HiSeq system.

The sequence data were aligned to the human genome reference version 19 (hg19) using NextGene V2.3.4 to ensure adequate coverage and an appropriate mean depth of reading across the target regions. Information on conserved nucleotide bases and corresponding amino acids, frequencies within normal populations (sourced from the 1000 Genomes Project, ExAC, dbSNP DNA, and locus-specific databases), predictions regarding biological functions, and data acquired from The Human Gene Mutation Database (HGMD), ClinVar, and Online Mendelian Inheritance in Man (OMIM) were also gathered through NextGene V2.3.4. Variants were meticulously screened according to established criteria. The interpretation of pathogenic variants adhered to the guidelines set forth by the American College of Medical Genetics (ACMG) for assessment of sequence variants published in 2015, employing the Human Genome Variation Society (HGVS) nomenclature.

To confirm variants identified in the proband through WES, Sanger sequencing was performed, which also facilitated examination of co-segregation of identified variants within the family. The genome sequencing endeavor was executed in partnership with MyGenostics Co.

### 2.4. Bioinformatic analysis

To demonstrate spatial structure of the *AVPR2* protein and the affected protein regions after the mutation we used the SWISS-MODEL database (*https://swissmodel.expasy.org/*) to query the wild-type three-dimensional

model of the *AVPR2* gene. SWISS-MODEL is an automated protein structure homology modeling server that can be accessed through the Expasy web server or the program DeepView (Swiss Pdb Viewer). The purpose of this server is to allow all life science researchers around the world to access protein modeling. The wild-type model is named O88721.1.A, with a coverage range of 1-371, a sequence similarity of 57%, and a confidence level of 87.60%. The data obtained from the homology model is visualized using PyMOL (*https://pymol.org/2/*)

2.5. Ethical approval

The Institutional Human Ethics Review Board at Shandong Provincial Hospital affiliated to Shandong First Medical University approved this study (LCYJ:NO. 2019-147). The legal guardians of the participant were given written information to obtain the signed consent to participate in the study. This study conforms to the provisions of the Declaration of Helsinki.

**3. Results and Discussion**

3.1. Clinical characteristics and indicators of the patient

The patient had normal mental and nutritional status and a height of 152 cm (P50-75). He had obesity, acanthosis, male female breast, Turner stage B3, a micropenis (4 cm × 1 cm), micro-testis (2 mL). His parents had no similar symptoms. Evaluation of hormone levels revealed showed reduced testosterone (TO) (0.06 ng/ml), luteinizing hormone (LH) (2.14 mIU/mL) and follicle stimulating hormone (FSH) (5.39 mIU/mL) levels. The following parameters were used: normal adrenocorticotropic hormone (ACTH) (38 pg/mL, reference ranges: 7.2–63.3 pg/mL); cortisol (351 nmol/L, reference ranges: 166-507 nmol/L); insulin-like growth factor-1 (IGF-1) (295 ng/mL, reference ranges: 45–305 ng/mL); thyroid-stimulating hormone (TSH) (1.44 μIU/mL, reference ranges: 0.7–4.17 μIU/mL); free thyroxine (FT4) (20.3 pmol/L, reference ranges: 11.45–17.63 pmol/L); and prolactin (4.47 ng/ml, reference ranges: 4.04–15.2 ng/mL). Additionally, by regular blood tests, Glycosylated Hemoglobin, Type A1C (HbA1C), Neurospecific Enolase (NSE), Carcinoembryonic Antigen (CEA), Alpha-fetoprotein (AFP), and Human Chorionic Gonadotropin (HCG) were normal. An OGTT test indicates that the child currently has no abnormal glucose tolerance, but there is hyperinsulinemia and insulin resistance. Bone age of this 11.5-year old boy was 13. Abdominal ultrasound, adrenal ultrasound, and MRI of the pituitary were normal.

It is especially important to note serum electrolyte levels. Upon admission, the child's blood biochemistry indicated serum sodium (Na) 149.9 mmol/L (normal reference range 135-145 mmol/L), and chloride (Cl) 112.4 mmol/L (normal reference range 98-110 mmol/L). Considering the child's symptoms of polydipsia and polyuria, we conducted a water deprivation and vasopressin test on the patient. Water deprivation and vasopressin tests lasted for 9 hours, with urine osmolality of 125, 100, 125 mOsm/ L, all less than 300 mOsm/ L; urine specific gravity was 1.002, 1.001, 1.002, all less than 1.018, indicating impaired urine concentrating ability, supporting the diagnosis of diabetes insipidus. Administered pituitrin 6 U for the vasopressin test, urine osmolality was 260, 125 mOsm/L, both less than 300 mOsm/L; urine specific gravity was 1.003, 1.002, both less than 1.018; before water deprivation, plasma osmolality before the vasopressin test and 2 hours after the vasopressin test were 293.91, 310.82, 300.30 mOsm/ L, and blood sodium were 149.23, 156.3, 151.4 mmol/ L, respectively. After using pituitrin, the child's urine osmolality and specific gravity did not increase, which is thus not consistent with central diabetes insipidus, considering nephrogenic diabetes insipidus. We started oral hydrochlorothiazide, observing changes in the child's urine output.

NDI is a rare disorder characterized by the kidneys' inability to concentrate urine despite normal or elevated levels of the antidiuretic hormone, arginine vasopressin (AVP). This condition leads to significant clinical manifestations, including polyuria and polydipsia, which can result in severe dehydration and electrolyte imbalances, presenting considerable health challenges for affected individuals (*3,13*), and matched our patient's condition.

Cannon (*12*) documented three occurrences of male-to-male transmission of diabetes insipidus in a Mormon lineage traced back to 1813. He observed, however, a decrease in penetrance among females, as carriers did not exhibit the condition. This observation led to the hypothesis that the disorder within this family could indeed be X-linked. Subsequently, Cutler *et al*. (*14*) established the renal etiology of the condition within this family. Ten Bensel and Peters (*15*) reported hydronephrosis in affected male siblings within the lineage described by Cannon (*12*), and they concluded that the pedigree, which spanned five generations and included twelve affected males, was characteristic of X linkage. Nakano (*16*) documented familial nephrogenic diabetes insipidus across four generations of a Samoan family.

In a retrospective study, van Lieburg *et al.* (*17*) analyzed clinical data from thirty male patients diagnosed with nephrogenic diabetes insipidus, ranging in age from one month to forty years, across eighteen Dutch families. They identified seventeen distinct mutations in the *AVPR2* gene in twenty-eight patients, while two patients presented mutations in the *AQP2* gene. Notably, eighty-seven percent of the patients received their diagnosis within the first 2.5 years of life. The predominant symptoms at the time of clinical evaluation included vomiting, anorexia, failure to thrive, fever, and constipation. Most patients were treated with

hydrochlorothiazide-amiloride, which did not result in significant adverse effects. Two patients developed severe hydronephrosis alongside a minor urinary tract rupture following slight trauma, and two others experienced acute urinary retention episodes. Height standard deviation (SD) scores for age predominantly remained below the 50th percentile, whereas weight-for-height SD scores indicated catch-up growth after several years of being underweight. The majority of patients demonstrated normal intelligence, which contrasts with the prevailing notion that mental retardation is the most common long-term consequence of nephrogenic diabetes insipidus. No significant correlation between clinical manifestations and genetic information was identified, except for a potentially milder phenotype observed in patients harboring the *AVPR2* G185C mutation (300538.0003), and no clear relationship between clinical and genetic data could be found.

3.2. Genetic analysis and pathogenicity prediction

In this study, A novel variant in the *AVPR2* gene was observed by WES in the proband and confirmed by Sanger sequencing (*18*). Pedigree chart of the child and genetic testing results in Figure 1. *AVPR2* variant NM_000054.6:exon3:c.245G>A(p.Cys82Tyr) was identified. The score was PP3+PS4+PM2, which was regarded as an uncertain mutation according to the ACMG Guidelines (*19*). Sanger sequencing confirmed that this new variant was not transmitted from the mother of this patient. Although the genetic results are ambiguous, the clinical manifestations of the child and the mode of inheritance are consistent, and the child's uncle also exhibits the same manifestations. Therefore, it can be clinically diagnosed as X-NDI.

The PP3 protein function comprehensive prediction software REVEL predicts that it may be harmful; PS4_Supporting this variant has been detected in 1 case of diabetes insipidus (internal case database); PM2_Supporting the frequency in the normal population database is -; through family verification analysis, the father of the tested individual did not provide a sample, and the mother of the tested individual has a heterozygous variant at this locus.

Three-dimensional protein structure analysis of *AVPR2* indicates that the identified mutation c.245G>A (p.Cys82Tyr) changes the 82nd amino acid from cysteine to tyrosine. Before the mutation, the 82nd cysteine formed two hydrogen bonds with the 78th isoleucine and the 86th leucine. After mutation, the 82nd tyrosine forms two hydrogen bonds with the 78th isoleucine and the 86th leucine, predicting that stability of the protein structure remains unchanged (Figure 2).

Conservation analysis of *AVPR2* amino acids in humans, mice, pigs, bovines, and mantles suggests that c.245G>A (p.Cys82Tyr) causes a substitution of a highly conserved amino acid (Figure 3A), functional prediction of the missense mutation c.245G>A (p.Cys82Tyr) using PolyPhen-2 software indicates strong pathogenicity, classifying it as a deleterious mutation (Figure 3B). This mutation is not recorded in the ExAc, EVS, dbSNP, and 1000 Genomes databases.

