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# Genetic enteropathies linked to epithelial structural abnormalities and enteroendocrine deficiency : a systematic review

Morgane Caralli

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FACULTE DE MEDECINE

HYACINTHE BASTARAUD

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# **Histoire Naturelle des diarrhées congénitales génétiques, revue systématique de la littérature**

## **THESE**

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Par

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## **LISTE DES ABBREVIATIONS**

TE : tufting enteropathies

MVID : microvillous inclusion disease

THE : tricho-hepato-enteric syndrome

ED : enteroendocrine deficiencies

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis

SD: standard deviation

## **RESUME :**

**Introduction :** Les diarrhées congénitales et les entéropathies liées à des anomalies de la structure épithéliale comprennent trois entités rares différentes : La dysplasie épithéliale intestinale, aussi appelée entéropathie en touffes (TE) liée aux mutations EPCAM et SPINT2 ; La maladie des inclusions microvillositaires (MVID) liée aux mutations MYO5B et STX3 ; Le syndrome tricho-hépto-entérique (THE) lié aux mutations TTC37 et SKIV2L. Les entéropathies auto-immune liées aux mutations PCSK1 et NEUROG3 partagent des caractéristiques cliniques communes avec la TE, le THE ou la MVID notamment le recours à une nutrition parentérale à long terme. Bien que de nombreux cas aient été rapportés dans la littérature, les données sur la morbi-mortalité n'ont pas été clairement établies du fait de la rareté de ces maladies.

**Méthodes :** Nous avons effectué une revue systématique de tous les cas publiés depuis le 13 Janvier 2019 et avons récupéré 86 articles décrivant 323 patients . La recherche a été effectuée dans Medline (PubMed) et Google scholar. Une analyse statistique a été réalisée à l'aide de biostatgv(<https://biostatgv.sentiweb.fr/>).

**Résultats :** Le taux de mortalité était de 20,28%, avec un âge médian au décès de 13,5 mois, dans la moitié des cas le décès était dû à des infections. La nutrition parentérale était nécessaire chez 95,4% des patients et le sevrage de la nutrition parentérale a été réalisé chez 29,35% des patients à un âge médian de 23 mois.

**Conclusion :** Dans cette étude, nous avons recueilli des données publiées sur 323 patients atteints de huit entéropathies congénitales différentes. Ceci a permis de mieux décrire l'histoire naturelle de ces maladies et de dégager quelques nouvelles caractéristiques cliniques

## **Genetic enteropathies linked to epithelial structural abnormalities and enteroendocrine deficiency: a systematic review**

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## **Genetic enteropathies linked to epithelial structural abnormalities and enteroendocrine deficiency: a systematic review**

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### **ABSTRACT**

**Objectives:** Congenital diarrhea and enteropathies linked to epithelial structural abnormalities comprise three different rare diseases: the tufting enteropathies (TE; EPCAM and SPINT2 mutations), microvillous inclusion disease (MVID; MYO5B and STX3 mutations), and tricho-hepato-enteric syndrome (THE; TTC37 and SKIV2L mutations). Moreover, enteroendocrine deficiencies (ED; PCSK1 and NEUROG3 mutations) share common clinical characteristics with TE, THE, and MVID in that the treatment requires, in most cases, long-term parenteral nutrition. Although numerous cases have been reported in the literature, aggregated data on morbidity and mortality are missing owing to the rarity of the diseases.

**Methods:** We performed a systematic review of all published cases and retrieved 86 articles describing 323 patients (164 males and 135 females).

**Results:** The mortality rate was 20.28%, with a median age at death of 13.5 months (range 0–228 months); the mortality risk was 30.8/1000 patients year; in half of the cases, death was caused by infections. Parenteral nutrition was required in 95.4% of patients and weaning off from parenteral nutrition was achieved in 29.35% at a median age of 23 months (range 3.3–276 months). The patients with ED linked to PCSK1 were nearly all weaned at a median age of 14 months, but most of the patients became overweight. MVID patients with MYO5B mutations were most often born preterm. ED linked to NEUROG3 mutation and THE patients usually presented with intrauterine growth retardation.

**Conclusion:** This review presents data from 323 patients with congenital diarrhea linked to EPCAM-TE, SPINT2-TE, TTC37-THE, SKIV2L-THE, MYO5B-MVID, STX3-MVID, NEUROG3-ED, and PCSK1-ED mutations.

**Key Words:****What Is Known?**

- Congenital diarrhea linked to epithelial structural abnormalities or enteroendocrine deficiency has considerable morbidity and mortality.
- Most published literature comprises case reports or small case series.

**What Is New?**

- The overall mortality rate for congenital diarrhea linked to epithelial structural abnormalities or enteroendocrine deficiency is 20%, and ~30% of these patients are weaned at a median age of 23 months.
- Differences in disease manifestations according to the causative gene include syndromic presentation with EPCAM TE, SKIV2L THE, and TTC37 THE; preterm birth with MYO5B, MVID, TTC37, and SKI2L THE; and small-for-gestational-age with NEUROG3 ED, TTC37, and SKIV2L THE



## **INTRODUCTION**

Among patients with congenital diarrheas and enteropathies, a subset requires long-term parenteral nutrition, notably in patients with conditions linked to epithelial structural abnormalities such as tufting enteropathies (TE; EPCAM and SPINT2 mutations), tricho-hepato-enteric syndrome (THE; TTC37 and SKIV2L mutations), microvillous inclusion disease (MVID; MYO5B and STX3 mutations), and enteroendocrine deficiency (ED; PCSK1 and NEUROG3 mutations) <sup>1,2</sup>. Most of the genetic defects responsible for these syndromes have been described in the past decade, and reports of new cases have been regularly published. Consequently, data on the mortality, morbidity (specifically parenteral dependency), and growth are scattered across numerous case reports.

In order to gain a clearer picture of the evolution of these rare diseases, we performed a systematic assessment of published cases of congenital diarrhea and enteropathies that are linked to EPCAM TE, SPINT2 TE, TTC37 THE, SKIV2L THE, MYO5B MVID, STX3 MVID, NEUROG3 ED, and PCSK1 ED to provide an overview of mortality, morbidity, and treatment of these severe congenital diseases.

