Review

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Systematic review of phenotypes and genotypes of patients with gastrointestinal defects and immunodeficiency syndrome-1 (GIDID1) (related to TTC7A)

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SUMMARY The objective was to conduct a comprehensive review of the morbidity and mortality observed in published patients with gastrointestinal defects and immunodeficiency syndrome-1 (GIDID1) related to TTC7A abnormalities. This included phenotypic, genotypic, and therapeutic aspects. Twenty-seven articles were included, which represented a total of 83 patients. Mortality was of 65.8% of the cases with a mean death at 11.8 months. The mortality rate was 197.1 per 1,000 patients-years, which is significantly higher than other enteropathy types caused by defects in epithelial trafficking and polarity (such as *MOY5B, STX3, EPCAM, SPINT2, TTC37* and *SKIV2L*). Prematurity was also significant, with an average gestational age of 34.8 weeks. Antenatal signs were observed in 30 patients, including 14 cases of hydramnios. Three distinct phenotypic associations were identified: immune deficiency and multiple intestinal atresia without enteropathy (ID/MI), immune deficiency and enteropathy without atresia (ID/E), and immune deficiency with multiple intestinal atresia and enteropathy (ID/MIA/E). The mortality rates for these groups were 91.6%, 47.3% and 55.5%, respectively ($p = 0.03$), at earlier age of mortality for the ID/MIA phenotype and a later one for the ID/E phenotype. ELA syndrome (Enteropathy, Lymphopenia and Alopecia) was only observed in the ID/E group. Among the three genotypes (double variant Nonsense NS/NS, variant Missense/Nonsense MS/NS, double variant Missense MS/MS), NS/NS was significantly associated with the ID/MIA phenotype (77.8%), while MS/MS was associated with the ID/E phenotype (73.7%). Few therapies have been shown to be effective in treating enteropathy, particularly immunosuppressive therapies and hematopoietic stem cell transplants. The use of Leflunomide in one patient did not yield successful treatment outcomes. In conclusion, we confirm association between mortality and phenotype, which is itself linked to genotype.

Keywords gastrointestinal defect and immunodeficiency-1, TTC7A, immune deficiency, enteropathy, intestinal atresia

1. Introduction

Gastrointestinal defects and immunodeficiency syndrome-1 (GIDID1) is a clinical condition that has been described since 1974 (*1*). It was initially characterized by the presence of multiple intestinal atresias in the context of consanguinity. However, it wasn't until 2013 that GIDID1 was specifically associated with an abnormality oh the TTC7A gene located on chromosome 2p21 (OMIM: 243150). This condition is inherited in an autosomal-recessive manner and can lead to both intestinal abnormalities such as apoptotic enterocolitis, multiple intestinal atresias, recurrent intestinal strictures (*2*), as well as immune deficiencies (*3*). Pathophysiologically, the loss function in the TPR domain results in abnormalities in protein interactions and transcription (*3-5*). In enterocytes, this leads to disruptions in apicobasal polarization due to the absence of regulatory control over the RhoA signaling pathway (*6*). In T cells, it impairs their proliferation,

adhesion, and migration capabilities within the thymus (*7*). These factors contribute to a state of continuous apoptotic enteropathy and lymphocyte depletion, resulting in reverse bipolarity (*8*).

The prognosis for individuals with this condition is extremely severe, with an elevated early mortality rate. In fact, more than half of children succumb to the disease before reaching their first year of life (*9*). GIDID1 remains a rare disorder, usually only documented in case reports or small series.

The objective of this study is to conduct a systematic review of published cases to provide insights into the various phenotypes and their evolution, the effectiveness of different therapeutic approaches, the correlation between phenotype and genotype, and the association with morbidity and mortality.

2. Systematic Review

We conducted a systematic review of published case involving patients with GIDID1. The search was conducted following the PRISMA methodology on NCBI, using the keywords "tetratricopeptide repeat domain 7A" and "TTC7A". The most recent search was conducted in July 2023. Articles containing clinical data were included, while those lacking phenotypic or genotypic information were excluded. For each patient, information on sex, antenatal manifestations, and anthropometric data at birth, clinical course, and therapies administered and their effectiveness, mutations, type of pathogenic variant, as well as morbidity and mortality, were collected.