A total of 348 mutation sites related to the *AVPR2* gene have been reported, including missense/nonsense mutations 211 (61%), small deletions 62 (18%), gross deletions 30 (9%), small insertions 25 (7%), splicing 6 (2%), complex rearrangements 5 (1%), small indels 5 (1%), and gross insertions/duplications 4 (1%) (Figure 4). However, *AVPR2* mutation locations have not been related to any clinical disorders yet.

The majority of congenital NDI cases are attributed to mutations in the *AVPR2* gene, which encodes the

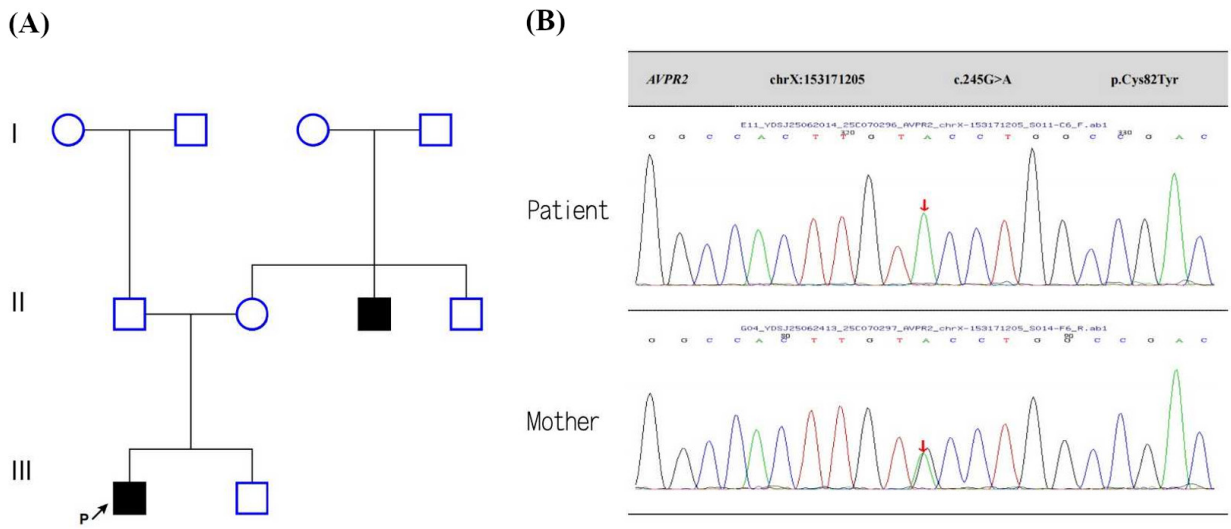


**Figure 1. The Pedigree chart of the child and genetic analysis. (A)** The pedigree of this family. **(B)** *AVPR2* gene mutation analysis of the patient (GenBank accession number: NM_000054.6).

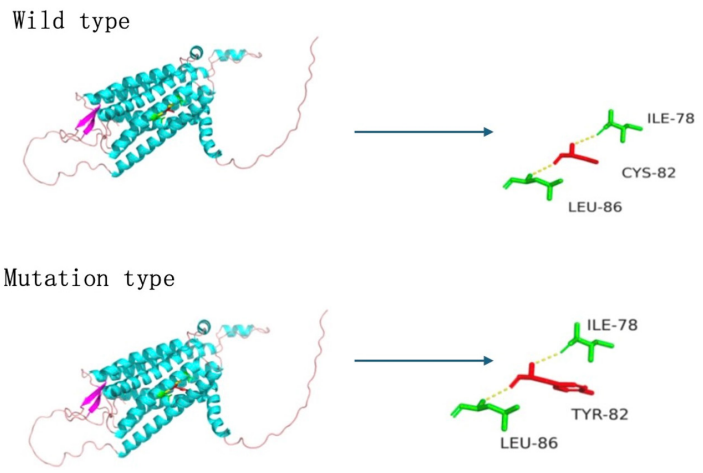


**Figure 2. Three-dimensional protein structure analysis of *AVPR2*.** Blue represents α-helix, purple represents β-sheet, and pink coils represents Loop structures. The observed hydrogen bonds are shown as stick structures, with blue dashed lines indicating hydrogen bonds.

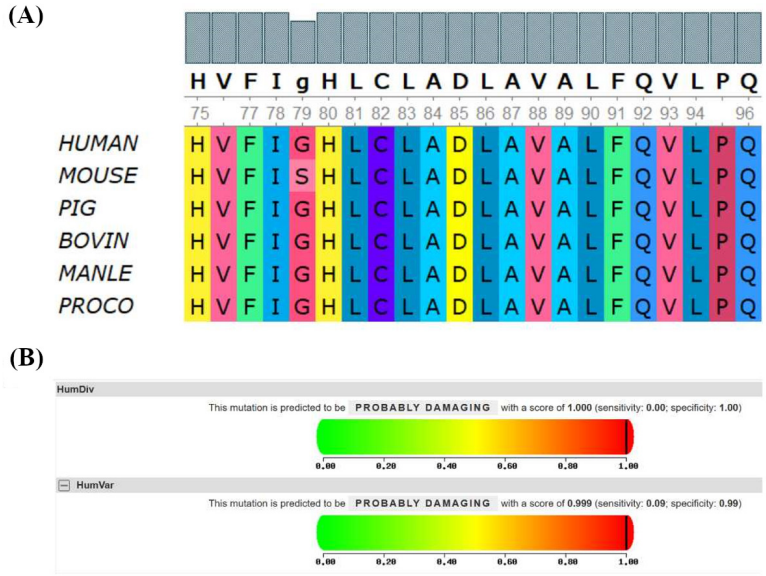


**Figure 3. The conservation analysis of the protein sequence and protein structure prediction. (A)** Multiple amino acid alignments of *AVPR2* homologs in the uniprot database. **(B)** The score of the newly disruptive c.245G>A (p.Cys82Tyr) mutation in Polyphen-2.

vasopressin V2 receptor located on the X chromosome, while a smaller percentage is linked to mutations in the *AQP2* gene, which encodes the aquaporin-2 water channel (*20,21*). Understanding the genetic underpinnings of NDI is critical for improving diagnostic and therapeutic strategies, especially as current treatments remain limited in efficacy and often come with significant side effects (*22,23*).

Our research employs WES to comprehensively analyze genetic variants and their potential impacts on protein function, thus elucidating the pathogenic mechanisms associated with this condition (*24,25*). This approach not only enhances our understanding of the genetic landscape of NDI but also aids in the development of targeted therapies. The findings presented herein will be discussed in relation to the patient's clinical profile, treatment plan, and significance of genetic biomarkers in guiding management strategies for nephrogenic diabetes insipidus (*26,27*).

This study represents a significant advancement in our understanding of NDI by identifying a novel variant in the *AVPR2* gene, which is crucial for the kidney's response to vasopressin. The implications of this discovery are profound, as it fills a critical knowledge gap regarding genetic underpinnings of NDI. Previous studies have extensively documented various mutations in the *AVPR2* gene, yet our research demonstrates for the first time in humans long-term efficacy of specific pharmacological interventions targeting this novel mutation, aligning with earlier animal studies that suggested unique therapeutic pathways (*23,26*). This integration of genetic analysis with clinical data not only enhances our diagnostic capabilities but also provides a foundation for developing targeted treatment strategies,

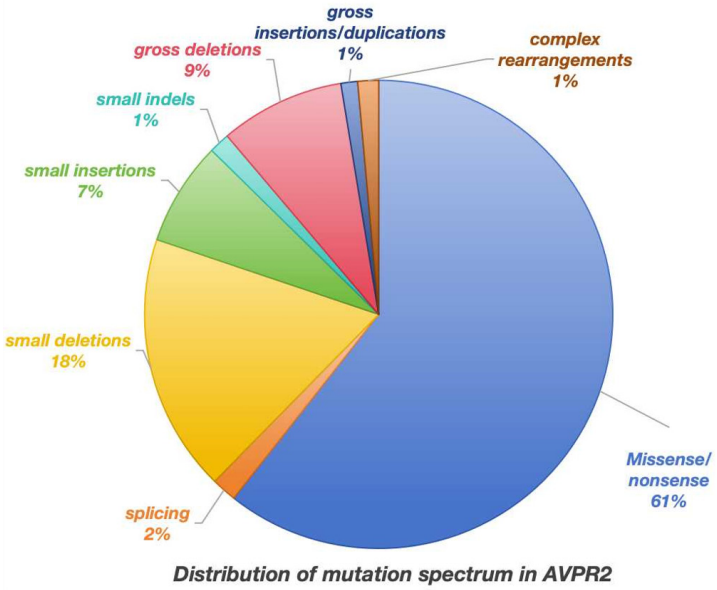


**Figure 4. Distribution of mutation spectra in AVPR2.** A total of 348 mutations in *AVPR2* include missense/nonsense mutations 211 (61%), small deletions 62 (18%), gross deletions 30 (9%), small insertions 25 (7%), splicing 6 (2%), complex rearrangements 5 (1%), small indels 5 (1%), and gross insertions/duplications 4 (1%).

emphasizing potential for personalized medicine in managing this rare disorder.

3.3. Treatment and follow-up

After hydrochlorothiazide 25 mg po bid for approximately one month, both Na 143.8 mmol/L and Cl 106.3 mmol/L recovered a normal level. Urine osmolality 175 mOsm/L (normal reference range 600–1000mmol/L), so we let the patient continue oral hydrochlorothiazide 25 mg po bid, while adding indomethacin 12.5mg po bid. The patient is under continued follow-up.