## **METHODS**

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Article were included if they report clinical data about patient with congenital diseases linked to EPCAM, SPINT2, TTC37, MYO5B, SKIV2L, STX3, NEUROG3 and PCSK1 mutations, article without clinical data, review, animal models or functional were not included. A systematic search was conducted on January 13, 2019 in Medline (PubMed) using the following terms: “SKIV2L tricho-hepato-enteric”, “SKIV2L trichohepatoenteric”, “SKIV2L diarrhea”, “SKIV2L exome”, “TTC37 diarrhea”, “TTC37 trichohepatoenteric”, “TTC37 tricho-hepato-enteric”, “TTC37 exome”, “Proprotein Convertase 1/3 Deficiency diarrhea”, “PCSK1 diarrhea”, “PCK1 exome”, “NEUROG3 and diarrhea”, “congenital malabsorptive diarrhea NEUROG3”, “congenital malabsorptive diarrhea neurogenin-3”, “NEUROG3 exome”, “EPCAM Tufting enteropathy”, “EPCAM diarrhea”, “EPCAM Exome”, “SPINT2 diarrhea”, “SPINT2 tufting enteropathy”, “SPINT2 exome”, “STX3 and microvillus inclusion disease”, “STX3 and

microvillous inclusion disease”, “STX3 exome”, “MYO5B diarrhea”, “MYO5B liver”, “MYO5B cholestasis”, “Microvillus inclusion disease MYO5B or Microvillous inclusion disease MYO5B”, and “MYO5B exome”.

Another search was performed in Google scholar using a function that was previously cited <sup>3,4, 5,6,7,8,9,10</sup>. Articles were screened and included if they provided the clinical descriptions of relevant patients. If a patient was described in several articles, relevant data from all of the articles were added. For all patients, data on sex, prenatal manifestations, mortality and cause of death, anthropometric data at birth and at last the recorded examination, extra-digestive symptoms (e.g., heart, kidney, liver, facial dysmorphism, diabetes mellitus, diabetes, choanal atresia, and obesity) were recorded. Data on non-diarrheal phenotypes linked to MYO5B and STX3 defects were collected for ancillary analysis.

### **Statistical Analysis**

Percentile birth weight and birth height were calculated using Audipog (<https://www.audipog.net/Courbes-morpho>), and follow-up Z-scores of weight and height were calculated using Peditool (<https://www.peditools.org/>). Analyses were performed using biostatgv (<https://biostatgv.sentiweb.fr/>).

## **RESULTS**

The searches in scientific databases resulted in the identification and screening of 199 articles, and 86 were included in the analysis (Supplementary Figure 1). In the entire cohort, there were data for 323 patients (164 males and 135 females). The clinical progression was described for 281 patients, with a median follow-up of 55.5 months (range 0–576 months). At the last evaluation, 20.28% of these patients had died, with a median age at death of 13.5 months (range 0–228 months). The cause of death was specified for 31 patients as follows: infections in 14 patients, liver failure in 4 patients, seizure in 3 patients, cardiac arrest in 3 patients, infections and liver failure in 2 patients, hemorrhage in 2 patients, central line-related death in 2 patients, and dehydration in 1 patient. The survival rate on a Kaplan–Meier analysis was 89.02% (SD±2%) at 12 months, 78.99% (SD±2.79) at 60 months, 75.09% (SD±3.27%) at 120 months, and 66.93% SD(±5.04) at 228 months (Figure 1 and for detailed results according to gene defect and Supplementary Figure 2). Among 217 cases with the treatment

information, 207 required parenteral nutrition, with a median age of initiation at 2 months (range 0–36 months). Of the 184 patients receiving parenteral nutrition, 54 were weaned off from parenteral nutrition at a median age of 23 months (range 3.3–276 months). The detailed description of the results according to gene defects are presented in Table 1.

The median gestational term was 38 weeks (range 30–42 months), the median birthweight percentile was 16.92% (range 0–98.02%), and the median birth length percentile was 40.63% (range 0.07–99.27%). Table 2 and Figure 1 provide a detailed account of the gene defects.

Prenatal signs were described for 12 patients (6 with MYO5B MVID, 4 with SPINT2 TE, and 1 with NEUROG3, SKIV2L THE). The main clinical features were polyhydramnios in 7 patients (3 with MYO5B MVID and 4 with SPINT2 TE), oligohydramnios in 2 patients (NEUROG3 ED and SKIV2L THE mutations), and bowel dilatation in 5 patients (only MYO5B MVID mutations). Two patients with MYO5B MVID presented with an association of two different prenatal signs.

The median Z-Score of the last-recorded weight was  $-0.385$  (range  $-8.4$  to  $4.52$ ) for the 46 patients for whom this information was available, and the median Z-Score of the last-recorded height was  $-1.5$  (range  $-5.7$  to  $2.15$ ) for 49 patients (Detailed account of gene defects in Supplementary Table 1 and Figure 1). Obesity was reported in 21 patients (1 with NEUROG3 ED and 20 with PCSK1 ED).

With regard to the associated features, immune deficiency was reported in 25 patients (17 with TTC37 THE and 8 with SKIV2L THE). Congenital cardiac defects were reported in 18 patients (2 with EPCAM TE, 1 with SPINT2 TE, 9 with TTC37 THE, 5 with SKIV2L THE, and 1 with PCSK1). Ocular abnormalities were reported in 26 patients (1 with EPCAM TE, 23 with SPINT2 TE, 1 with MYO5B MVID, and 1 with STX3 MVID). Facial dysmorphism was reported in 86 patients (8 with EPCAM TE, 13 with SPINT2 TE, 2 with MYO5B MVID, 47 with TTC37 THE, 14 with SKIV2L THE, 1 with PCSK1, and 1 with NEUROG3). Liver disease was reported in 36 patients (1 with SPINT2 TE, 4 with MYO5B MVID, 1 with STX3 MVID, 11 with TTC37 THE, 16 with SKIV2L THE, 2 with NEUROG3, and 1 with PCSK1). Choanal atresia was reported in 19 patients (all with SPINT2 TE), and arthritis was reported in 13 patients (8 with EPCAM TE, 1 with SPINT2 TE, 1 with MYO5B TE, 1 with NEUROG3, and 1 with PCSK1). Kidney abnormalities were described in 14 patients (1 with EPCAM TE, 3 with SPINT2 TE, 6 with MYO5B MVID, 1 with STX3

MVID, and 3 with TTC37 THE). Diabetes mellitus was described in 9 patients (8 with NEUROG3 ED and 1 with PCSK1 ED) and diabetes insipidus in 18 patients (18 with PCSK1 ED) (Supplementary Table 2).

We evaluated the clinical characteristics of the patients with regard to the 10 following items: sex, status, age at last follow-up, gestational term, birth length, birth weight, parenteral nutrition, parenteral weaning, last-recorded weight, and last-recorded height; the mean number of available items per patient was  $4.58 (\pm 2.19)$ . Overall, a negative correlation was noted between the number of patients reported per article and the number of available items ( $\rho -0.3399$ ; 95% confidence interval [CI]  $-0.5197$  to  $-0.1313$ ],  $p=0.0019$ ).