The type of immune deficiency has been defined as follows (*10*):

i) CVID (Common Variable Immune Deficiency): Characterized by age-related hypogammaglobulinemia, with may be associated with normal or decreased circulating B cell counts, co-activation defects, or defects in B cell survival.

ii) CID (Combined Immune Deficiency): Defined by CD3 T-cell lymphopenia of less than 1000/µL before 2 years of age, less than 800/µL between 2 and 4 years of age, or less than 600/µL after 4 years. Il also includes lymphocyte proliferation capacity less than 30% of normal.

iii) SCID-Like (Severe Combined Immunodeficiency): Characterized by CD3 T-cell lymphopenia of less than 300/µL and lymphocyte proliferation capacity less than 10% of normal as measured by the PHA test. "SCID-Like" is preferred to the term "SCID" to distinguish it from primary SCID, which is not associated with gastrointestinal enteropathy.

Enteropathy was defined as diarrhea with more than 7 daily episodes persisting for more than 2 weeks, often presenting with bloody diarrhea (*11*).

Genotypes were categorized as homozygous or composite heterozygous, and based on their consequences on the protein, they were classified as Nonsense (NS) (indicating loss of function due to gain arrest, insertion, deletion, frame shift, splicing site, or long deletion) or Missense (MS).

The statistical analyses were carried out using the BiostatTGV software.

3. Main Findings

A total of 58 articles were identified, and 27 were included, encompassing a total of 83 patients (Prisma Flow Chart SI). Articles lacking phenotypic or genotypic information were excluded. Among these patients, 74 had pathogenic variations missense or nonsense in *TTC7A*, while the remaining 8 were siblings of affected individuals, exhibiting a concordant phenotypic presentation (*6,12*), and one had an in-frame long deletion mutation in exon 1 (c.133_154del) resulting in p.(Gly45_Ala55del), which could not be classified as either missense or nonsense variant. The sex ratio was approximately equal, and inbreeding was observed in 40.9% of cases, significantly more often associated with the ID/E phenotype ($p = 0.001$) (Table 1). The average follow-up period was 40.5 months, with the longest follow-up extending to 50 years, particularly for the ID/E phenotype.

3.1. Prematurity and antenatal signs

Prematurity was observed in 85.7% of cases, with an average gestational age of 34.8 weeks, often accompanied by eutrophic parameters. No significant differences were observed in terms of birth gestational age among different phenotypes (Figure 1). Antenatal signs were described in 30 patients, including 19 cases of intestinal dilatation/atresia, 14 cases of hydramnios/polyhydramnios, and 10 cases of intraluminal calcification. There was no significant difference between prematurity and the presence of hydramnios when compared to other antenatal signs. Similarly, there was no significant difference in prematurity between those who exhibited antenatal signs and those who did not.

3.2. Clinical description

Clinically, this condition manifested itself as early-onset diarrhea, with an average onset at an age of 8.6 months, with 32 cases considered. Digestive atresia could be located anywhere from the stomach to the anus, as specified in 45 cases, with a predominant occurrence in the small intestine (62.2%), followed by the colon (37.8%), leading to microcolon formation in 15.5% of cases, and in the pyloric stomach (35.5%) (Figure 2). These atresias were observed as both single in 4 cases (pyloric, ileum, anus) and as multiple occurrences in 41 cases (91.1%). Subsequent anatopathological studies

Table 1. Epidemiological and clinical description of patients with GIDID1 whole cohort and according to the 3 most common phenotypic combinations