The identification of the *AVPR2* variant and its correlation with clinical symptoms underscores the necessity for early genetic testing and tailored therapeutic approaches. Successful treatment of our patient with a combination of hydrochlorothiazide and indomethacin demonstrates a promising avenue for enhancing patient outcomes. These findings suggest that similar patients may benefit from a multidisciplinary approach that includes genetic counseling and individualized treatment plans, leading to improved quality of life and reduced healthcare costs associated with complications from uncontrolled NDI (*3,13*).

Nonetheless, this study is not without limitations. The relatively small sample size and the nature of a single-case study may restrict the generalizability of our findings. Absence of extensive long-term follow-up data also limits our understanding of the chronic effects of the identified *AVPR2* mutation and pharmacological treatments employed. Future research should aim to include larger cohorts and longer follow-up periods to validate these findings and explore long-term efficacy and safety of the identified therapeutic strategies. Additionally, incorporation of experimental validation techniques could further strengthen our conclusions regarding pathogenicity of the *AVPR2* variant and its role in NDI (*26,28*).

In conclusion, this study presents a compelling case of a novel *AVPR2* variant associated with nephrogenic diabetes insipidus, underscoring the critical importance of early diagnosis and personalized treatment strategies. Successful management of the patient through pharmacological interventions illustrates potential for improved outcomes when genetic insights are integrated into clinical practice. Future investigations should aim to expand genetic screening efforts and explore functional consequences of identified variants, ultimately enhancing our understanding of this condition and informing development of targeted therapeutic approaches.

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***Brief Report***

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# Identification of a novel *de novo AFF4* variant (c.778A>G) associated with CHOPS syndrome

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**SUMMARY**: CHOPS (cognitive impairment, coarse facies, heart defects, obesity, pulmonary involvement, short stature, and skeletal dysplasia) syndrome is an extremely rare disorder with multiple congenital anomalies caused by missense variants in the ALF transcription elongation factor 4 gene (*AFF4*). This study aimed to identify causative variants in a Chinese family with CHOPS syndrome. A Chinese girl with short stature, obesity, and developmental delay underwent comprehensive clinical and genetic evaluations, including karyotyping analysis, multiple ligation-dependent probe amplification, detection of aberrant methylation, whole exome sequencing, Sanger sequencing, and copy number variation analysis, followed by *in silico* analyses. Reverse transcription, polymerase chain reaction, and Sanger sequencing were performed to evaluate the gene expression levels. The patient exhibited cognitive impairment, coarse facial appearance, obesity, short stature, skeletal involvement, and ophthalmic abnormalities. Genetic analyses identified a *de novo* heterozygous c.778A>G (p.Met260Val) variant in *AFF4* in the proband, absent in parents and little sister, with no other remarkable results. This novel variant was classified as pathogenic, without apparent effect on relative gene expression. The identification of this *de novo* missense variant as the genetic cause of CHOPS syndrome in this Chinese family broadens the genetic and phenotypic spectrum of the disorder.

***Keywords***: CHOPS syndrome, *AFF4* gene, novel variant, *de novo* variant, whole exome sequencing

## 1. Introduction

CHOPS syndrome (OMIM 616368) is an extremely infrequent genetic disease with multiple congenital anomalies caused by missense variants in the ALF transcription elongation factor 4 gene (*AFF4*, OMIM 604417) (*1,2*). Since three originally reported individuals with *AFF4* variants shared highly similar phenotypes, including cognitive impairment, coarse facies, heart defects, obesity, pulmonary involvement, short stature, and skeletal dysplasia, the acronym "CHOPS" has been given to this specific clinical entity (*2*). The clinical features of CHOPS patients, such as short stature, intellectual disability, and craniofacial features, resemble those of Cornelia de Lange syndrome (CdLS), a multisystem developmental disorder sharing common molecular pathogenesis caused by transcriptional elongation abnormalities, but the recognizable symptoms and distinct molecular etiologies suggest they are unique clinically diagnostic entities (*1-3*). Currently, the diagnosis of rare pediatric disorders relies heavily on genetic diagnostics, and the use of genomic technologies to identify novel variants is essential for deepening the understanding of rare diseases and ultimately improving patient outcomes (*4*).

The *AFF4* gene encodes the AFF4 protein, a member of the AF4/FMR2 family, which serves as a central scaffold protein of the super elongation complex (SEC) involved in the regulation of transcription elongation (*5*). The SEC encompasses eleven-nineteen Lys-rich leukemia (ELL) family members ELL1/ELL2/ELL3, ALL1-fused gene from chromosome 9 (AF9)/eleven-nineteen leukemia (ENL), AF4/FMR2 family member 1 (AFF1, also termed AF-4)/AFF4, and

positive transcription elongation factor b (P-TEFb) (*5-7*). The AFF4 protein, located downstream of the transcription start sites, plays a pivotal role in regulating RNA polymerase II (RNAP2) transcription (*5*). This protein is also important in tumorigenesis, osteogenesis, odontogenesis, and adipogenic differentiation (*6*). Gain-of-function variants in *AFF4* lead to resistance to proteasomal degradation and resultant transcriptional activation, which underlies CHOPS syndrome (*1,2*). Hitherto, only 16 cases of CHOPS syndrome have been reported worldwide, and they all carried heterozygous *AFF4* missense variants enriched in the highly conserved ALF (AF4-LAF4-FMR2) domain of AFF4 (*1-3,8-10*).

In this study, we identified a *de novo* heterozygous *AFF4* missense variant in a Chinese family with CHOPS syndrome through whole exome sequencing (WES) combined with Sanger sequencing. The heterozygous variant in *AFF4* (NM_014423.3), c.778A>G (p.Met260Val), was novel and classified as "pathogenic" following the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines. Herein, we also present the clinical and genetic findings of the patient and summarize the phenotypic and molecular characteristics of previously reported CHOPS syndrome cases.

## 2. Patient and Methods

### 2.1. Subject and clinical evaluation

A 9-year-old Chinese girl suspected of CHOPS syndrome, along with her available family members, was recruited from the Third Xiangya Hospital, Central South University, Changsha, China (Figure 1A). Detailed physical, neurocognitive, auditory, and ophthalmic examinations, laboratory tests, and radiographic assessments were performed by professionals to evaluate her growth pattern, craniofacial issues, intellectual disability, hearing loss, ocular signs, and anomalies in cardiac, pulmonary, skeletal, and other systems. Clinical data and peripheral blood samples were collected from the proband (II:1) and the available unaffected family members (I:1, I:2, and II:2). The study was conducted according to the tenets of the Declaration of Helsinki and under approval of the Institutional Review Board of the Third Xiangya Hospital. Written informed consent was obtained from all participants or their guardians.

### 2.2. G-banding karyotyping analysis

Conventional G-banding karyotyping analysis was performed at the Prenatal Diagnosis Center, Guizhou Provincial People's Hospital, Guiyang, China. In brief, a peripheral blood sample was taken from the patient for cell culture, colchicine treatment, and chromosome binding. After chromosome banding through trypsin using Giemsa staining, karyotyping analysis was carried out under a microscope (CytoVision®, Leica Biosystems, Germany).

### 2.3. Multiple ligation-dependent probe amplification (MLPA) and detection of aberrant methylation

Genomic DNA (gDNA) was extracted from the blood sample of the proband to perform MLPA and detection of aberrant methylation on the 15q11 region for Prader Willi Syndrome (PWS) or Angelman syndrome (AS) by BGI-Shenzhen (Shenzhen, China). Qualified DNA was denatured at 98°C for 5 min and hybridized with probes at 54°C for 15 min. Amplified probes were sequenced on Applied Biosystems 3730xl DNA analyzer (Thermo Fisher Scientific, Waltham, MA, USA) and data were analyzed using Coffalyser.Net software (MRC Holland, Amsterdam, Netherlands).

### 2.4. WES

WES was performed on the patient by BGI-Shenzhen. The gDNA was isolated from blood sample of the patient

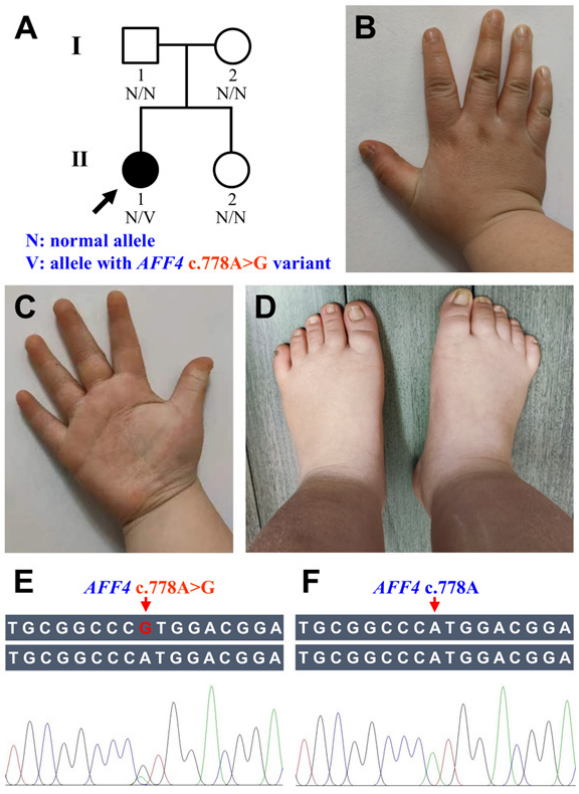


**Figure 1. Pedigree, clinical, and molecular characterization of a Chinese proband with CHOPS syndrome. (A)** Pedigree of a Chinese patient with CHOPS syndrome. Square represents male and circle represents female. Full black symbol and white symbol represent patient with CHOPS syndrome and unaffected individual, respectively. An arrow indicates the proband. **(B-D)** Hands and feet of CHOPS syndrome. **(E, F)** Sequencing of the *AFF4* c.778A>G variant in the proband and the wild-type c.778A in proband's unaffected father. *AFF4*, the ALF transcription elongation factor 4 gene.

using magnetic silica-coated sub-microspheres, and 50 ng of gDNA was fragmented randomly. Generated fragments of 100–500 bp were processed for end-repair, A-tailing, and adaptor ligation. Polymerase chain reaction (PCR) amplification and purification were conducted for further DNA nanoball preparation. Exome capture and enrichment were performed with KAPA HyperExome Probes (Roche, Basel, Switzerland). A DNA library was constructed utilizing combinatorial probe-anchor synthesis technology and DNA nanoballs, and sequencing was conducted on MGISEQ-2000 (MGI, Shenzhen, China).