Comparison between the different syndromes showed the following findings:

- The sex ratio differed statistically between PCSK1 ED and SPINT2 TE or TTC37 THE (2.56 versus 0.66,  $p=0.0136$  or 0.87,  $p=0.0264$ , respectively).
- In the Kaplan–Meier analysis, survival was lower for patients with MYO5B MVID ( $p=0.009$ ), TTC37 THE ( $p=0.029$ ), and SPINT2 TE ( $p=0.00014$ ) than in those with EPCAM TE, and was lower for those with SPTIN2 TE ( $p=0.035$ ) than for patients with PCSK1 ED.
- TTC37 patients required parenteral nutrition less often than patients with EPCAM TE (75% versus 100%,  $p=2.39E-05$ ) or patients with MYO5B MVID (75% versus 100%,  $p=0.0035$ ).
- In the case of parenteral nutrition, weaning off from parenteral nutrition was more frequent in patients with PCSK1 ED than for all other conditions (92% for PCSK1 ED versus 16.8% for EPCAM TE,  $p=9.02E-12$ ; 7.1% for SPINT2 TE,  $p=1.68E-07$ ; MYO5B MVID 19%,  $p=2.34E-07$ ; STX3 MVID 0%,  $p=0.0031$ ; SKIV2L THE 50%,  $p=0.0288$ ; TTC37 THE 22.2%,  $p=3.54E-06$ ; and NEUROG3 ED 30%,  $p=0.0005$ ). Moreover, there was a statistically significant difference for weaning off from parenteral nutrition between the EPCAM TE (16.8%) and SKIV2L THE groups (50%),  $p=0.0288$ .
- The gestational term was shorter for patients with MYO5B MVID versus PCSK1 ED (36 weeks versus 41 weeks,  $p=0.0045$ ), SKIV2L THE versus PCSK1 ED (36 weeks versus 41 weeks,  $p=0.0065$ ), TTC37 THE versus EPCAM TE or PCSK1 ED (35.7 weeks versus 40 weeks,  $p=0.0231$ , and versus 41 weeks,  $p=0.0001$ , respectively).
- The birth weight was lower for patients with: SKIV2L THE versus those with EPCAM TE, MYO5B MVID, and PCSK1 ED (0.39th versus 59.88th,  $p=0.002$ ; 62.07th,  $p=0.0002$ ; 51.87th,  $p=0.0012$ ); TTC37 THE versus EPCAM TE, MYO5B MVID, and PCSK1 ED

(3.22th versus 59.88th,  $p=0.0031$ ; 62.07th,  $p=6.72E-05$ ; and 51.87th,  $p=0.0036$ , respectively) and NEUROG3 ED versus EPCAM TE, MYO5B MVID, and PCSK1 ED (0.46th versus 59.88th,  $p=0.008$ ; 62.07th,  $p=0.022$ , and 51.87th,  $p=0.0092$ , respectively).

A subgroup analysis of 15 patients with MYO5B PFIC (12 males and 3 females) showed that 10 patients had sufficient clinical information with a median follow-up of 28.5 months (range 7–89 months). Moreover, 9/10 were alive and 1 had died at 27 months. The median Z-scores of the last-recorded weight and the last-recorded height were  $-2.83$  (range  $-3.48$  to  $0.81$ ,  $n=9$ ) and  $-1.315$  (range  $-4.22$  to  $2.73$ ,  $n=8$ ), respectively. All patients were born at term, and none required parenteral nutrition. There was no difference between the MYO5B PFIC and MYO5B MVID groups with regard to mortality ( $p=0.42$ ). The median percentile of birth weight was 62.07 ( $n=11$ ) for MYO5B MVID and 27.705 ( $n=2$ ) for MYO5B PFIC ( $p=0.051$ ).

There were three patients with an STX3-related syndrome with congenital cataract associated with intellectual disability, but no diarrhea described; however very few clinical data were in these reports.

## **DISCUSSION**

In this review, we gathered published data from 323 patients with eight different congenital enteropathies. Altogether, these data confirm the high morbidity and mortality encountered in these diseases, with 20.28% of the described cases having died at the time of the last-recorded follow-up. Nearly all patients required parenteral nutrition, and weaning was achieved in 41.5% of patients. There was an important variation in outcomes according to the mutated gene.

Despite the overall similarity, we described some differences depending on the genotype. For example, prenatal signs were mostly seen with MYO5B MVID and SPINT2 TE. Furthermore, the reports indicated some specific link like immune deficiency and facial dysmorphism in TTC37 and SKIV2L TE, choanal atresia, and eye abnormalities in SPINT2 TE, diabetes mellitus in NEUROG3 ED, and diabetes insipidus in PCSK1 ED. The report on PCSK1 ED showed a strikingly different clinical pattern from that of the other enteropathies, with early parenteral weaning at 14 months and subsequent obesity, which confirms the data published by Pepin et al.(2018)<sup>11</sup>. A puzzling feature of PCSK1 ED is the sex ratio with a

nearly three times higher incidence in males than in females, although we cannot rule out a stochastic effect ( $p=0.07$ ).

Furthermore, we report here some features that have not been clearly reported to date in the published literature; these include preterm birth for MYO5B MVID and low birth weight for NEUROG3 ED and SPINT2 TE. However, more data are needed to confirm these findings.

The syndromic nature of TTC37 and SKIV2L THE and SPINT2 ED was confirmed with several non-digestive features that were clearly linked to the disease. Currently, there are two diseases that are linked to an MYO5B defect: MVID and PFIC phenotypes, although some patients present with combined MVID-PFIC, as described by Girard et al. (2010)<sup>12</sup>. Recently, Overeem et al. (2019)<sup>13</sup> reported that these differences were linked to a rab11a-mediated gain-of-toxic function of some variants.

One of the limitations of this analysis is the missing data for some items (notably, the last-recorded anthropometric data were present only for a small subset of the whole cohort). In some cases, most data were obtained from only one article with an atypical phenotype. For example, in TTC37, the last-recorded height was based on data from 11 patients; however, 7 of these patients were from a report by Fabre et al. 2018<sup>14</sup>, which described a milder phenotype associated with a terminal mutation of TTC37. Thus, the last-recorded height was mostly based on the clinical findings from a milder phenotype. Another limitation is that these data originated from different countries and different times, with probably very important differences in the patient management. We excluded redundant reports for patients and verified the data for redundancy; however, we cannot definitively rule out the possibility that some patients could have been described several times; however, even in such a case, the impact on this analysis would be minor and it would not change the overall conclusion.

Consequently, more data are needed to confirm these findings, and we emphasize the importance of reporting fully described new cases in the context of rare diseases. Indeed, except for EPCAM TE, each disease counts for less than 60 patients reported. A caveat is that larger series usually present fewer informations. This shows the importance of case reports in rare diseases and suggests that, in cases of publications of data from patients with congenital enteropathy, a mandatory set of data points (e.g., status, last-recorded information, and anthropometric data) should be made requisite in order to allow better delineation of the associated syndromes.