Items	TOTAL *n* = 83	Combinations of phenotypes*			*p*
		ID/MIA *n* = 12	ID/E *n* = 19	ID/MIA/E *n* = 21	
Epidemiology					
Male / Female	40/35	7/4	10/9	6/12	0.24
Consanguinity: Y/N (%)	27/39 (40.9)	2/10 (16.7%)	14/4 (77.7%)	3/15 (16.7%)	0.0001
Age at last eval. in month	40.5	17.6	91.3	42.5	0.036
(range, *n*)	(0.03-600, *n* = 78)	(0.2-96, *n* = 12)	(5- 600, *n* = 19)	(1.2-228, *n* = 20)	
Dead/Alive	52/27 (65.8%)	11/1 (91.6%)	9/10 (47.3%)	11/9 (55.5%)	0.036
Death rate per 1000 patients-year	197.1	625.6	62.2	155.5	NA
Age at death in month	11.8	10.5	34.7	12.6	0.18
(range, *n*)	(0.06-168, *n* = 51)	(0.2-46, *n* = 11)	(5.6-168, *n* = 9)	(1.2-41, *n* = 11)	
Birth auxological data					
Birth weight percentil	31.7	22.5	39.3	35	0.89
(range, *n*)	(1.06-88, *n* = 12)	(1.06-44, *n* = 2)	(39-40, *n* = 3)	(20-50, *n* = 2)	
IUGR: weight < 10th percentil (*n*)	4 (*n* = 12)	1 (*n* = 2)	0	0	NA
Birth size percentil	21.8	38	20	26.3	NA
(range, *n*)	(0.7-50, *n* = 9)	(*n* = 1)	(*n* = 1)	(2.5-50, *n* = 2)	
IUGR: size < 10th percentile (*n*)	3 (*n* = 9)	0	0	1 (*n* = 2)	NA
Mean birth term	34.8	34.6	35.6	35	0.46
(range in weeks, *n*)	(23-40, *n* = 28)	(32-38, *n* = 3)	(35-36, *n* = 3)	(33-39, *n* = 9)	
Prematurity: Y/N	24/4 (85.7%)	2/1 (66.7%)	3/0 (100%)	8/1 (88.8%)	0.46
(mean, range in weeks)	(34, 23-36)	(33, 32-34)	(35, 35-36)	(34, 33-36)	
ID					
Total: Y/N	62/3 (95.4%)	12 (100%)	19 (100%)	21 (100%)	NA
Type ID					
CVID (Y%)	22 (35.5%)	2 (16.7%)	11 (57.9%)	7 (33.3%)	
CID (Y%)	14 (22.5%)	3 (25%)	8 (42.1%)	0	< 0.0001
SCID-Like (Y%)	26 (42%)	7 (58.3%)	0	14 (66.7%)	
Parenteral Nutrition					
Y/N (Y%)	49/4 (92.4%)	9/0 (100%)	9/4 (69.2%)	18/0 (100%)	0.009
Age at PN start	2,6	2,2	0,9	3,5	0.43
(range, *n*)	(0.03-7, *n* = 19)	(0.03-7, *n* = 5)	(0.3-1.4, *n* = 3)	(0.03-6, *n* = 10)	
Weaning: Y/N (Y%)	2/49 (3.9%)	0/8 (0%)	0/9 (0%)	1/13 (7.1%)	0.51
Age at weaning month	24	-	-	24	NA
(range, *n*)	(24, *n* = 1)			(*n* = 1)	
Treatments					
Surgery: Y/N (Y%)	34/2 (94.4%)	8/0 (100%)	0/2 (0%)	18/0 (100%)	0.003
HSCT: Y/N (Y%)	13/63 (17.1%)	2/10 (16.7%)	2/17 (10.5%)	8/13 (38.1%)	0.10
Efficiency HSCT: Y/N (Y%)	6/7 (46.1%)	0/2	0/2	5/3 (62.5%)	0.36

*Phenotype combinations are described in only 52 patients despite a total cohort of 83 patients.

confirmed the presence of apoptotic enterocolitis. Immune deficiency was present in 95.4% of cases and, on average, was diagnosed at an age of 18.4 months (as specified in a 54 cases).

The clinical course was characterized by recurrent atresias, which were described in 13 cases (*3-6,12-15*), recurrent infections in 37 cases, ELA syndrome (enteropathy, lymphopenia and alopecia) emerging from 2 years of age in 5 cases (*7,16,17*), and autoimmune diseases appearing in 12 cases at an average age of 3 years. The auto-immune conditions included auto immune thyroiditis (*n* = 1), auto-immune hemolytic anemia (*n* = 1), psoriasis (*n* = 1), type 1 diabetes (*n* = 2), auto-immune dermatitis (*n* = 1), auto-immune hepatitis (*n* = 1) and auto-immune gastritis (*n* = 1) or enteric (*n* = 3) (*7, 18-22*).

3.3. The three distinct phenotypes

Based on data from 55 patients and considering the three primary signs (multiple intestinal atresia, immune deficiency, enteropathy), three distinct phenotypic combinations were identified (Figure 3): immune deficiency and multiple intestinal atresia without enteropathy (ID/MIA), immune deficiency and enteropathy without atresia (ID/E), immune deficiency, multiple intestinal atresia and enteropathy (ID/MIA/E), with proportions 21.8%, 34.5% and 38.1%, respectively (more details provided in Table 1). Regarding genotypes, 63% were homozygous, with a notable prevalence of double missense (MS) variant mutations with phenotype ID/E ($p < 0.001$) (Table 2).