2.5. Variant analysis and Sanger sequencing

After strictly filtering of the raw data obtained from the sequencing platform, the generated clean data was aligned with the human genome GRCh37/UCSC hg19 utilizing Burrows-Wheeler Aligner software. Genome Analysis Toolkit tools were used for base quality score recalibration and detection of single nucleotide variants (SNVs) and insertions/deletions (indels). High-confident SNVs and indels were further filtered and annotated against multiple databases of the human genome, including the Single Nucleotide Polymorphism database (dbSNP, build 156), Exome Sequencing Project 6500 (ESP6500, V2), the 1000 Genomes Project (1000G, Phase3), the Genome Aggregation Database (gnomAD, v4.1.0), the Exome Aggregation Consortium (ExAC, r0.3.1), the BGI-Phoenix genetic database (BPGD, V3.1), the BGI in-house variant database secondaryFinding Var (V1.1_2020.3), dbscSNV (v1.1), SpliceAI (v1.3), dbNSFP (v2.9.1), ClinVar, and the Human Gene Mutation Database (HGMD), as well as databases of mitochondrial genome containing Human Mitochondrial Genome Database (MtDB, *http://www.mtdb.igp.uu.se/*), MITOMAP (*https://www.mitomap.org/*), gnomAD (v.3.1), MitImpact_db (v3.0.6), APOGEE (v.1.0), MitoTIP (3.0.6), and HmtVAR (*https://www.hmtvar.uniba.it*). Variant pathogenicity was predicted based on multiple tools: MutationTaster (*http://www.mutationtaster.org/*), Sorting Intolerant from Tolerant (SIFT, *http://provean.jcvi.org/*), Protein Variation Effect Analyzer (PROVEAN, *http://provean.jcvi.org/*), Polymorphism Phenotyping version 2 (Polyphen-2, *http://genetics.bwh.harvard.edu/pph2/*), LoGoFunc predictor (*https://itanlab.shinyapps.io/goflof/*), PhyloP, and Genomic Evolutionary Rate Profiling (GERP) (*11-18*). Sanger sequencing was used to validate the potential variants identified by WES in the patient and her parents, using the following five pairs of primer sequences:

5'-ATCAACGCTCCAAATCACCTCG-3'
and 5'-ACAGATCTACGCATCCACTTGG-3',
5'-TCCCAACAATTCTGCAGTGA-3'
and 5'-GCTAAGCTTTCTATTTGGGCATA-3',
5'-TCTTCACGGTGCTGTAGAGTTT-3'
and 5'-CCATGTCCTCATCCACAATTTC-3',
5'-TGAGCCAAAGATGGATAACTGC-3'
and 5'-GACACTACTATCCACAGGTTCT-3',
5'-ATCCTATCCCAGTGCTGGTTCG-3'
and 5'-CACGTTAACTCCGCTCAACACC-3'.

For the second verification and analysis, Sanger sequencing for the candidate pathogenic variant was performed on family members with the following primers:

5'-TGGGCAGCACTCAACTCAAT-3'
and 5'-TGGTGAGATGTGCTTTGCTG-3'.

2.6. Copy number variation (CNV) analysis

The WES data were used to detect exome CNVs with ExomeDepth (BGI-Shenzhen). Sequence alignment, deduplication, GC bias correction, and CNV analysis algorithm setting were conducted. Following quality control, variation analysis results were filtered against databases including the Online Mendelian Inheritance in Man (OMIM), HGMD, and the Database of Genomic Variants, producing semiautomatic interpretation and classification.

2.7. Conservation analysis and variant evaluation

Conservation of protein sequences was analyzed by the Basic Local Alignment Search Tool (BLAST, *https://blast.ncbi.nlm.nih.gov/BlastAlign.cgi*). Three-dimensional structures of the wild-type and mutant AFF4 proteins were predicted using SWISS-MODEL tool (*http://www.swissmodel.expasy.org*), based on the model retrieved from the AlphaFold Protein Structure Database (AF-Q9UHB7-F1, *https://alphafold.com/*). PyMOL software (version 2.5.8, Schrödinger, LLC, Portland, USA) was used to visualize protein structures. Identified variant was classified following the ACMG/AMP variant classification guidelines (*19*).

2.8. RNA isolation, PCR, and gene expression analysis

Total RNA was isolated from the patient's leukocytes using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and the extracted RNA was converted to complementary DNA (cDNA) using the First Strand cDNA Synthesis Kit (Toyobo, Japan). PCR amplification was conducted using the following primers:

5'-GGGCAGCACTCAACTCAAT-3'
and 5'-AGGTTCTGTTTTGCATGGTGT-3'.

PCR amplification products were checked by agarose gel electrophoresis and subsequently sequenced on Applied Biosystems 3730xl DNA analyzer (Thermo Fisher Scientific). Gene expression analysis was

conducted by Sanger sequencing of *AFF4* cDNA and comparison of the areas under peaks of wild-type and mutant alleles, which were quantified and calculated using ImageJ software (v1.54d, National Institutes of Health, USA). Statistical analysis was performed using Student's *t*-test *via* GraphPad Prism (v8.2.1, GraphPad Software, LLC, Boston, MA, USA) and $p < 0.05$ was considered statistically significant.

## 3. Results and Discussion

### 3.1. Clinical findings

The patient, a 9-year-old Chinese girl with non-consanguineous parents, was born at full term *via* vaginal delivery without postnatal problems. She showed a round face with a coarse appearance, facial fullness, arched eyebrows, and long eyelashes, along with brachydactyly (Figure 1B-D). At the age of 6 years, she was noted to have short stature. Her height was 101.8 cm, and her weight was 23.5 kg, indicating obesity. The ultrasound scan revealed no abnormalities of the uterus or its appendages. Based on extensive radiological screening, including skeletal maturation assessment, full-spine radiographs in frontal and lateral views, chest X-ray, and dedicated magnetic resonance imaging of the pituitary, and auxological and biochemical investigations, she was diagnosed with growth hormone deficiency, short stature, and vitamin D deficiency. Recombinant human growth hormone medication was started. Her height and weight began to increase over time, and after six months of treatment, ophthalmic examination showed increased intraocular pressure associated with the therapy, as well as amblyopia, myopia, and astigmatism.

At her latest clinic visit at 9 years old, her height was 116.5 cm (3rd percentile), her weight was 33.0 kg (75th–90th percentile), and her BMI was 24.31 kg/m$^2$. Her full-scale intelligence quotient was 72 based on the Wechsler Intelligence Scale for Children, indicating a marginal defect. Ultrasonic measurement of bone mineral density showed relatively low bone mineral density. Cardiac ultrasonography showed no significant cardiac abnormalities, except for mild pulmonary valve regurgitation. The results of auditory evaluations, including pure tone audiometry, otoacoustic emission, tympanometry, and acoustic reflex testing, were normal. Fiberoptic nasopharyngoscopy indicated adenoid hypertrophy (Table 1).

We reviewed the literature and summarized 17 patients with CHOPS syndrome worldwide, relating to 8 heterozygous *AFF4* variants, as shown in Table 1 (*1-3,8-10*). The patients usually exhibited cognitive impairment and characteristic facial features (100%, 17/17), short stature and skeletal involvement (100%, 17/17), obesity (94%, 16/17), heart defects (76%, 13/17), pulmonary involvement (76%, 13/17), and other features including hearing loss (59%, 10/17), ocular abnormalities (59%, 10/17), genitourinary abnormalities (47%, 8/17), and gastrointestinal issues (47%, 8/17). Our patient exhibited symptoms similar to those observed in previous CHOPS sufferers, including characteristic facial features, intellectual disability, obesity, short stature, and brachydactyly, as well as ocular abnormalities and adenoid hypertrophy. Intriguingly, a previously reported 7-year-old boy carrying a different substitution (c.779T>C, p.Met260Thr) occurring at the same position as our variant exhibited similar manifestations, including cognitive impairment, coarse facial features, obesity, short stature, brachydactyly, and ophthalmic abnormalities (*1*). However, our patient showed growth hormone deficiency, vitamin D deficiency, and adenoid hypertrophy, which were not observed in that boy, who exhibited additional symptoms including aspiration history, mixed hearing loss, and skin changes absent in our patient (*1*). Characteristic facial features, obesity, intellectual disability, and short stature also occur in other rare genetic disorders, such as PWS and AS (*20,21*). The obesity observed in CHOPS syndrome and PWS may result from excessive food-seeking behaviors or reduced resting energy expenditure due to impaired hypothalamic function (*1,2,20*).

