Mini-Review

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Advances in research on congenital and hereditary intestinal diseases: From molecular mechanisms to precision medicine

Lichao Yang[1,2], Yu Wang[3], Lianwen Yuan[1], Wei Tang[2,*]

[1] Department of General Surgery, The Second Xiangya Hospital of Central South University, Changsha, China;
[2] National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;
[3] Department of Reproductive Medicine, The First Affiliated Hospital of Naval Medical University, Shanghai, China.

SUMMARY: Congenital and hereditary intestinal diseases are a group of major disorders caused by gene mutations or embryonic developmental anomalies and are characterized by diverse clinical manifestations and complex management. This review systematically explores the molecular genetic basis and pathogenic mechanisms of common intestinal diseases, including familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), Lynch syndrome (LS), Hirschsprung disease (HSCR), congenital short bowel syndrome (SBS), and cystic fibrosis (CF). It focuses on cross-disease commonalities in translational research frontiers such as gene-environment interactions, organoid-based precision medicine, the immune microenvironment, and metabolic and microbiome remodeling. The review also forecasts future directions, including gene therapy, targeted drugs, and other cutting-edge research advances.

Keywords: congenital intestinal diseases, hereditary gastrointestinal disorders, precision medicine, organoid models

1. Introduction

Congenital and hereditary intestinal diseases are key categories of conditions affecting human digestive health, and they are often closely related to key gene mutations, embryonic developmental abnormalities, or metabolic dysregulation (*1*). "Congenital" diseases typically refer to anatomical or functional abnormalities present at birth, stemming from disturbances during embryonic development. In contrast, "hereditary" diseases refer to pathological states caused by genetic material alterations (*e.g.,* DNA sequence mutations and chromosomal rearrangements) that may manifest at birth or later in life. Although distinct in definition, these two categories often overlap in clinical practice — some diseases have a clear genetic basis and also present clinical manifestations at birth. For instance, hereditary precancerous conditions caused by high-penetrance mutations, such as familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), and Lynch syndrome (LS) (*2*), typically develop in adolescence or early adulthood. In contrast, Hirschsprung disease (HSCR) and congenital short bowel syndrome (SBS) often present as structural or functional abnormalities in the neonatal period (*3*).

These diseases impact patients' lives long term and impose a psychological burden on patients and their families (*4*). On one hand, some diseases have high morbidity or mortality rates; on the other hand, their heterogeneity and complexity lead to difficulties in diagnosis, limited treatment options, and a long-term reliance on comprehensive medical interventions. Therefore, in-depth analysis of the molecular pathogenesis of these common congenital/hereditary intestinal diseases not only aids in understanding their pathophysiological basis but also provides theoretical support for developing precise diagnostic tools and targeted therapeutic strategies.

2. Disease-specific mechanisms

2.1. Hereditary polyposis and cancer syndromes

2.1.1. FAP

FAP is an autosomal dominant syndrome driven by germline mutations in the *APC* gene, with its core pathogenic mechanism being constitutive activation of the Wnt/β-catenin signaling pathway (*5*). Recent studies have shown that *APC* truncation mutants can mediate aberrant overexpression of METTL3, which impairs tumor immune surveillance by m6A methylation of HIF1α mRNA (*6*). Upregulation of translation control factors like eIF3a is considered an important cooperative mechanism for sustained Wnt pathway activation in FAP,

suggesting the therapeutic potential for interventions at the translational level (*7*). More importantly, research has confirmed that morphologically normal colon epithelium in FAP patients already exhibits metabolic reprogramming and monoclonal evolution, revealing the early basis for intestinal field cancerization and the widespread tendency for carcinogenesis (*8*). Epigenetic analyses have further confirmed that although DNA methylation changes are subtler compared to LS, genome-wide methylation dynamics are still an integral part of FAP tumorigenesis (*9*). These findings not only deepen the understanding of FAP carcinogenesis initiation but also highlight the value of epigenetic drugs and immunotherapy as potential combination strategies.

2.1.2. PJS

PJS is caused by germline mutations in the *STK11/LKB1* gene, with its molecular pathological core being dysregulation of the AMPK/mTOR signaling pathway and loss of apicobasal cell polarity (*10*) . The LKB1 protein encoded by *STK11* is a key upstream activator of AMP kinase; its functional inactivation releases inhibition of the mTORC1 pathway, aberrantly promoting cell growth. The latest research has revealed its downstream effects, including activation of the CRTC2-IL-17 signaling axis and overexpression of interleukin-11 in polyp-specific fibroblasts, providing potential new targets for targeted therapy (*11,12*).