3.4. Clinical management

Parenteral nutrition (PN) was initiated in 92.4% of the cases (specified in a 51 cases), at an average age of 2.6

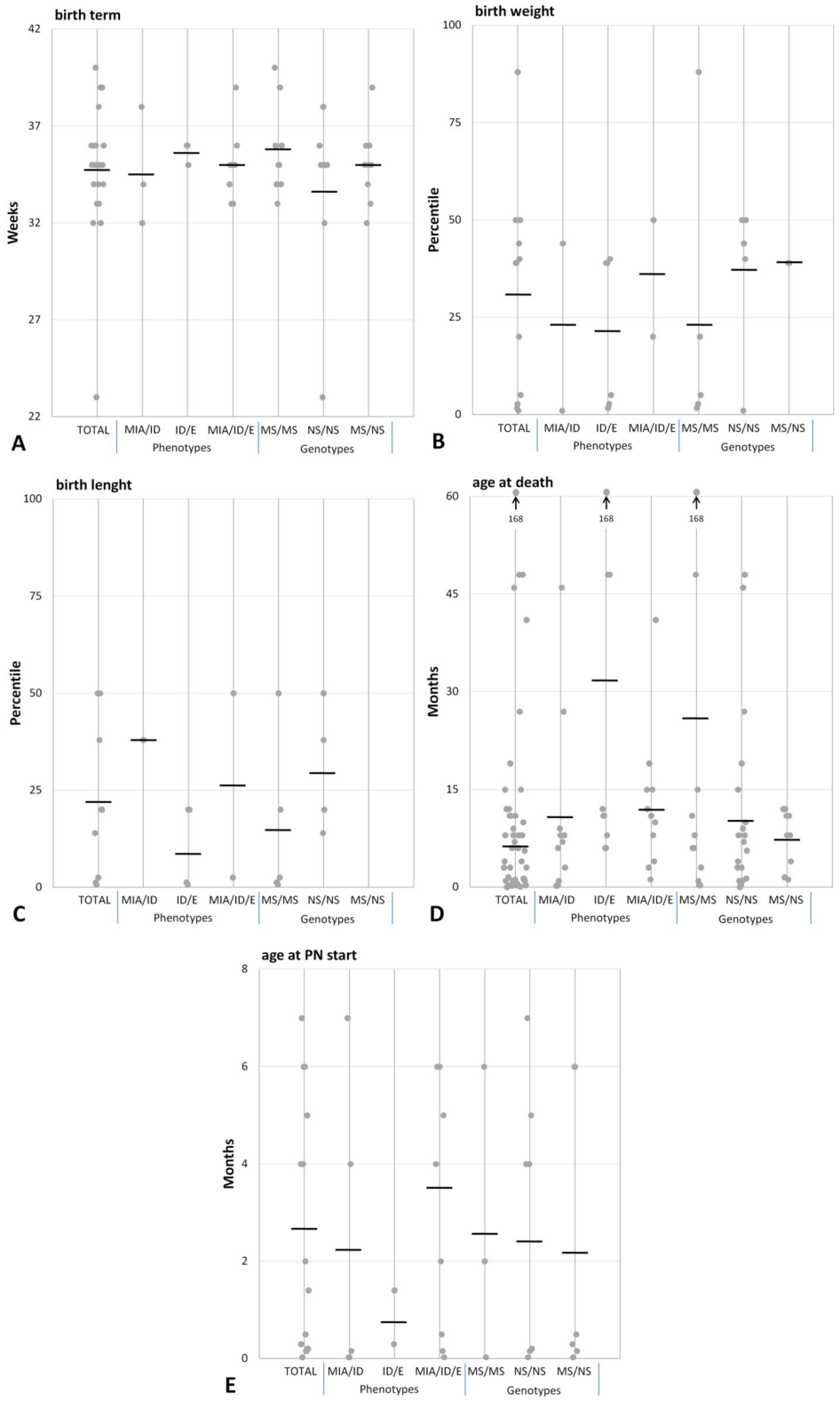

Figure 1. Median for term (A), birth weight (B) and height (C), age at death (D), and age at onset and end of parenteral nutrition (PN) (E) as a function of genotypes and phenotypes of patients with GIDID1.

months, and was successfully discontinued in only 2 cases, at 24 months in one case. The initiation of PN was early in cases of digestive atresia and delayed in cases without digestive atresia.