In conclusion, we gathered published data from 323 patients with congenital diarrhea linked to EPCAM TE, SPINT2TE, TTC37 THE, SKIV2L THE, MYO5B MVID, STX3 MVID, NEUROG3 ED, and PCSK1 ED mutations, leading to a better description of the natural history of these diseases and unraveling some new characteristic clinical features.

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## **ANNEXES**

**Table 1.** Clinical information of the patients analyzed for the whole cohort and according to the gene defect. Data are presented as the median, interquartile range, and number of cases

**Figure 1.** A: Survival probability according to Kaplan–Meier analysis for the whole cohort, B Age at death in months, C, Age at parenteral weaning in months, D, Gestational term in weeks, E, Birthweight in percentile, F, Birth length in percentile, G, Last-recorded length by Z-score, H, Last-recorded length by Z-score according to the gene defect

### **Supplementary Digital Content**

**Table 1** Gestational term, birth weight, birth length, last-recorded weight, and last-recorded BMI for the whole cohort and according to the gene defect. Data are presented as median, interquartile range, and number of cases

**Table 2** Associated features for the whole cohort according to the gene defect

**Figure 1** PRISMA Flow Chart

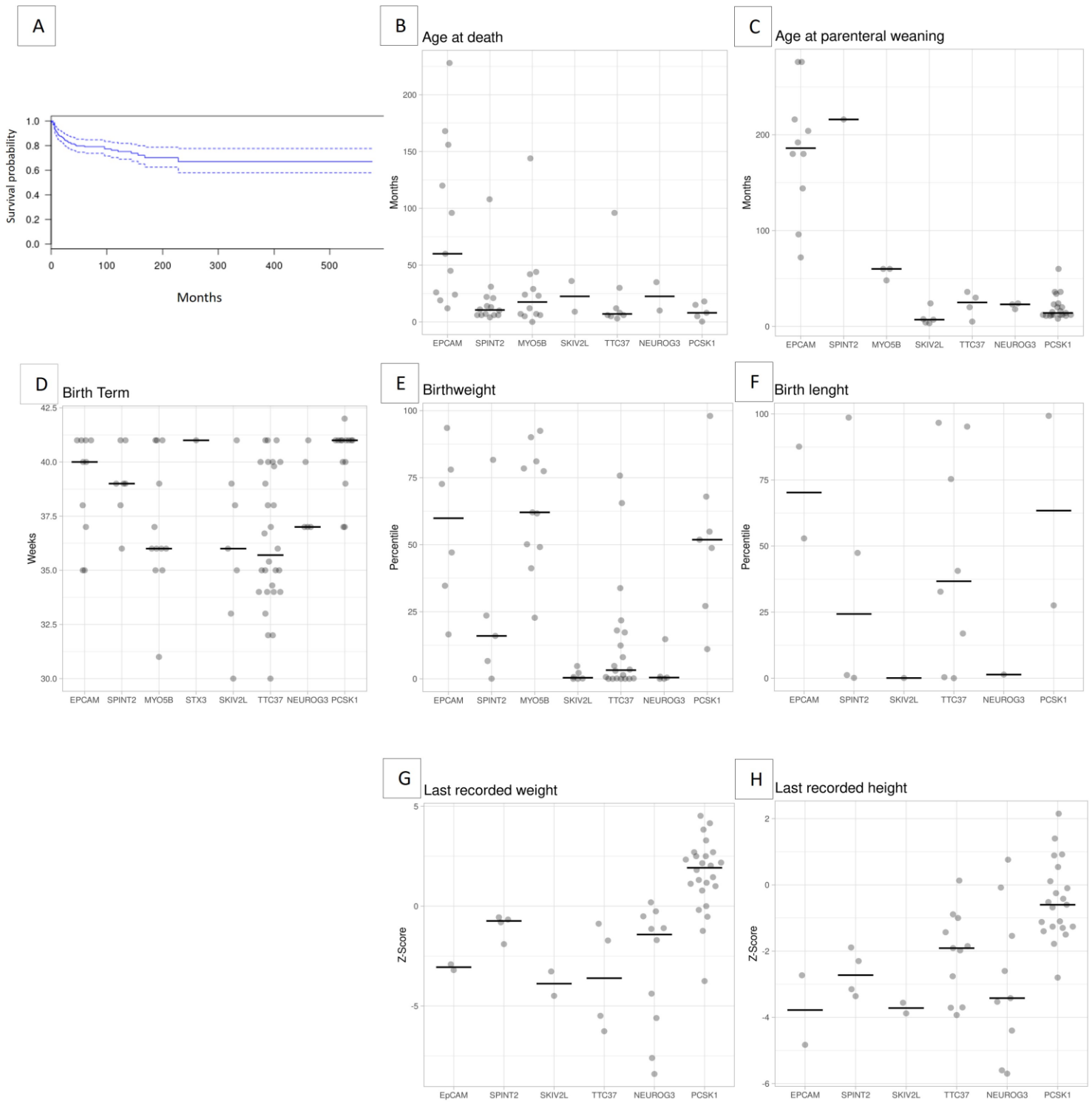
**Figure 2** Survival probability according to the Kaplan–Meier analysis according to the genes

**List of included articles**

**Table 1 :** Clinical information on patients' analyzed for the whole cohort and according to the gene defect. For each data, given numbers are median, range and number of cases.

	N	Male/Female	Alive/Death	Age at last evaluation in month	Risk of death/1000/yours	Median age at death in month (range, number of observation)	Parenteral nutrition/Absence of parenteral nutrition	Median age at parenteral nutrition beginning in month (range, n)	Parenteral nutrition/weaning/Absence of parenteral nutrition	Median age at parenteral nutrition weaning in month (range, n)
<i>EPCA M</i>	105	53/39	85/13	108 (3-480, n=64)	15	60 (12-228, n=11)	89/0 (100%)	2 (1-2, n=3)	14/69 (16.8%)	186 (72-276, n=10)
<i>SPIN T2</i>	35	14/21	21/14	36 (2-216, n=35)	76.5	10.5 (4-108, n=14)	16/1 (94.1%)	0.7 (0-2.5, n=5)	1/13 (7.1%)	216 (n=1)
<i>MYO5 B</i>	49	27/19	36/13	36 (0-336, n=43)	53.1	17.5 (0-144, n=12)	31/0 (100%)	1.2 (0.06-36, n=7)	4/17 (19%) (2 IT)	60 (48-60, n=3)
<i>STX3</i>	4	2/2	4/0	18 (12-	0	-	3/0 (100%)	-	0/3	-