2.1.3. LS

LS is a high-penetrance autosomal-dominant, hereditary cancer predisposition syndrome. Its molecular basis lies in germline mutations in key DNA mismatch repair (MMR) system genes (*13*). An MMR functional deficiency leads to a Microsatellite Instability-High (MSI-H) state, accompanied by extensive DNA methylation changes, collectively driving tumorigenesis (*9,14*). Research on its pathogenic network has expanded to broader aspects, including potential lipid metabolism dysregulation triggered by *MLH1* variants (*15*), epigenetic reprogramming by the histone methyltransferase EZH2 suppressing anti-tumor immunity (*16*), and the potential promoting role of specific gut microbes in colorectal cancer development (*17*). The molecular mechanism of LS is no longer limited to mutation accumulation mediated by dMMR, but presents a more complex collaborative pathological network across dimensions like epigenetics, metabolic rewiring, and gut microbiota.

2.2. Congenital intestinal structural/Neurodevelopmental abnormalities

2.2.1. HSCR

The primary cause of HSCR is the impaired migration, proliferation, or differentiation of enteric neural crest cells (ENCCs) during embryogenesis. Besides *RET* as the main causative gene (*18*), genome-wide association studies have identified multiple susceptibility loci including *JAG1* and *HAND2* (*19*). At the molecular level, secretagogin affects ENCC migration *via* Lymphoid Enhancer Factor-1 (*20*), while the histone methyltransferase SMYD2 regulates cell behavior by modulating METTL3 expression affecting m6A methylation levels, revealing the important role of epigenetic regulation in HSCR (*21*).

2.2.2. SBS

Congenital SBS can be caused by mutations in genes regulating intestinal development, such as *FOXF1* associated with intestinal malrotation, and *CLMP* and *FLNA*, which are closely related to intestinal length development (*22*). Recent studies have found that defects in the immunoglobulin-like cell adhesion protein *CLMP* and the smooth muscle cell proliferation key regulator *SNRK* are the genetic basis for a human congenital SBS-like pathology (*23*).

2.3. CF

CF is caused by mutations in the *CFTR* gene. Its core pathophysiology is defective chloride channel function leading to impaired epithelial ion transport and thickened mucus (*24,25*). In the intestinal system, besides mechanical obstruction, activation of inducible nitric oxide synthase in inflammatory cells produces excess nitric oxide, slowing intestinal motility and contributing to ileus (*26*). Due to the disease's characteristics, patients often have genotype-associated intestinal inflammation (*27*). Table 1 systematically summarizes the key genes, core mechanisms, clinical management, and research frontiers for these six major congenital and hereditary intestinal diseases.

3. Common translational frontiers and precision medicine platforms

3.1. Organoid models and precision medicine

Patient-derived intestinal organoid models provide a revolutionary platform for disease research and individualized therapy. In CF, the forskolin-induced swelling (FIS) assay based on organoids allows precise characterization of *CFTR* function and effectively predicts patient response to modulators (*28,29*). In FAP, these organoids can be used to model tumorigenesis processes and screen intervention strategies (*30-32*). For SBS, preclinical studies have confirmed that transplantation of ileum-derived organoids into the colon can restore absorptive function, providing proof-of-concept for regenerative medicine (*33*).

Table 1. Comparative summary of congenital and hereditary intestinal disorders: From genes to clinical translation