### 3.2. Exclusion of chromosomal and other genomic disorders

Considering the overlap of clinical manifestations with other genetic disorders, karyotyping analysis, MLPA, DNA methylation analysis, and CNV analysis were performed. Karyotyping analysis of the patient's peripheral blood revealed a chromosome karyotype of 46, XX, without chimerism. MLPA and methylation detection showed unremarkable results and lack of large segment variation or abnormal DNA methylation on chromosome 15q11 region, excluding diagnosis of PWS or AS. No clinically significant chromosomal microdeletions or microduplications (over 100 kb) were found in this sample through CNV analysis. These results ruled out PWS, AS, and other significant genomic disorders.

### 3.3. WES and variant analysis

WES of the proband (II:1) produced a total of 29,462.20 Mb of raw data. The target sequence covered 99.88% and 99.80% of bases at >10× and >20×, respectively, with a mean sequencing depth across the target region of 405.47×. Five potential phenotype-related heterozygous variants were identified in the proband through WES and validated by Sanger sequencing, c.778A>G in *AFF4*, c.247dup in the component of oligomeric golgi complex 6 gene (*COG6*), c.129dup in the cereblon gene (*CRBN*), c.8612A>C in the lysine methyltransferase 2A gene (*KMT2A*), and c.1282A>C in the oligophrenin 1 gene (*OPHN1*). Sanger sequencing confirmed that the

**Table 1. Clinical and genetic characteristics of CHOPS syndrome patients with *AFF4* variants**

| Case no. | Variant | Age (y)/ Sex | Cognitive impairment and coarse facies | Heart defects | Obesity | Pulmonary involvement | Short stature and skeletal dysplasia | Hearing loss | Ocular abnl | GU | GI | Additional features (*Ref.*) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | c.758C>G, p.Pro253Arg | 9/F | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Otorrhea, chronic bilateral otitis media, polycythemia, steroid-induced diabetes mellitus, iatrogenic adrenal insufficiency, and prematurity (*1*) |
| 2 | c.758C>T, p.Pro253Leu | 9/F | Yes | Yes | Yes | Yes | Yes | NR | NR | NR | NR | Sinusitis, recurrent otitis media with effusion, and Moyamoya-like vasculopathy (*3*) |
| 3 | c.760A>G, p.Thr254Ala | 17/M | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NR (*1,2*) |
| 4 | c.760A>G, p.Thr254Ala | 2/M | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NR | NR (*9*) |
| 5 | c.761C>G, p.Thr254Ser | 20/F | Yes | Yes | Yes | Yes | Yes | NR | NR | Yes | Yes | Coarse hair (*1,2*) |
| 6 | c.763G>A, p.Ala255Thr | 11/F | Yes | Yes | Yes | Yes | Yes | NR | NR | NR | NR | Hypothyroidism (*1*) |
| 7 | c.772C>T, p.Arg258Trp | 12/F | Yes | Yes | Yes | Yes | Yes | NR | Yes | Yes | Yes | Eczema (*1,2*) |
| 8 | c.772C>T, p.Arg258Trp | 23/M | Yes | NR | Yes | NR | Yes | Yes | Yes | Yes | NR | Gynecomastia, acanthosis nigricans, and hirsutism (*1*) |
| 9 | c.772C>T, p.Arg258Trp | 2/F | Yes | Yes | Yes | Yes | Yes | Yes | NR | NR | Yes | Obstruction of nasolacrimal duct, chronic bilateral otitis media, sacral mass (removed), and jaundice (*1*) |
| 10 | c.772C>T, p.Arg258Trp | 6/M | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NR | Yes | Growth hormone deficiency (*1*) |
| 11 | c.772C>T, p.Arg258Trp | 7/F | Yes | Yes | Yes | NR | Yes | Yes | Yes | NR | Yes | Low lying conus with lipoma of the filum terminale (*1*) |
| 12 | c.772C>T, p.Arg258Trp | 1/M | Yes | NR | Yes | NR | Yes | Yes | NR | Yes | NR | NR (*1*) |
| 13 | c.772C>T, p.Arg258Trp | 17.5/F | Yes | Yes | Yes | Yes | Yes | NR | NR | NR | NR | NR (*8*) |
| 14 | c.772C>T, p.Arg258Trp | 13/M | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NR | NR | NR (*9*) |
| 15 | c.772C>T, p.Arg258Trp | 0/M | Yes | Yes | NR | Yes | Yes | NR | NR | Yes | Yes | Congenital hypothyroidism and nervous system involvement (*10*) |
| 16 | c.778A>G, p.Met260Val | 9/F | Yes | No | Yes | No | Yes | No | Yes | No | No | Adenoid hypertrophy, growth hormone deficiency, and vitamin D deficiency (*This study*) |
| 17 | c.779T>C, p.Met260Thr | 7/M | Yes | NR | Yes | Yes | Yes | Yes | Yes | NR | NR | Sun-exposed erythema and mottling (*1*) |

*AFF4*: the ALF transcription elongation factor 4 gene, y: years, F: female, M: male, Ocular abnl: ocular abnormalities, GU: genitourinary abnormalities, GI: gastrointestinal abnormalities, NR: data not reported in the original publication.

asymptomatic father (I:1) carried variants in *COG6*, *CRBN*, and *OPHN1*, and the asymptomatic mother (I:2) carried the *KMT2A* variant, while the *AFF4* variant was absent in all tested asymptomatic family members (I:1, I:2, and II:2), suggesting that the candidate pathogenic *AFF4* variant was *de novo* with paternity and maternity confirmed (ACMG/AMP: PS2, Figure 1E, F). Based on clinical features, auxiliary examinations, Sanger sequencing, and co-segregation analysis, the *de novo AFF4* variant was proposed as the genetic cause of the family, while another four variants were excluded. The heterozygous c.778A>G (p.Met260Val) variant in *AFF4*, a CHOPS syndrome-associated gene, was predicted to be deleterious by bioinformatics tools (ACMG/AMP: PP3), *via* a gain-of-function mechanism (Table 2). It was absent in multiple databases including ESP6500, 1000G, gnomAD, and ExAC, and has not been reported in the literature (ACMG/AMP: PM2, Table 2). Conservation analysis showed residue p.Met260 in the AFF4 protein is highly evolutionarily conserved from zebrafish to human (Figure 2A). The residue is located within a mutational hotspot area, in which all previously identified missense variants are reported to be pathogenic, including different amino acid substitutions at the same position, moreover, the two variants altered the significantly conserved amino acid residue and the resulting conformational changes are shown in Figure 2B (ACMG/AMP: PM1 and PM5) (*1*). cDNA sequencing confirmed the presence of the mutant allele c.778A>G, and comparative analysis of electropherograms from the patient showed no statistically significant difference between the wild-type and mutant alleles ($p$ = 0.2151, Figure 2C), indicating that the mutant allele was not degraded and that the c.778A>G variant did not affect the relative gene expression. According to ACMG/AMP guidelines, the *AFF4* c.778A>G (p.Met260Val) variant was classified as "pathogenic" (PS2+PM1+PM2+PM5+PP3).

The *AFF4* gene, located on chromosome 5q31, is a fusion partner of the *KMT2A* gene (*22*). *AFF4* comprises 21 exons and encodes a 1,163-amino-acid protein AFF4 that serves as a scaffold for the SEC complex assembly (*22*). The AFF4 protein plays a monitoring role in transcription elongation, competing with AFF1 for binding to other SEC components (*16*). The SEC includes P-TEFb, a C-terminal domain kinase composed of cyclin-dependent kinase 9 (Cdk9) and cyclin T1/T2, contributing to the regulation of transcription elongation by the release of paused RNAP2 (*7,23*). In cells, the majority of P-TEFb is found reserved in the inactive 7SK small nuclear ribonucleoprotein particle complex, and upon signal stimulation, it is released and recruited by Brd4 and SEC, forming active complexes to stimulate transcription of inducible genes (*24*). The N-terminus of AFF4 (residues 1–300) can facilitate the autophosphorylation of Cdk9 at residue p.Thr186 by binding the Cdk9 T-loop to either Brd4 or AFF1/AFF4, which is essential for reconstituting P-TEFb and promoting the release of paused RNAP2 or restarting global gene transcription (*24*).