				72, n=3=						
<i>SKIV2</i> <i>L</i>	2 6	12/9	11/2	46.5 (1- 276, n=12)	24.1	22.5 (9-36, n=2)	12/0 (100%)	2.5 (1-6, n=4)	5/5 (50%)	7 (3.3- 24, n=5)
<i>TTC3</i> <i>7</i>	5 8	26/30	28/8	33 (1- 168, n=36)	52.3	7 (3- 96, n=8)	21/7 (75%)	2 (0.5- 14, n=15)	4/14 (22.2%)	25 (5- 36, n=4)
<i>NEUR</i> <i>OG3</i>	1 4	7/6	12/2	89 (10- 288, n=14)	13.9	22.5 (10-35, n=2)	10/0 (100%)	16.5 (1-32, n=2)	3/7 (30%) (1IT)	23 (18- 24, n=3)
<i>PCSK</i> <i>1</i>	3 2	23/9	27/5	45.5 (0.3- 576, n=32)	22.8	8 (0.3- 18, n=8)	25/2 (92.6%)	2.5 (0.03- 10, n=18)	23/2 (92%)	14 (8- 60, n=21)
<b>Total</b>	<b>3 2 3</b>	<b>164/13 5</b>	<b>224/57 (20.28 %)</b>	<b>55.5 (0- 576, n=24 7)</b>	<b>30.8</b>	<b>13.5 (0-228)</b>	<b>207/10 (95.4%)</b>	<b>2 (0- 36, n=54)</b>	<b>54/130 (41.5%)</b>	<b>23 (3.3- 276, n=47)</b>



**Figure 1.** A: Survival probability according to Kaplan–Meier analysis for the whole cohort, B Age at death in months, C, Age at parenteral weaning in months, D, Gestational term in weeks, E, Birthweight in percentile, F, Birth length in percentile, G, Last-recorded length by Z-score, H, Last-recorded length by Z-score according to the gene defect



	1)										
<i>TTC3</i> 7	35. 7 (30 - 41, n= 28)	1.97 (0.98- 3.52, n=20)	3.22 (0-75. 77, n=20)	47 (42-5 3, n=7)	40.3 (0.37- 96.5, n=7)	8.7 (8-20 , n=4)	-3.6 05 (-6. 26 to -0.8 8, n=4)	98 (76.0 - 129. 4, n=11 )	-1.9 1 (-3. 93 to 0.13, n=11 )	14.54 (11.9- 18.85, n=4)	1 (0-93, n=3)
<i>SKIV</i> 2L	36 (30 - 41, n= 7)	1.6 (1.276 -2.45, n=6)	0.39 (0-4.7 5, n=6)	44 (n=1)	0.07 (n=1)	6 (5.5- 6.5, n=2)	-3.8 8 (-4. 49 to -3.2 7, n=2)	65.5 (60- 71, n=2)	-3.7 2 (-3. 88 to -3.5 6, n=2)	13.55 (11.9- 15.2, n=2)	-
<i>NEU</i> <i>ROG</i> 3	37 (37 - 41, n= 5)	2.334 (1.66- 3.56, n=9)	0.46 (0.02- 14.77, n=5)	43 (n=1)	1.37 (n=1)	24.8 (8.6- 51.0, n=10)	-1.4 2 (-8. 4 to 0.19, n=10 )	133 (81.2 - 161. 5, n=9)	-3.4 2 (-5. 7 to 0.76, n=9)	17.9 (13.0- 21.58, n=9)	30.5 (0-95, n=8)
<i>PCSK</i> 1	41 (37 - 41, n= 14)	3.4 (2.95- 4.58, n=22)	51.87 (11.07 -98.02, n=7)	52.75 (50.0- 55.5, n=2)	63.415 (27.56 -99.27, n=2)	20.25 (5.1- 69.0, n=14)	1.92 (-3. 75 to 4.52, n=24 )	94 (73- 156, n=11 )	-0.6 (-2. 8 to 2.15, n=21 )	22.01 (16.44 -34.2, n=10)	99 (85-1 00, n=8)
<b>Total</b>	<b>38</b> <b>(30</b> <b>-</b> <b>42,</b> <b>n=</b>	<b>2.91</b> <b>(0.98</b> <b>-4.58,</b> <b>n=80)</b>	<b>16.92</b> <b>(0-98.</b> <b>02,</b> <b>n=60)</b>	<b>47.5</b> <b>(42.0</b> <b>-55.5,</b> <b>n=17)</b>	<b>40.63</b> <b>(0.07-</b> <b>99.27,</b> <b>n=17)</b>	<b>17.15</b> <b>(5.1-</b> <b>69.0,</b> <b>n=36</b> <b>)</b>	<b>-0.3</b> <b>85</b> <b>(-8.</b> <b>4 to</b> <b>4.52</b> <b>,</b>	<b>99</b> <b>(60-</b> <b>161.</b> <b>5,</b> <b>n=3</b> <b>,</b>	<b>-1.5</b> <b>(-5.</b> <b>7 to</b> <b>2.15</b> <b>,</b> <b>n=4</b>	<b>17.98</b> <b>(11.9-</b> <b>34.2,</b> <b>n=31)</b>	<b>74</b> <b>(0-10</b> <b>0,</b> <b>n=23)</b>

	84)						n=4 6)	9)	9)		
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Data are presented as median, range, and number of cases