Disease	Key Gene(s)	Core Pathogenic Mechanism	Main Clinical Manifestations	Diagnostic Methods	Clinical Management	Research Hotspots & Advances	*Ref.*
Familial Adenomatous Polyposis (FAP)	*APC*	Constitutive activation of the Wnt/β-catenin signaling pathway, leading to uncontrolled cell proliferation.	Hundreds to thousands of colorectal adenomas, inevitable progression to CRC; elevated risk of duodenal/thyroid cancer.	Colonoscopy, *APC* genetic testing, upper endoscopy surveillance.	Prophylactic colectomy (IRA/IPAA); lifelong endoscopic surveillance.	Interception Therapy: Wnt inhibitors (PORCNi), *APC* vaccines, chemopreventive agents (HAMSB).	(*5,45*)
Peutz-Jeghers Syndrome (PJS)	*STK11/LKB1*	Dysregulation of AMPK/mTOR pathway and loss of cell polarity, leading to hamartomatous polyp formation.	GI hamartomatous polyps, mucocutaneous pigmentation; high risk of intussusception; significantly increased cancer risk in multiple organs.	Clinical criteria, *STK11* genetic testing, video capsule endoscopy/enteroscopy.	Endoscopic polypectomy to prevent intussusception; multi-system cancer screening.	Targeted Therapy: mTOR inhibitors (*e.g.,* Everolimus), IL-11 inhibitors; gut microbiota-metabolite modulation.	(*11,12*)
Lynch Syndrome (LS)	*MLH1, MSH2, MSH6, PMS2*	Defective DNA mismatch repair (dMMR), resulting in Microsatellite Instability-High (MSI-H) and accelerated tumorigenesis.	Early-onset colorectal cancer; high risk of extracolonic cancers (endometrial, gastric, urothelial, *etc.*).	Tumor MMR protein IHC, MSI testing, germline genetic testing.	Personalized colonoscopy surveillance; prophylactic surgery; genetic counseling and family testing.	Precision Immunotherapy: PD-1/PD-L1 inhibitors; Prevention: Neoantigen vaccines.	(*39,40*)
Hirschsprung Disease (HSCR)	*RET*	Impaired migration, proliferation, or differentiation of enteric neural crest cells, leading to aganglionosis in the distal gut.	Functional intestinal obstruction in neonates, abdominal distension, constipation; can be complicated by HAEC.	Rectal suction biopsy, contrast enema, *RET* genetic testing.	Surgical resection of the aganglionic segment (*e.g.,* Swenson, Duhamel procedures).	Regenerative Medicine: Stem cell/enteric neural crest cell transplantation; Complication Management: HAEC mechanism research, 5-HT agonists.	(*18,19*)
Short Bowel Syndrome (SBS)	*CLMP*	Massive intestinal resection or congenital maldevelopment, resulting in critically reduced absorptive surface area.	Severe diarrhea, steatorrhea, malnutrition, dependence on parenteral nutrition (PN).	Clinical presentation, imaging, surgical history, nutritional assessment.	Enteral/parenteral nutrition support, dietary management.	Enhancing Intestinal Adaptation: GLP-2 analogs (Teduglutide, Glepaglutide); Surgical Innovation: STEP/LILT procedures; Regenerative Medicine: Organoid transplantation.	(*22,23*)
Cystic Fibrosis (CF)	*CFTR*	Dysfunctional *CFTR* chloride channel, leading to thick, dehydrated secretions and ductal obstructions.	Chronic lung disease, pancreatic insufficiency (steatorrhea), meconium ileus, malnutrition.	Sweat chloride test, *CFTR* genetic testing, newborn screening.	Lifelong multidisciplinary care (pulmonary, GI, nutrition); pancreatic enzyme replacement.	*CFTR* Modulator Therapy: Correctors/potentiators (*e.g.,* ETI triple therapy); Personalized Prediction: Organoid-based drug testing (FIS assay).	(*24,25*)

3.2. Microbiome and metabolic remodeling

The gut microbiome and its metabolites play crucial roles in disease progression. PJS patients exhibit gut microbiota dysbiosis characterized by enrichment of Veillonellaceae bacteria and reduced synthesis of short-chain fatty acids (SCFAs); levels of these metabolites negatively correlate with polyp burden (*34,35*). In LS, colibactin-producing Escherichia coli is associated with the risk of metachronous colorectal cancer and adenoma development (*17*). Moreover, the gut microbiota remodeling effects demonstrated by *CFTR* modulators and GLP-2 analogs in treating their respective diseases suggest the therapeutic potential of microecological intervention (*36,37*). Figure 1 illustrates the complex interactions between the microbiome, metabolism, and the immune system — a network shared as a pathological basis by many hereditary intestinal diseases.

3.3. Tumor immune microenvironment and immunotherapy

In-depth analysis of the immune microenvironment in precancerous lesions has laid the foundation for immune intervention. The immune signature of PJS polyps resembles that of colorectal cancer tissue, suggesting active immune editing (*38*). LS-associated dMMR/MSI-H tumors are highly sensitive to immune checkpoint inhibitors, marking the advent an era of precision immunotherapy (*39*). The highly expressed frameshift-derived neopeptides in this syndrome provide promising targets for preventive vaccine development (*40*). These findings collectively indicate that the timing for immune intervention could be significantly advanced to the precancerous stage, providing a rationale for 'interception therapy' for hereditary cancers.

3.4. Early detection and risk stratification strategies

Advances in endoscopic monitoring have significantly improved the detection rate of early lesions. For example, linked color imaging and chromoendoscopy can significantly enhance the identification of neoplastic lesions in LS (*41*). Genotype-based individualized monitoring schemes have become standard practice; for instance, colonoscopy screening intervals can be tailored based on the specific MMR gene mutation, which is a strategy that has proven cost-effective (*42*). Figure 2 systematically illustrates this integrated pathway: from initial genetic diagnosis to treatment plan validation based on functional platforms like organoids, culminating in dynamically optimized long-term comprehensive management.