Immunosuppressants, such as corticosteroids, azathioprine or anti-TNF-alpha drugs, were used in 15 cases (*4,5,11,12,23,24*). They were found to be effective in alleviating diarrhea in only 2 cases using corticosteroids, azathioprine and anti TNF-alpha (*5,24*).

One case of severe pruritus at 3 years of age proved unresponsive to multiple therapies including corticosteroids, histamine blockers, gabapentin,

clonidine, mirtazapine, amitriptyline, and mepolizumab (anti-IL5). It could be successfully treated with Dupilumab (anti-IL4) at the dosage of 100 mg subcutaneously every 2 weeks (*22*).

Hematopoietic Stem Cell Transplantation (HSCT) was performed in 13 cases, with a median age of 8.6 months, resulting in an extension of survival in 5 cases (38.5%) (*3,4,6,7,12,14,17,18*). No intestinal/liver transplants were performed successfully ($n = 1$) (*17*).

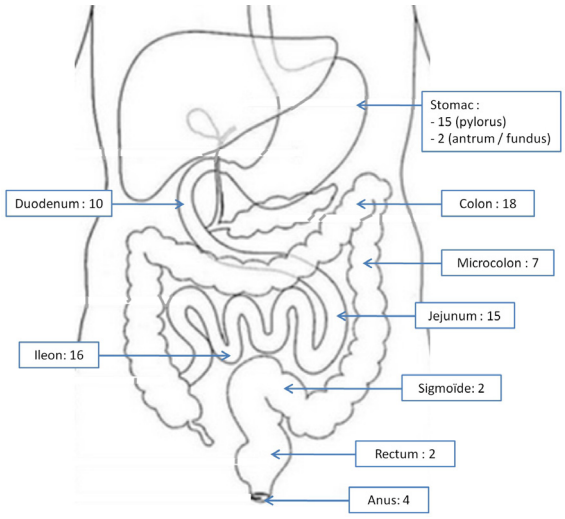

Figure 2. Affected digestive segments in MIA of patients with GIDID1 ($n = 45$), of whom 41 have multiple atresias, and 4 have single (1 pylorus, 1 ileum, 2 anus).

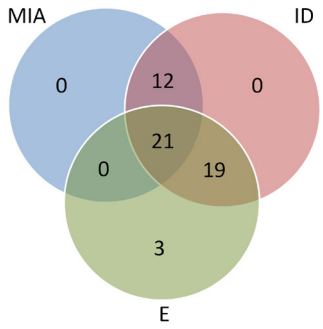

Figure 3. Venn diagram of the 3 combinations most common phenotypic results of patients with GIDID1 ($n = 55$).

Treatment with Leflunomide, initiated at 4 months of age, was found to be ineffective (*25*).

3.5. Mortality

Mortality was recorded at 65.8%, with a mean age at the time of death being 11.8 months. It was notably severe and occurred early, with 82.3% of the cases resulting in death before the age of 12 months ($p < 0.05$). The mortality rate was 197.1 per 1,000 patients-years (Table 3). The survival curve based on the most frequent phenotypic associations revealed that the rates for these groups were 91.6%, 47.3%, and 55.5%, respectively ($p = 0.03$), with an earlier mortality age for the ID/MIA phenotype and a later one for the ID/E phenotype (Figure 1, Figure 4, and Table 1). The causes of mortality were provided for 35 cases. The primary cause was infectious

Table 3. Death rate per 1000 patients-year of enteropathy caused by defect of epithelial trafficking and polarity (MYO5B, STX3, EPCAM, SPINT2, TTC37, SKIV2L and TTC7A) or by enteroendocrine cell dysfunction (PCSK1 and NEUROG3), and smooth muscle disorders (ACTG2, MYH11, FLNA, RAD21)

Gene	Death reppored	Total patients described	Death/year of follow up for 1,000
STX3	0	3	0
FLNA	0	7	0
MYH11	2	16	3.52
RAD21	1	3	11.6
ACTG2	20	65	13.5
EPCAM	11	71	15
NEUROG3	2	14	13.9
SKIV2L	2	12	24.1
PCSK1	5	32	22.8
TTC37	8	36	52.3
MYO5B	12	43	53.1
SPINT2	14	35	76.5
TTC7A	52	79	197.1
TTC7A ID/MIA	11	12	625.6
TTC7A ID/E	9	19	62.2
TTC7A ID/MIA/E	11	20	155.5
TTC7A MS/NS	9	17	340.7
TTC7A NS/NS	23	25	784.1
TTC7A MS/MS	12	28	61.1

Data from this study, 32 and 33. Detail according phenotype and variant combination for TTC7A.