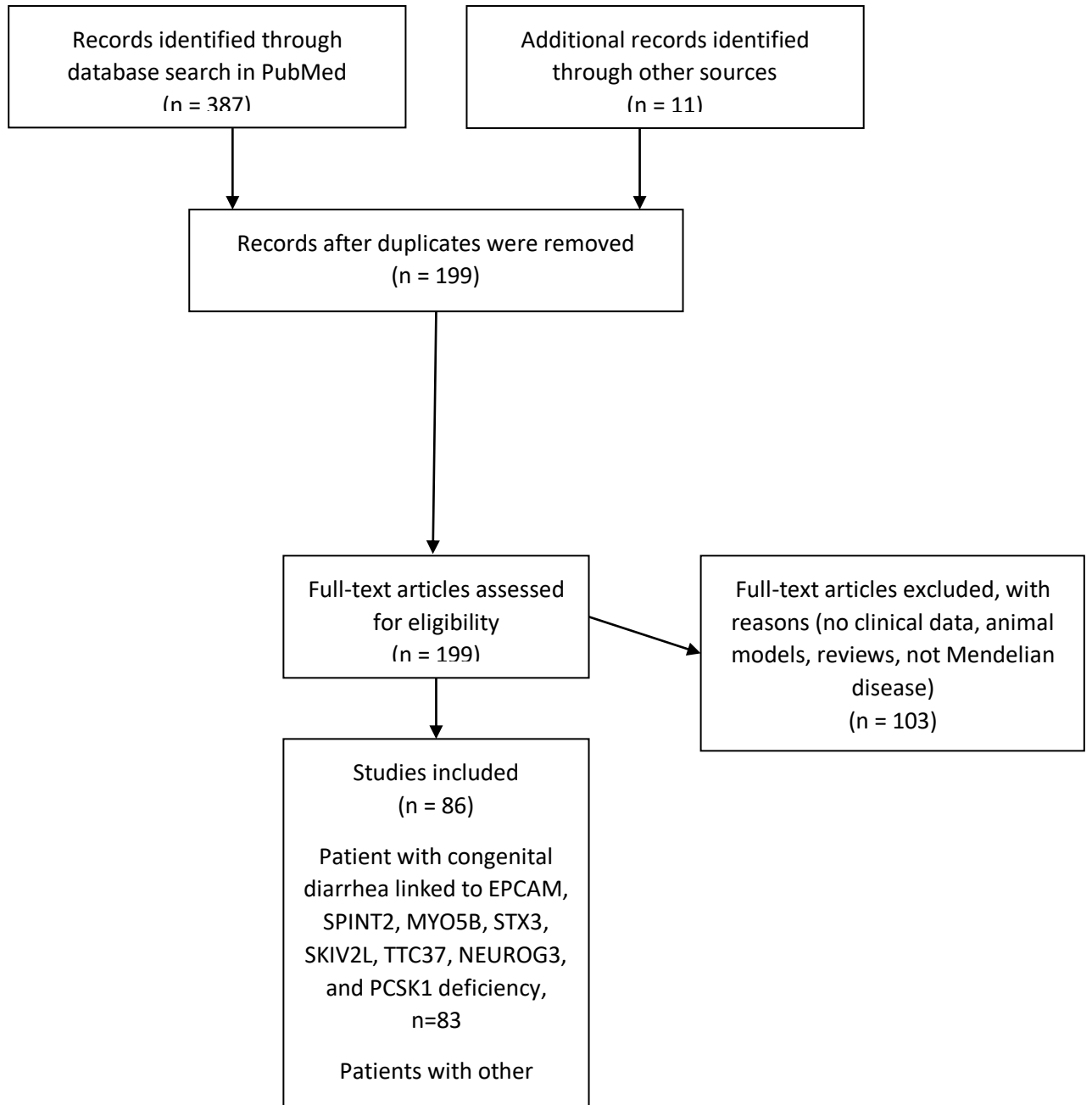


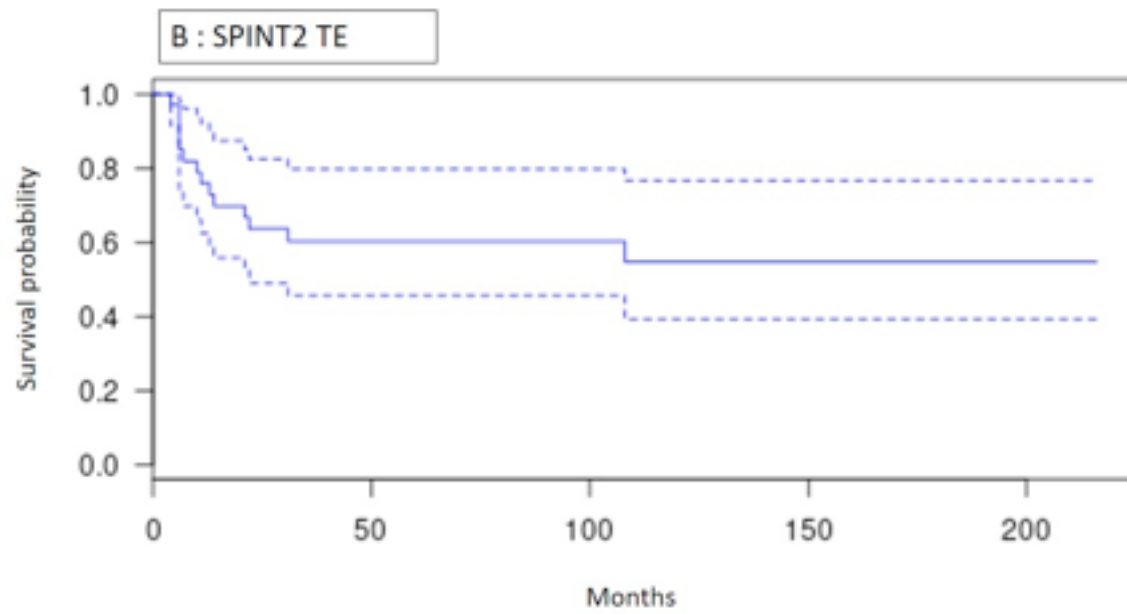
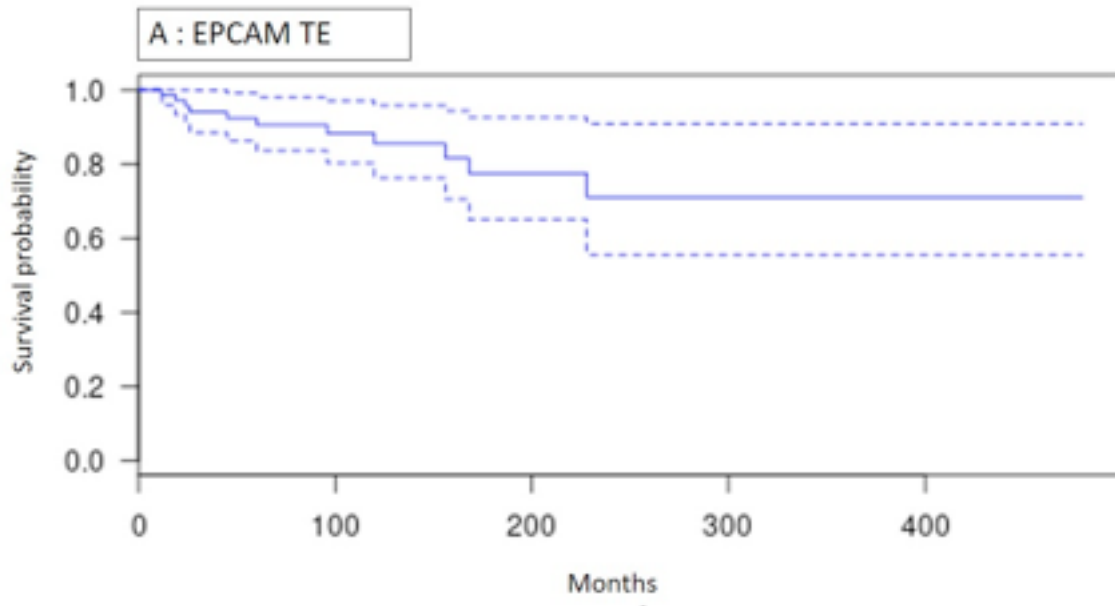
**Table 2** Associated features for the whole cohort according to the gene defect