4. Directions for future research

4.1. Gene editing and precision genomic medicine

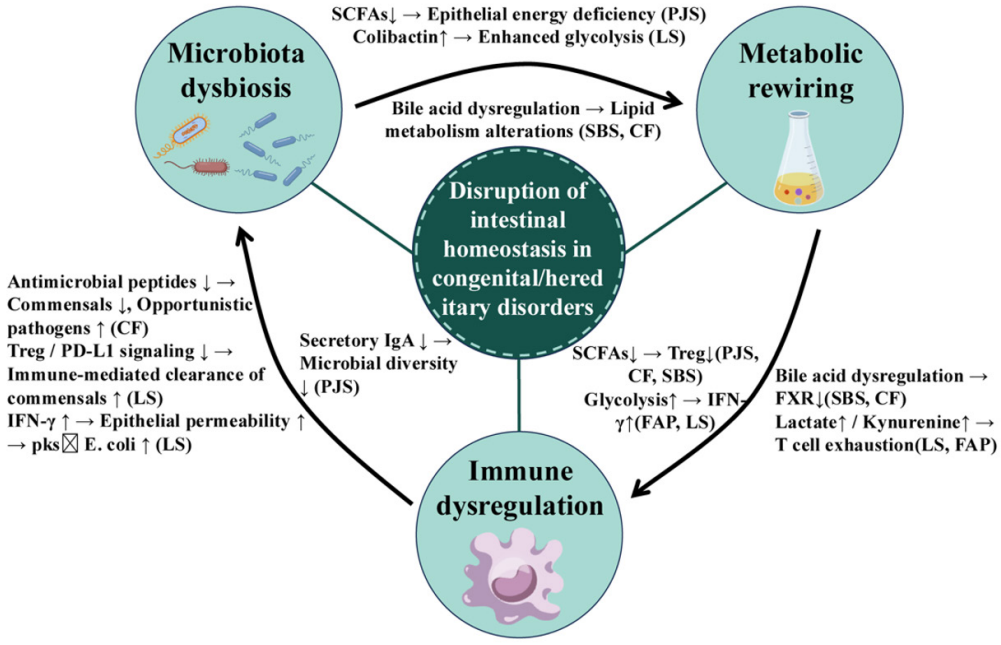

Figure 1. The core microbiota-metabolism-immune interactome in hereditary intestinal disorders. This diagram summarizes a shared pathophysiological network across different diseases. Microbiota Dysbiosis (*e.g.,* SCFA reduction in PJS, colibactin-producing E. coli expansion in LS) drives Metabolic Rewiring, which in turn shapes Immune Dysregulation (*e.g.,* Treg suppression and IFN-γ upregulation). Conversely, immune alterations reciprocally impact the microbiota *via* factors like antimicrobial peptides and secretory IgA. The dynamic interplay between these three core components creates a self-reinforcing cycle that ultimately leads to a Disruption of Intestinal Homeostasis, manifesting as impaired epithelial barrier function, chronic inflammation, and aberrant proliferation. Disease-specific examples (PJS, LS, FAP, CF, and SBS) of validated interactions are annotated. Arrows indicate the direction of "leads to" or "promotes".

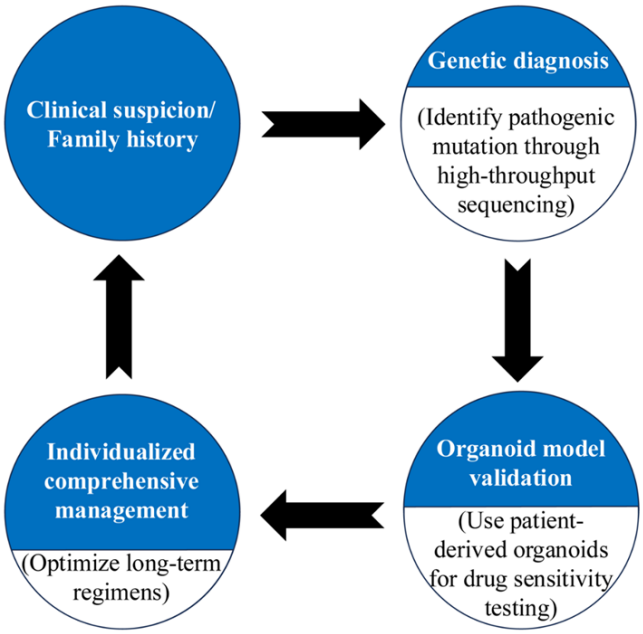

Figure 2. A clinical pathway for precision medicine for congenital and hereditary intestinal diseases. This schematic outlines an integrated, closed-loop pathway from clinical suspicion to individualized management. The journey begins with Clinical Suspicion/Family History, leading to a definitive Genetic Diagnosis through high-throughput sequencing. The pathway then integrates Multi-omic Risk Stratification and functional validation using Organoid Models (*e.g.*, drug sensitivity testing) to inform Individualized Comprehensive Management strategies, including targeted therapies, endoscopic surveillance, surgery, and nutritional support. This framework facilitates long-term, dynamically optimized care, representing a paradigm shift from fragmented interventions to a unified, proactive model of precision medicine.