AFF4 includes an N-terminal intrinsically disordered region that interacts with other SEC subunits and a C-terminal homology domain (CHD) conserved among AFF1–AFF4 (*25*). The CHD of AFF4 can fold into a domain encompassing eight helices and mediates AFF4 homodimerization or heterodimerization with AFF1 (*25*). The domain contains a surface loop region that serves as a substrate for the P-TEFb Cdk9, promoting release of promoter-proximal paused RNAP2 (*25*). All identified *AFF4* variants associated with CHOPS syndrome are *de novo* missense variants clustered in a 13-amino-acid region (residues 251–263) located on conserved ALF homology domain of the AFF4 protein (Figure 2D), and all were predicted to be deleterious by *in silico* tools (*1,26*). The ALF homology domain is a 175-amino-acid motif with an average sequence identity of 82% among the AFF1, AF4/FMR2 family member 2 (AFF2, also termed LAF-4), and AF4/FMR2 family member 3 (AFF3, also termed FMR-2) proteins (*27*). The *de novo* c.772C>T (p.Arg258Trp) variant is the most common variant, accounting for over half of CHOPS syndrome cases, indicating that nucleotide 772 is a mutational hotspot. A likely explanation is that the C>T transition is the most common genetic change, resulting from replication of the U:G mispair after spontaneous hydrolytic deamination of cytosine and producing an aberrant uracil (*28*). The *AFF4* variants p.Pro253Arg, p.Thr254Ala, p.Thr254Ser, p.Ala255Thr, and p.Arg258Trp showed gain-of-function effects, leading to resistance to proteasomal degradation by SIAH1 and resulting in excessive accumulation of mutant AFF4. This accumulation causes alterations in RNAP2 distribution and transcriptional elongation abnormalities, which underlie CHOPS syndrome (*1,2*). The novel heterozygous *de novo AFF4* c.778A>G (p.Met260Val) variant identified in this study was absent from multiple databases. *In silico* analyses and ACMG/AMP criteria evaluation suggested that it was a "pathogenic" variant *via* a gain-of-function mechanism. Since p.Met260Val also locates in the critical ALF homology domain, a similar gain-of-function pathogenic mechanism may underpin development of CHOPS syndrome. Further cellular and animal model experiments are needed to thoroughly elucidate the detailed mechanisms by which abnormally elevated AFF4 proteins cause transcriptional abnormalities and affect downstream signaling pathways, which would deepen the understanding of their role in the overlapping clinical manifestations observed in other rare disorders, such as CdLS, PWS, and AS.

In conclusion, we identified a novel *de novo AFF4* variant, c.778A>G (p.Met260Val), as the genetic cause of CHOPS syndrome in a Chinese family. This discovery broadens the phenotypic and genetic spectrum of CHOPS syndrome and may enhance our understanding of its clinical and genetic features.

**Table 2. Summary of *AFF4* variants in patients with CHOPS syndrome**

| Items | Variant 1 | Variant 2 | Variant 3 | Variant 4 | Variant 5 | Variant 6 | Variant 7 | Variant 8 |
|---|---|---|---|---|---|---|---|---|
| Exon | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Nucleotide change | c.758C>G | c.758C>T | c.760A>G | c.761C>G | c.763G>A | c.772C>T | c.778A>G | c.779T>C |
| Amino acid change | p.Pro253Arg | p.Pro253Leu | p.Thr254Ala | p.Thr254Ser | p.Ala255Thr | p.Arg258Trp | p.Met260Val | p.Met260Thr |
| dbSNP rs number | No | No | rs786205233 | rs786205679 | No | rs786205680 | rs2150098305 | rs1761368316 |
| 1000G | No | No | No | No | No | No | No | No |
| ESP6500 | No | No | No | No | No | No | No | No |
| ExAC | No | No | No | No | No | No | No | No |
| gnomAD | No | No | No | No | No | No | No | No |
| ClinVar | No | Pathogenic/ Likely pathogenic | Pathogenic | Pathogenic/ Likely pathogenic | No | Pathogenic/ Likely pathogenic | Likely pathogenic | Uncertain significance |
| HGMD accession number | CM199228 | No | CM152549 | CM152550 | CM199227 | CM152551 | No | CM199229 |
| MutationTaster | Disease causing | Disease causing | Disease causing | Disease causing | Disease causing | Disease causing | Disease causing | Disease causing |
| PolyPhen-2 | Probably damagin g | Probably damaging | Probably damaging | Probably damaging | Probably damaging | Probably damaging | Possibly damaging | Possibly damaging |
| PROVEAN | Deleterious | Deleterious | Deleterious | Deleterious | Deleterious | Deleterious | Deleterious | Deleterious |
| SIFT | Damaging | Damaging | Damaging | Damaging | Damaging | Damaging | Damaging | Damaging |
| LoGoFunc | Gain of function | Gain of function | Gain of function | Gain of function | Gain of function | Gain of function | Gain of function | Gain of function |
| ACMG/AMP classification | Pathogenic | Pathogenic | Pathogenic | Pathogenic | Pathogenic | Pathogenic | Pathogenic | Pathogenic |
| ACMG/AMP criteria | PS2+PS3+PM2+ PP3+PP4 | PS2+PM2+PM5+ PP3+PP4 | PS2+PS3+PM2+ PP3+PP4 | PS2+PS3+PM2+ PP3+PP4 | PS2+PS3+PM2+ PP3+PP4 | PS2+PS3+PM2+ PP3+PP4 | PS2+PM2+PM5+ PP3+PP4 | PS2+PM2+PM5+ PP3+PP4 |

*AFF4*: the ALF transcription elongation factor 4 gene, dbSNP: Single Nucleotide Polymorphism database, rs: Reference SNP, 1000G: 1000 Genomes Project, ESP6500: Exome Sequencing Project 6500, ExAC: Exome Aggregation Consortium, gnomAD: Genome Aggregation Database, HGMD: Human Gene Mutation Database, PolyPhen-2: Polymorphism Phenotyping version 2, PROVEAN: Protein Variation Effect Analyzer, SIFT: Sorting Intolerant from Tolerant, ACMG/AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology, PS: pathogenic strong, PM: pathogenic moderate, PP: pathogenic supporting.

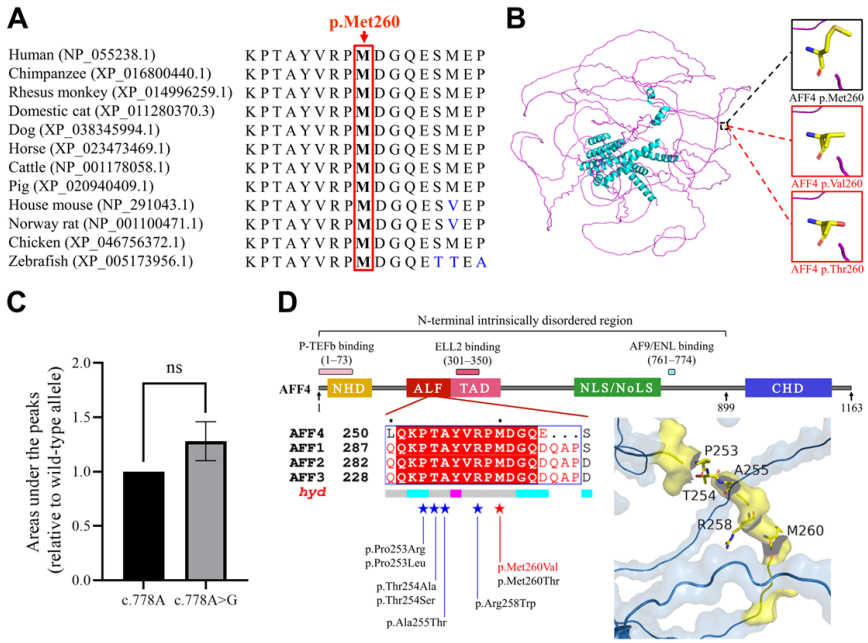


**Figure 2. Effect of the *AFF4* c.778A>G (p.Met260Val) variant and schematic representation of the AFF4 protein illustrating the identified variants in CHOPS syndrome. (A)** Conservation analysis of the AFF4 p.Met260 residue. **(B)** Cartoon model of the AFF4 protein structure by PyMOL based on the SWISS-MODEL: the methionine and the altered valine and threonine at position 260 are shown as stick models. **(C)** The areas under the peaks of wild-type and c.778A>G mutant alleles by sequencing analysis of *AFF4* complementary DNA from the proband. **(D)** Scheme of AFF4 protein demonstrating the location of the *de novo* missense variants identified in the patients with CHOPS syndrome. All reported *AFF4* variants are located within the highly conserved ALF homology domain of AFF4. The interaction regions of AFF4 with P-TEFb, ELL2, and AF9/ENL are shown as rectangles on top of the human AFF4 scheme. Sequence alignments of human AFF1–AFF4 proteins suggest conservation of the 13-amino-acid region in ALF homology domain. Sequences used (proteins and UniProtKB accession numbers): AFF1 (P51825), AFF2 (P51816), AFF3 (P51826), and AFF4 (Q9UHB7). The hydropathy is rendered by a bar below, where pink indicates hydrophobic, grey indicates neutral, and cyan indicates hydrophilic. Sequence alignments and hydropathic properties were visualized using the ESPript 3.0 web server *(26)*. Highly conserved 13-amino-acid residues are highlighted with red background. Mutated residues reported in previous studies and in this study are indicated by stars under the sequences. Three-dimensional structure model of wild-type AFF4 protein (residues 250–265) visualized by PyMOL is shown at the bottom right corner. The 13-amino-acid region is marked in yellow as surface and the corresponding mutant residues were labeled and depicted as sticks. AF9/ENL, ALL1-fused gene from chromosome 9/eleven-nineteen leukemia; AFF1–AFF4, AF4/FMR2 family member 1–4; *AFF4*, the ALF transcription elongation factor 4 gene; ALF, AF4-LAF4-FMR2; CHD, C-terminal homology domain; ELL2, RNA polymerase II elongation factor ELL2; *hyd*, hydropathy; NHD, N-terminal homology domain; NLS, nuclear localization signal; NoLS, nucleolar localization signal; ns, not significant; P-TEFb, positive transcription elongation factor b; TAD, transactivation domain..