Table 2. Genetic phenotypic description of patients with GIDID1 whole cohort and according to the 3 most common phenotypic combinations

Items	Total $n = 84$	Combinations of phenotypes*			p
		ID/MIA $n = 9$	ID/E $n = 19$	ID/MIA/E $n = 21$	
Homozygous	53 (63%)	4 (44.4%)	12 (63.1%)	4* (20%)	0.020
Composite heterozygous	31 (37%)	5 (55.5%)	7 (36.9%)	16* (80%)	
MS/NS	17 (20.2%)	1 (11.1%)	3 (15.8%)	9* (45%)	0.0007
NS/NS	28 (33.3%)	7 (77.8%)	2 (10.5%)	5* (25%)	
MS/MS	39 (46.4%)	1 (11.1%)	14 (73.7%)	6* (30%)	

*Mutations are described in only 50 patients despite a total cohort of 83 patients. Moreover, it was not possible to define variant type for 2 cases (*18*).

diseases (n = 14, 40%), followed by post-therapeutic complications (n = 8, 22.9%), occlusive issues (n = 7, 20%), and liver pathologies (liver failure and portal hypertension) in 4 cases, with 3 of them requiring parenteral nutrition. Finally, 2 cases (5.7%) were attributed to enteropathy. Deaths due to post-therapeutic complications occurred after hematopoietic stem cell transplantation (HSCT) in 8 out of 13 HSCT procedures performed. The survival curve based on genotypes (Figures 5 and 6) revealed a poor prognosis for patients with double NS variant, with over 77% of them passing away before the age of 10 months, and 92% of patients succumbing by the end of the follow-up period, at the latest, by 96 months.

3.6. Subgroup comparison

When the groups were compared, significant differences were observed. A notable difference in mortality was observed, with early severity in combinations involving gastrointestinal atresia (p < 0,05), particularly the ID/MIA combination, which exhibited severe mortality (91.6%) and an average age of death of 10.5 months (Table 1). This combination was more frequently associated with double NS variant (p < 0.001). The follow-up duration was longer for ID/E, with an average of 91.3 months (p < 0.05), and this phenotype showed a later age of death (p < 0.05). Inbreeding was significantly associated with the ID/E phenotype (p = 0.001), as well as ELA syndrome, which was exclusively present in this phenotypic combination, occurring in 3 families and encompassing a total of 5 cases (*7,16,17*). In 4 cases, these individuals also presented with onychopathies, such as distal sub-ungual hyperkeratosis of the nails (*7,16,17*). In ELA syndrome, enteropathy typically emerged within a few days of life, followed by lymphopenia between

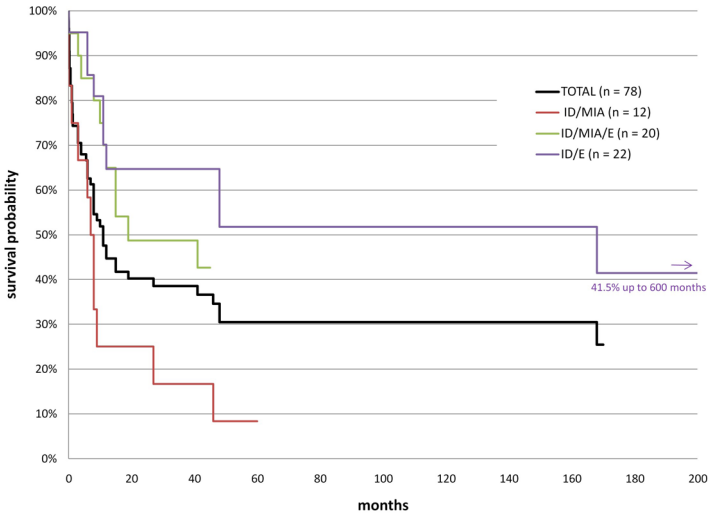

Figure 4. Survival curve of patients with GIDID1 as a function of all cases (n = 78) and the 3 most frequent phenotypic combinations (n = 54).