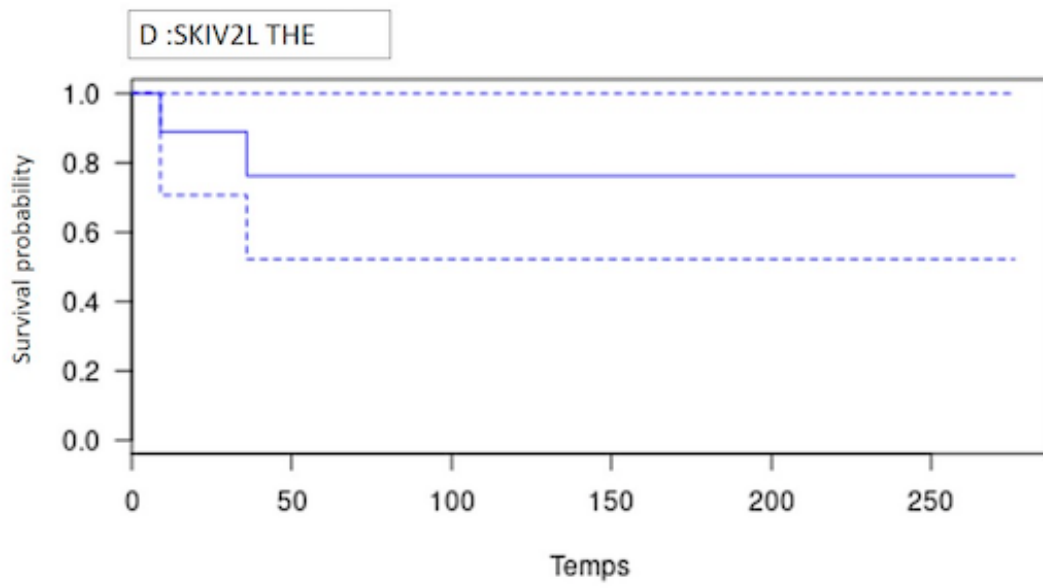
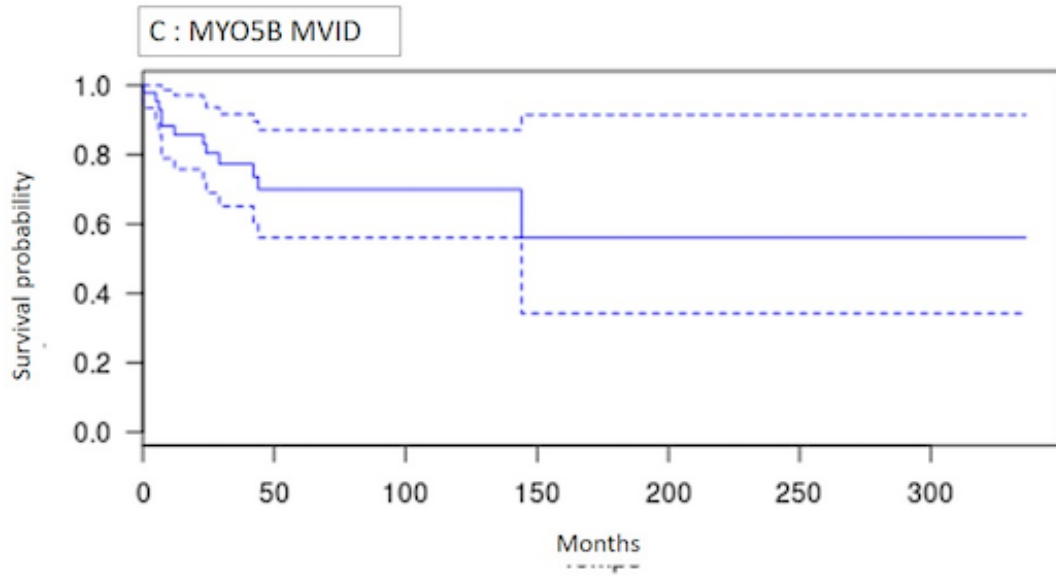
	Immune deficiency	Congenital cardiac defects	Ocular abnormalities	Facial dysmorphism	Obesity	Overweight	Choanal atresia	Arthritis	Kidney abnormalities	Liver disease	Diabetes mellitus	Diabetes	Endocrine abnormalities
<i>EPCAM</i>	-	2	1	8	-	-	-	8	1	-	-	-	
<i>SPINT2</i>	-	1	23	13	-	1	19	1	3	1	-	-	
<i>MYO5B</i>	-	-	1	2	-	-	-	1	6	4	-	-	
<i>STX3</i>	-	-	1	-	-	-	-	-	1	1	-	-	
<i>TTC37</i>	17	9	-	47	-	1	-	-	3	11	-	-	
<i>SKIV2L</i>	8	5	-	14	-	-	-	-	-	16	-	-	1
<i>NEUROG3</i>	-	-	-	1	1	-	-	1	-	2	8	-	5
<i>PCSK1</i>	-	1	-	1	20	1	-	2	-	1	1	18	23
<b>Total</b>	<b>25</b>	<b>18</b>	<b>26</b>	<b>86</b>	<b>21</b>	<b>3</b>	<b>19</b>	<b>13</b>	<b>14</b>	<b>36</b>	<b>9</b>	<b>18</b>	<b>29</b>