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***Letter***

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# Renal oncocytoma mimicking chromophobe renal cell carcinoma: Management using proposed diagnostic algorithm with emphasis on 99mTc-sestamibi SPECT/CT

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**SUMMARY**: Renal oncocytomas are benign renal tumours characterized by a central stellate scar that are indistinguishable on CT/MR imaging from malignant chromophobe renal cell carcinomas (ChrRCCs). Renal oncocytomas and ChrRCCs can be separate entities but can also co-exist on a spectrum in hybrid oncocytic/chromophobe tumours. In the past, invasive biopsy and pathologic diagnosis has been relied on to differentiate these lesion and direct management. Early research demonstrates the effectiveness of technetium 99m sestamibi (99mTc-sestamibi) single-photon emission computed tomography (SPECT)/CT in differentiating benign versus malignant renal tumours. A new diagnostic algorithm has previously been proposed to reduce unnecessary biopsy and/or targeted therapy in managing enhancing 1-4 cm renal masses by incorporating 99mTc-sestamibi SPECT/CT in management. We present a case of suspected renal oncocytoma found incidentally on surveillance imaging post-treatment of uveal melanoma. We illustrate the incorporation of the proposed diagnostic algorithm using 99mTc-sestamibi SPECT/CT for enhancing 1-4 cm renal masses into the existing diagnostic algorithm for incidental renal masses and demonstrate its use in our case of suspected renal oncocytoma.

***Keywords***: renal oncocytoma, chromophobe renal cell carcinoma, hybrid oncocytic/chromophobe tumour, 99mTc-sestamibi SPECT/CT

A renal oncocytoma is a benign renal tumour, representing 3-7% of all renal tumours (*1*). Renal oncocytomas are classically described as having a distinctive central stellate scar which can be seen in 33–80% of cases (2). On MRI they exhibit low T1 signal and high T2 signal in addition to a classic central stellate scar. In over 50% of cases, patients are asymptomatic (*1*). When symptomatic, the most common symptoms include flank pain, gross hematuria, or palpable mass (*1,2*). Renal oncocytomas are benign but share a similar imaging appearance to malignant chromophobe renal cell carcinoma (ChrRCC), as both arise from intercalated cells in the kidney, and thus require further differentiation (*1-4*). ChrRCCs represent 5% of all renal cell carcinomas and are the third most common subtype of renal cell carcinoma behind clear cell and papillary (*5*).

Renal oncocytoma and ChrRCC can be differentiated on pathology using a combination of histopathology and immunohistochemistry. On histopathology, renal oncocytomas have a nested or tubular architectural pattern while ChrRCCs have a solid or trabecular architectural pattern (*6*). On immunohistochemistry, renal oncocytomas will have minimal cytokeratin 7 (CK7) staining and positive staining for cluster of differentiation 117 (CD117) while ChrRCCs will have positive CK7 and CD117 staining (*6*). Pathological differentiation is complicated by the existence of hybrid oncocytic/chromophobe tumours (HOCTs) that display both features of renal oncocytomas and ChrRCCs. There is no consensus on whether HOCTs are malignant or benign, and they can occur in 10-32% of cases (*2,3*). Due to challenges associated with imaging and pathological diagnosis, renal oncocytomas are frequently surgically resected, accounting for 73% of all surgically resected renal tumours (*2,3*). Resection of benign renal tumors should be avoided as it may be associated with post-surgical morbidity and can precipitate renal dysfunction in individuals with pre-existing borderline renal function.

A systematic review and meta-analysis by Wilson *et al*. (2020) suggests that technetium 99m sestamibi (99mTc-sestamibi) single-photon emission computed tomography (SPECT)/CT could differentiate renal oncocytomas versus malignant renal lesions with 86% (95% CI: 66–95%) sensitivity and 90% (95% CI: 80–95%) specificity when considering HOCTs malignant

(*4*). When considering HOCTs benign, 99mTc-sestamibi SPECT/CT identified renal oncocytomas and HOCTs vs malignant lesions with 88% sensitivity and 95% specificity (*4*). The ability to differentiate renal oncocytomas from other renal lesions on 99mTc-sestamibi SPECT/CT is attributed to the high density of mitochondria compared to other lesions and the tendency for lipophilic cations like sestamibi to accumulate in mitochondria due to their negatively charged inner membrane potential (*3*). Emerging research in CT radionomics also shows promise in differentiation of oncocytomas and ChrRCCs although more work will be needed prior to implementation in a clinical setting (*7*). Diffusion kurtosis tensor MR imaging has been shown to be able to differentiate different pathological types of renal cell carcinoma, but more work is needed to assess its ability to distinguish ChrRCCs from oncocytomas (*8*).

Using the findings of the systematic review and meta-analysis by Wilson *et al*., a review article published in 2022 proposed using 99mTc-sestamibi SPECT/CT in a diagnostic algorithm in managing enhancing 1–4 cm renal masses (*3*). Benign lesions such as suspected renal oncocytomas measuring 1–4 cm with positive radiotracer uptake (tumor-to-renal parenchyma ratio ≥ 0.6) could be managed with active surveillance while those with negative radiotracer uptake could be directed toward biopsy for further characterization (*3*). The ≤ 4 cm threshold was chosen based on evidence showing increased detection of small renal masses with only slight reduction in mortality (*3,9*). The 1 cm lower bound was chosen based on already existing American College of Radiology (ACR) guidelines for addressing completely characterized incidental renal masses without fat that are < 1 cm. We demonstrate how the proposed diagnostic algorithm using 99mTc-sestamibi SPECT/CT can be incorporated into the existing ACR diagnostic algorithm for a completely characterized incidental solid renal mass without fat (Figure 1) (*3,10*). Detailed descriptions of the original individual diagnostic algorithms can be found in their respective articles (*3,10*).

An asymptomatic 80-year-old male presented for bi-annual surveillance imaging with MRI post-treatment for uveal melanoma. Initial MRI without and with contrast of the abdomen and pelvis (Figure 2) demonstrated an 8.3 × 8.2 × 6.5 cm well-circumscribed, exophytic mass arising from the upper pole of the left kidney. The mass was heterogeneously T1 hypointense and heterogeneously T2 hyperintense with early arterial enhancement that is prolonged on portal-venous and delayed phase. The central stellate scar was T1 hypointense and T2 hyperintense with no enhancement. The suspected diagnosis was a benign renal oncocytoma. Implementing the proposed diagnostic algorithm for management of a completely characterized solid renal mass without fat (Figure 1), a solid mass measuring 8.3 cm requires

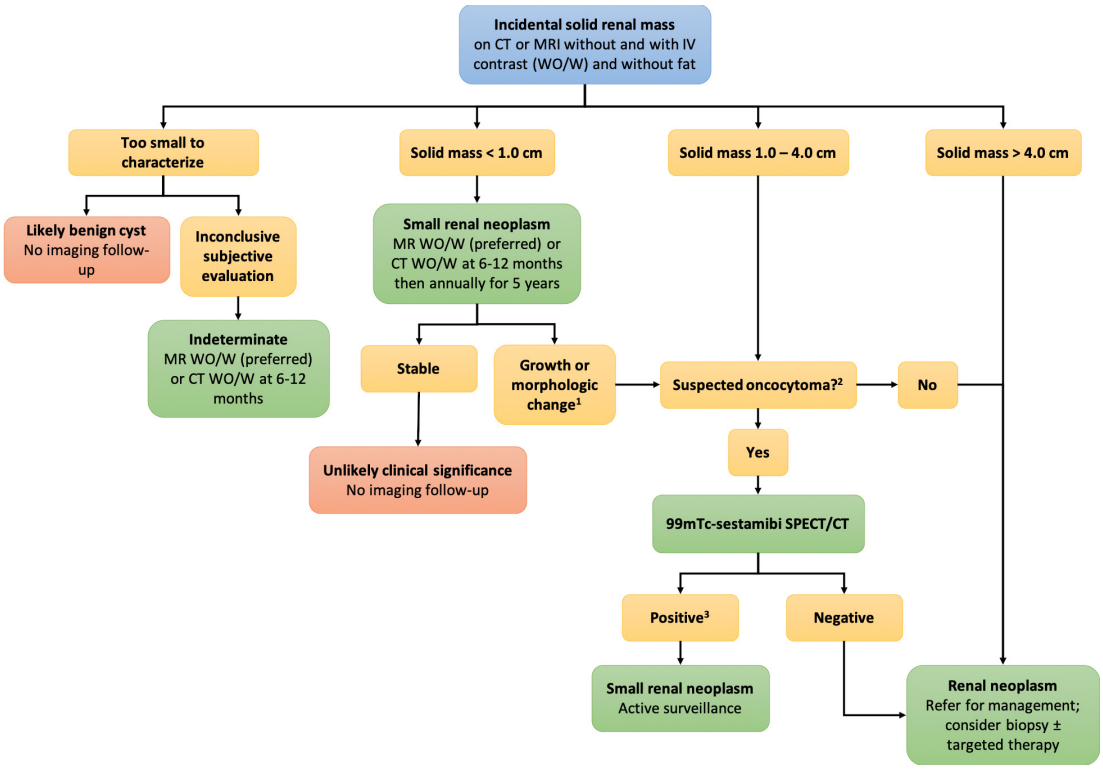


**Figure 1. Proposed diagnostic algorithm for a solid renal mass without fat that is completely characterized on CT or MRI without and with IV contrast that combines ACR guidelines with propose use of 99mTc-sestamibi SPECT/CT.** [1]Growth ≥ 4 mm per year or change in number of septa, contour, or attenuation; [2]Suspected renal oncocytoma based on classic imaging features such as a central stellate scar, low T1 signal, and high T2 signal; [3]A positive 99mTc-sestamibi SPECT/CT means a tumor-to-renal parenchymal ratio ≥ 0.6.