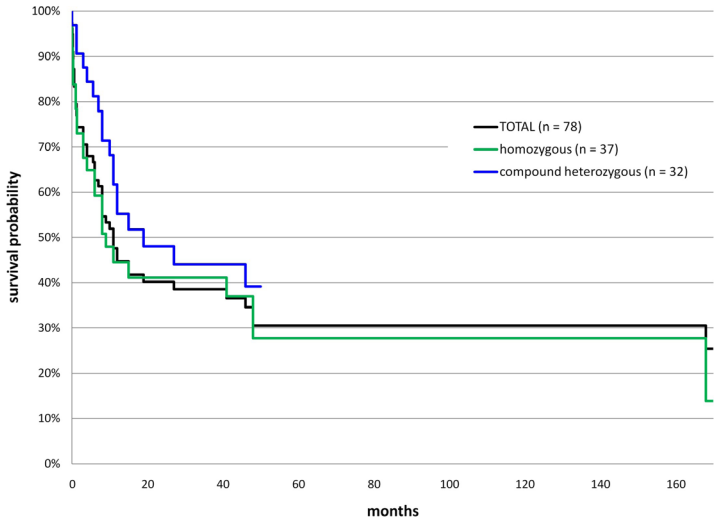

Figure 5. Survival curve of patients with GIDID1 as a function of all cases (n = 78) and homozygous or composite heterozygous genotype (n = 69).

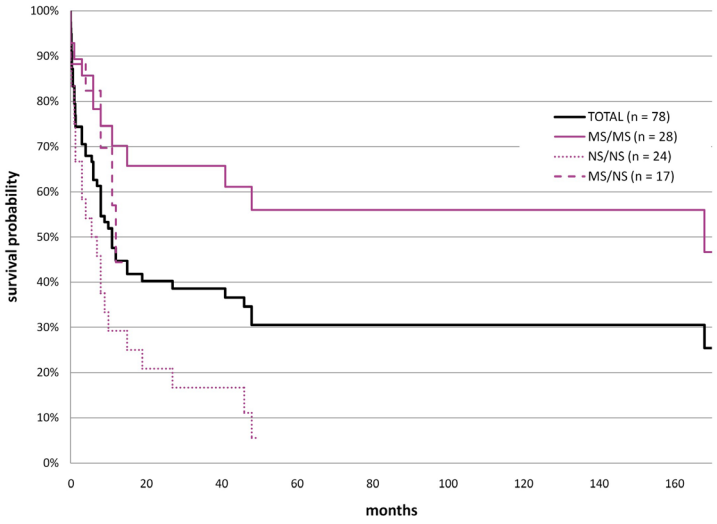

Figure 6. Survival curve of patients with GIDID1 as a function of all cases (*n* = 78) and combination of variants MS: missense, NS: nonsense (MS/MS, MS/NS, NS/NS) (*n* = 69).

6 months and 3 years, and alopecia starting at 2 years of age, leading to progressive hair loss and complete alopecia, including eyebrow loss.

Surgery was often performed in cases with the atresia phenotype, as well as parenteral nutrition ($p < 0.01$), which notably started earlier. The use of HSCT is more frequently associated with ID/MIA/E, without a significantly better efficacy (Table 1).

Regarding genotype/phenotype correlation, when comparing our three phenotypic associations to genotypic combinations involving double MS variant, double NS variant, and MS/NS variant, a significant difference was observed (Table 2). The ID/MIA association was strongly associated with double NS variant (77.8%), while the ID/E association was more strongly associated with double MS variant (73.7%) ($p < 0.001$). The ID/MIA/E group exhibited intermediate characteristics. Detailed phenotypic and genotypic characteristics are provided in Tables 1 and 2.

4. Discussion

Our literature review included a total of 83 cases, one-third more than the previous systematic review published in 2019 by Jardine *et al.* (*2*), which included only 55 cases.

In the cohort of patients we observed, we confirmed several previously highlighted elements: the presence of three primary phenotypic traits - MIA, ID and E (*23*); a high mortality rate, with 82.3% of deaths occurring before the age of 12 months, reaffirming the severity of this disease (*3-7,12,14,15,23,25,26*), and the crucial role of parenteral nutrition (PN), as 92.1% of patients required it (*3,5-7,11-15,17,18,22-29*).

4.1. GIDID1 is associated with preterm birth

Furthermore, we identified phenotypic associations and a connection with prematurity, with an average gestational age of 34.8 weeks. Notably, this prematurity did not appear to be related to the presence of antenatal signs and therefore seems to be intrinsic to TTC7A deficiency. Although the gestational term was not provided for 55 patients in our cohort, even if all of them had been born at term, it would still represent 28.9% of preterm births, exceeding the global population's prematurity rate, which stood at 11.1% in 2010 (*30*).