Gene editing technologies like CRISPR hold promise for curing monogenic hereditary diseases. Future research needs to focus on developing efficient and safe *in vivo* delivery systems to correct pathogenic mutations in somatic cells, *e.g.,* repairing *CFTR* gene function in CF patients or correcting pathogenic variants in key genes like *RET* causing HSCR (*43,44*). The core bottlenecks for clinical translation are: the lack of efficient and safe *in vivo* delivery systems, urgently requiring development of novel vectors targeting epithelia of multiple organs like the gut and lungs; and the verification of long-term safety and controllability, necessitating thorough evaluation of off-target effects and immunogenicity in relevant animal models.

4.2. Immune prevention and neoantigen vaccines

Immune prevention for hereditary cancer syndromes is a highly promising direction. The abundant neoantigens generated by frameshift mutations in LS are ideal targets for developing preventive vaccines (*40*). Similarly, *APC* interception vaccines for FAP have entered the proof-of-concept stage and are intended to stimulate the immune system to clear early lesions expressing mutant APC protein (*45*). The key future challenge lies in overcoming the immune-tolerant microenvironment of precancerous lesions and verifying whether the immune response elicited by a vaccine can provide durable, broad tissue protection in long-term follow-up, thereby effectively preventing multi-organ tumors.

4.3. Regenerative medicine and tissue engineering

For structural or functional deficiency diseases, regenerative medicine aims to achieve fundamental functional reconstruction. In HSCR, the research focus is on how to reconstruct a functional enteric nervous system in the aganglionic segment through stem cell/enteric neural crest cell transplantation (*46*). For SBS, using organoid tissue engineering technology to construct bioengineered intestine with absorptive function is one ultimate solution for intestinal failure (*33*). Achieving these goals requires overcoming major challenges such as cell sources and functional integration post-transplantation (*e.g.,* neural connection and vascularization).

4.4. Microbiome engineering and metabolic intervention

As the role of the gut microbiome in disease progression becomes clearer, its precise modulation will become an important adjunct treatment strategy (*47*). Future approaches may involve designing synthetic microbial communities or engineered bacteria to supplement SCFAs deficient in PJS patients, degrading potential carcinogens in the LS gut, or modulating CF-associated intestinal inflammation (*17,35,48*). Current research is mostly still at the level of describing correlations between microbiota and disease. In the future, research must move towards causal mechanism verification and, based on this, it must design synthetic microbial communities

or engineered bacteria capable of targeted colonization and on-demand secretion of specific metabolites (*e.g.,* supplementing SCFAs deficient in PJS), achieving precise and dynamic remodeling of the gut microecology.

4.5. Multi-omics integration and artificial intelligence (AI)-driven precision management

Utilizing multi-omics data and AI technology to build computational models capable of ultra-early warning, individualized prognosis prediction, and dynamic treatment adjustment is an inevitable trend in the future (*1,49*). The key challenges in this direction are the standardization and sharing of multi-center, multi-omics data and the development of next-generation AI algorithms that can interpret high-dimensional complex biological networks, rather than merely identifying associations.

5. Conclusion

In recent years, research on common congenital and hereditary intestinal diseases has been undergoing a transition from a "single-gene model" to a "systems biology framework", integrating multi-level networks like immunity, metabolism, and the microbiome, thereby enhancing the ability to explain phenotypic complexity. The understanding of disease mechanisms has also expanded from local intestinal pathology to dynamic coupling between multiple organs and the tumor microenvironment, revealing broader intervention windows. Organoid models are being heavily integrated with AI algorithms and high-throughput screening technologies, creating new platforms for precision medicine and individualized therapy. At the same time, the management of long-term complications from the neonatal period to adulthood has promoted the clinical implementation of the "whole-life-cycle care" concept. Overall, future research and clinical pathways for these intestinal diseases will accelerate towards multi-omics integration, automated screening, intelligent intervention, and dynamic health prediction.

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**Address correspondence to:*
Wei Tang, International Health Care Center, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo 162-8655, Japan.
E-mail: politang-tky@umin.ac.jp