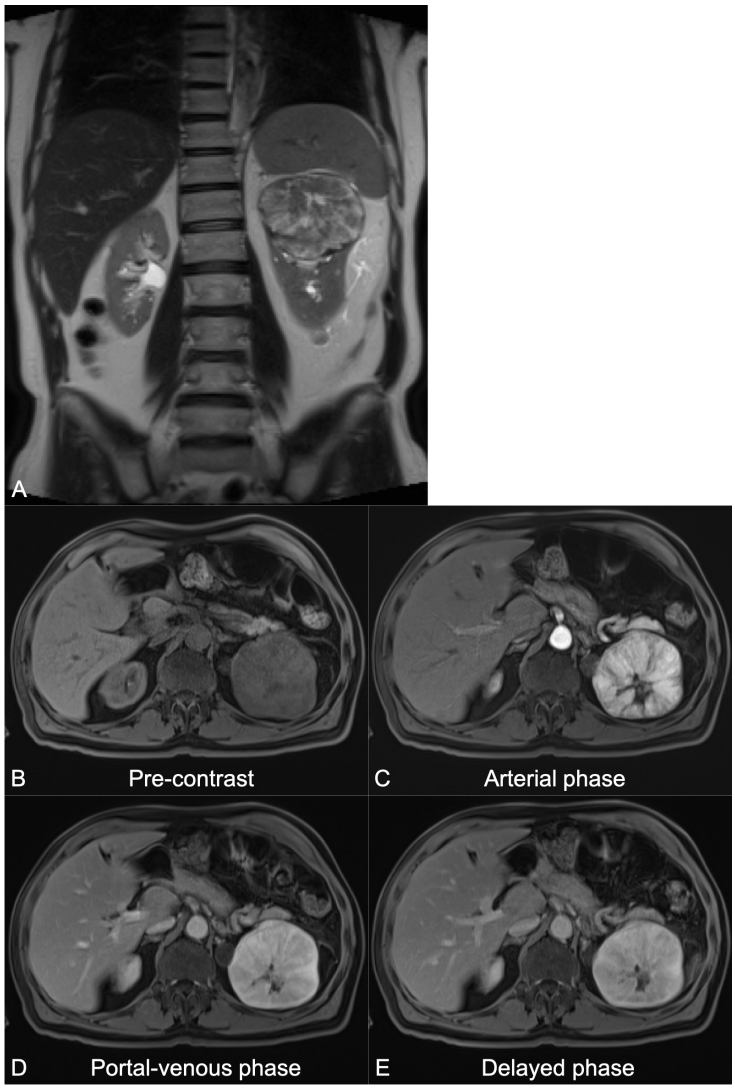


**Figure 2. MRI with and without contrast of the abdomen and pelvis showing a suspected renal oncocytoma in the upper pole of the left kidney. (A)** Coronal T2-weighted image; **(B)** Pre-contrast axial T1-weighted image; **(C)** Arterial phase (18 second post-contrast) axial T1-weighted image; **(D)** Portal-venous phase (2 minute post-contrast) axial T1-weighted image; **(E)** Delayed phase (5 minute post-contrast) axial T1-weighted image.

referral for management with consideration for biopsy. Urology was consulted and image-guided biopsy of the lesion for pathological diagnosis was recommended.

An ultrasound-guided left renal biopsy was performed and four kidney core samples were obtained and sent for pathologic diagnosis. On immunohistochemistry, the tumour showed negative CK7 staining and positive CD117 staining. The final diagnosis of the left kidney biopsy on the pathology report was an oncocytic renal neoplasm, favoring oncocytoma. The case was managed conservatively with reassessment of interval stability on his bi-annual MR surveillance for uveal melanoma.

We illustrated the previously proposed diagnostic algorithm using 99mTc-sestamibi SPECT/CT for differentiating benign versus malignant 1–4 cm renal masses in the context of the ACR guidelines for completely characterized solid renal masses without fat. It should be noted that this proposal is based on a single systematic review and meta-analysis consisting of 4 studies and 56 total patients. Validation of these results requires a larger sample size, and as a result, this has not been implemented in ACR guidelines. Hence, there is no current case managed using 99mTc-sestamibi SPECT/CT for active surveillance. However, we do present a case with classic features for a renal oncocytoma that when applied to the combined diagnostic algorithm, is appropriately directed toward referral with consideration for biopsy. If the proposed combined diagnostic algorithm is validated, a renal mass showing classic imaging features such as shown in our case but smaller and measuring 1-4 cm could be directed toward 99mTc-sestamibi SPECT/CT for further assessment. Early research (*3,4*) suggests that incorporating 99mTc-sestamibi SPECT/CT in assessing suspected renal oncocytomas could maintain high sensitivity and specificity in differentiating benign versus malignant renal lesions while reducing unnecessary invasive procedures.

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IRDR
Intractable & Rare Diseases Research

# Guide for Authors

**1. Scope of Articles**

***Intractable & Rare Diseases Research*** (Print ISSN 2186-3644, Online ISSN 2186-361X) is an international peer-reviewed journal. *Intractable & Rare Diseases Research* devotes to publishing the latest and most significant research in intractable and rare diseases. Articles cover all aspects of intractable and rare diseases research such as molecular biology, genetics, clinical diagnosis, prevention and treatment, epidemiology, health economics, health management, medical care system, and social science in order to encourage cooperation and exchange among scientists and clinical researchers.

**2. Submission Types**

**Original Articles** sshould be well-documented, novel, and significant to the field as a whole. An Original Article should be arranged into the following sections: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, and References. Original articles should not exceed 5,000 words in length (excluding references) and should be limited to a maximum of 50 references. Articles may contain a maximum of 10 figures and/or tables. Supplementary Data are permitted but should be limited to information that is not essential to the general understanding of the research presented in the main text, such as unaltered blots and source data as well as other file types.

**Brief Reports** definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 4 figures and/or tables and 30 references. A Brief Report contains the same sections as an Original Article, but the Results and Discussion sections should be combined.

**Reviews** should present a full and up-to-date account of recent developments within an area of research. Normally, reviews should not exceed 8,000 words in length (excluding references) and should be limited to a maximum of a maximum of 10 figures and/or tables and 100 references. Mini reviews are also accepted, which should not exceed 4,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 50 references.

**Policy Forum** articles discuss research and policy issues in areas related to life science such as public health, the medical care system, and social science and may address governmental issues at district, national, and international levels of discourse. Policy Forum articles should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references.

**Communications** are short, timely pieces that spotlight new research findings or policy issues of interest to the field of global health and medical practice that are of immediate importance. Depending on their content, Communications will be published as "Comments" or "Correspondence". Communications should not exceed 1,500 words in length (excluding references) and should be limited to a maximum of 2 figures and/or tables and 20 references.

**Editorials** are short, invited opinion pieces that discuss an issue of immediate importance to the fields of global health, medical practice, and basic science oriented for clinical application. Editorials should not exceed 1,000 words in length (excluding references) and should be limited to a maximum of 10 references. Editorials may contain one figure or table.

**News** articles should report the latest events in health sciences and medical research from around the world. News should not exceed 500 words in length.

**Letters** should present considered opinions in response to articles published in Intractable & Rare Diseases Research in the last 6 months or issues of general interest. Summaries of research results and sharing of experiences in clinical practice and basic research (findings based on case reports, clinical pictures, etc.) can also be published as Letters. Letters should not exceed 800 words in length and may contain a maximum of 10 references. Letters may contain one figure or table.

**3. Editorial Policies**

For publishing and ethical standards, *Intractable & Rare Diseases Research* follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals issued by the International Committee of Medical Journal Editors (ICMJE, *https://icmje.org/recommendations*), and the Principles of Transparency and Best Practice in Scholarly Publishing jointly issued by the Committee on Publication Ethics (COPE, *https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing*), the Directory of Open Access Journals (DOAJ, *https://doaj.org/apply/transparency*), the Open Access Scholarly Publishers Association (OASPA, *https://oaspa.org/principles-of-transparency-and-best-practice-in-scholarly-publishing-4*), and the World Association of Medical Editors (WAME, *https://wame.org/principles-of-transparency-and-best-practice-in-scholarly-publishing*).

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**Ethical Approval of Studies and Informed Consent:** For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section. When your manuscript contains any case details, personal information and/or images of patients or other individuals, authors must obtain appropriate written consent, permission and release in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. The consent form needs to comply with the relevant legal requirements of your particular jurisdiction, and please do not send signed consent form to *Intractable & Rare Diseases Research* to respect your patient's and any other individual's privacy. Please instead describe the information clearly in the Methods (patient consent) section of your manuscript while retaining copies of the signed forms in the event they should be needed. Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

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**Conflict of Interest:** All authors are required to disclose any actual or potential conflict of interest including financial interests or relationships with other people or organizations that might raise questions of bias in the work reported. If no conflict of interest exists for each author, please state "There is no conflict of interest to disclose".

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Inagaki Y, Tang W, Zhang L, Du GH, Xu WF, Kokudo N. Novel aminopeptidase N (APN/CD13) inhibitor 24F can suppress invasion of hepatocellular carcinoma cells as well as angiogenesis. Biosci Trends. 2010; 4:56-60.

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