We have showed that the presence of inbreeding is more significant for the DI/E association without MIA but this result is influenced by the existence of a family of 14 patients with this phenotype (*7*).

4.2. Survival difference according genotype

Differences in survival based on genotype have been previously suggested (*9,23*), and our study confirms this hypothesis. Specifically, we found that patients with a double MS variant exhibited better survival, whereas double NS variant patients had more frequent and earlier mortality, with the latter being more commonly associated with digestive atresia. This supports the idea that a double MS variant, likely a hypomorphic form, allows for better survival due to residual protein levels supporting essential cell functions. Also, when compared to certain enteropathies caused by defect in epithelial trafficking and polarity (*EPCAM, MYO5B, STX3, TTC37, SPINT2* and *SKIV2L*) enteropathy caused by enteroendocrine cell dysfunction (*PCSK1* and *NEUROG3*) or CIPO (Table 3), the mortality rate per 1,000 patient-year was notably higher, especially for the ID/MIA phenotype and the double NS variant (*31,32,33*).

4.3. Strong genotype-phenotype association

By comparing our three phenotypic associations to the genotypic associations of double MS, double NS and

MS/NS variant, we observed a significant difference: the ID/MIA category being strongly associated with double NS variant, whereas the ID/E category showed a stronger association with double MS variant It is challenging to determine whether the observed differences in survival are linked to genotype or phenotype, as these two factors are intrinsically interconnected. It appears that double NS variant is more commonly associated with intestinal atresia. This suggests that the complete absence of TTC7A has a more profound impact on the structure of the digestive tract (*3-5,11,14,15,28,34*), while a hypomorphic presence allows for a normally developed gastrointestinal tract but leads to a phenotype resembling very early onset-inflammatory bowel disease (VEO-IBD) (*3-5,7,10,14,25*). Additionally, the ELA syndrome (*7,16*) was exclusively linked to patients without intestinal atresia. This could imply either a correlation with specific genotypic variant, such as double MS variant, or the fact that it requires longer survival to manifest (average onset at 24 months).

4.4. No clearly effective therapeutic

Regarding therapeutic approaches, we suggest the ineffectiveness of HCST on enteropathy (*2,18,35*) although it allows for prolonged survival in over half of the cases for the ID/MIA/E phenotype. Surgeries were generally performed in cases of atresia, and we highlighted recurrent atresia (n = 13), which, in some instances, warranted multiple surgeries and could result in a short bowel syndrome (*3-6,12-15*). Leflunomide treatment, suggested to improve TTC7A deficiency in *in vitro* models (*2*) by reducing cellular apoptosis, did not yield positive results in the one patient treated, who happened to have a double NS variant (*25*). However, there is some indication of a positive, as one patient reported on the Boston Children's Hospital website showed improvements in enteropathy. Further observational studies are required to better evaluate the efficacy of leflunomide for specific mutation subtypes.

4.5. Limitations

We conducted an extensive literature review, thereby increasing our sample size by one-third compared to the previous cohort, thus enhancing our understanding of this complex pathology. However, limitations stem from a lack of data and details in some case, as the results were extracted from published sources. When information on the type of immune deficiency or the presence of the enteropathy was lacking, we made clarifications based on objective criteria published in 2014 (*10*). Cases with missing information on immune deficiency were categorized as "absence of data", as were cases lacking data of enteropathy.

It should be noted that a potential bias exists due to the presence of a published family comprising 14 patients (16,9% of cohort) (*7*), all of whom had double MS variant, likely hypomorphic. This bias impacts the ID/E phenotype or the double MS variant subgroup.

As with all rare diseases, it is crucial to publish cases with rigorous criteria to establish a more precise understanding of the disease's progression and effectiveness of therapeutic approaches.

5. Conclusion

Our literature review reaffirms the severity of the GIDID1 associated with TTC7A mutations. It verifies the existence of three major phenotypic associations and enriches our knowledge, particularly in terms of genotype correlation: a more severe prognosis is associated with the presence of digestive atresia and double NS variant. We also highlight the link between GIDID1 and prematurity, which had not been previously described. Further studies with detailed characterization of both phenotype and genotype are essential to enhance our understanding of this condition, including its phenotypic and therapeutic aspects.

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