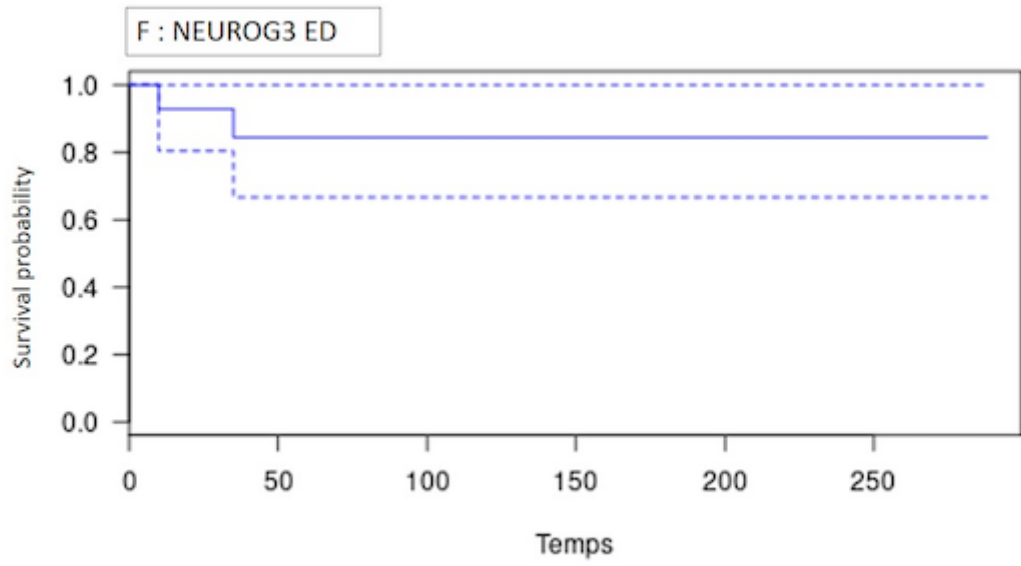
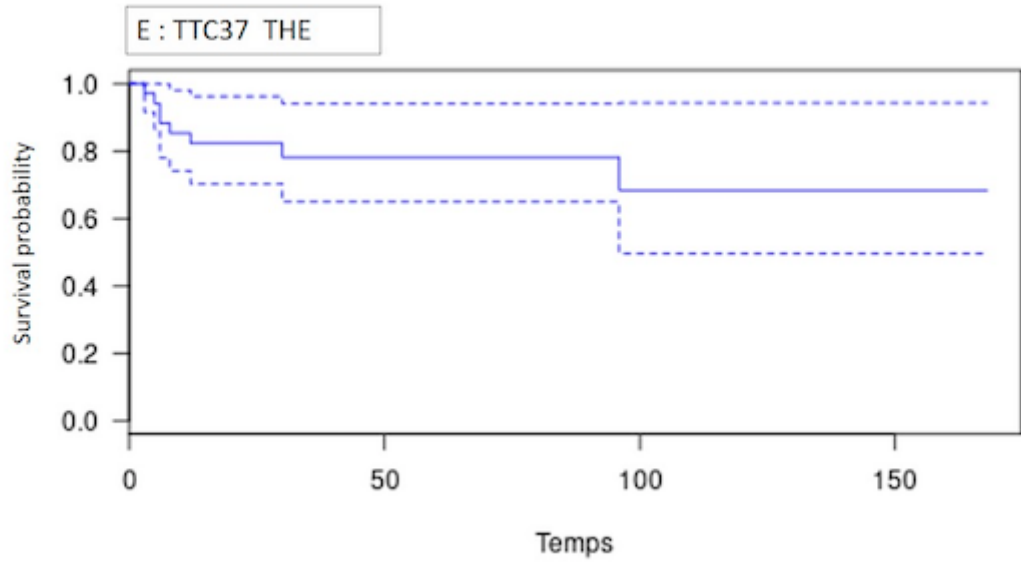


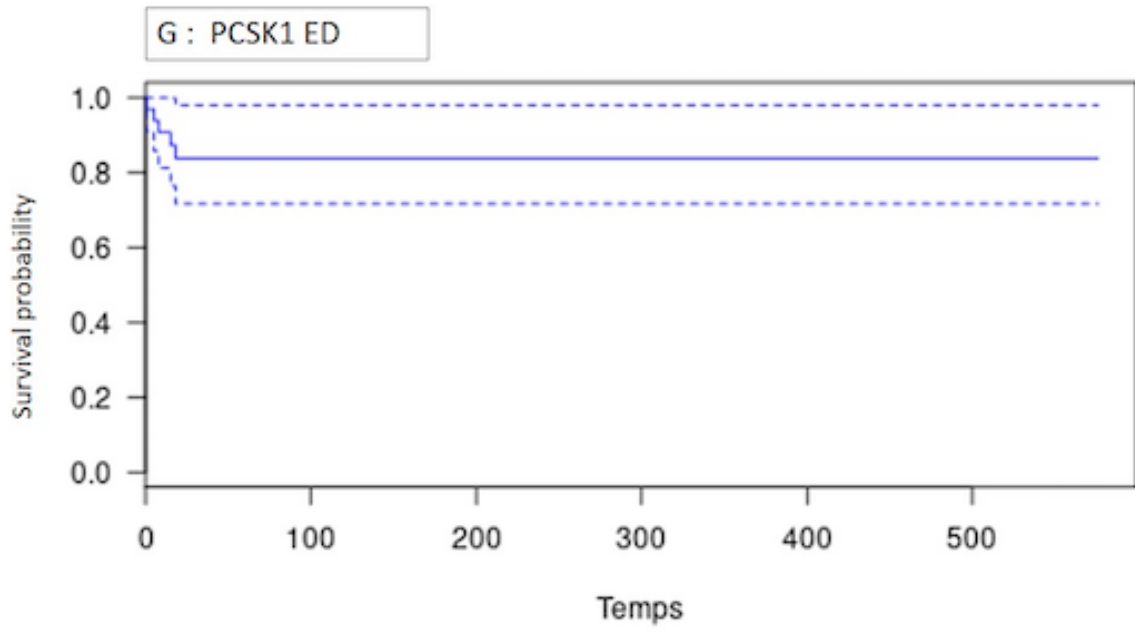
## PRISMA Flow Diagram











**Figure 2** Survival probability according to the Kaplan–Meier analysis according to the genes

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1. AlMahamed S, Hammo A. New mutations of EpCAM gene for tufting enteropathy in Saudi Arabia. *Saudi J Gastroenterol.* avr 2017;23(2):123- 6.
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## SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, en présence des maîtres de cette école et de mes condisciples, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité qui la régissent.

Mon premier souci sera, de rétablir, de préserver ou de promouvoir la santé dans tous les éléments physiques et mentaux, individuels collectifs et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients de décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai influencer ni par la recherche du gain ni par la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me sont confiés.

Reçue à l'intérieur des maisons, je respecterai les secrets des foyers.

Et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances, sans acharnement.

Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.

Que je sois modérée en tout, mais insatiable dans mon amour de la science.

Je n'entreprendrai rien qui ne dépasse mes compétences ; je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses,

Que je sois déshonorée et méprisée si j'y manque.

## **DEMANDE D'IMPRIMATUR**

**NOM ET PRENOM : CARALLI Morgane**

**SUJET DE LA THESE : Histoire Naturelle des diarrhées congénitales génétiques, revue systématique de la littérature**

**THESE : MEDECINE**

**Qualification : Pédiatrie**

**ANNEE : 2020**

**NUMERO D'IDENTIFICATION : 2020ANTI0608**

**MOTS CLEFS : Diarrhées congénitales, nutrition parentérale, EpCAM, PCSK1, TTC37, SKIV2L, SPINT2, NEUROG3, MYO5B, STX3**

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**Introduction :** Les diarrhées congénitales et les entéropathies liées à des anomalies de la structure épithéliale comprennent trois entités rares différentes : La dysplasie épithéliale intestinale, aussi appelée entéropathie en touffes (TE) liée aux mutations EPCAM et SPINT2 ; La maladie des inclusions microvillositaires (MVID) liée aux mutations MYO5B et STX3 ; Le syndrome tricho-hépto-entérique (THE) lié aux mutations TTC37 et SKIV2L. Les entéropathies auto-immune liées aux mutations PCSK1 et NEUROG3 partagent des caractéristiques cliniques communes avec la TE, le THE ou la MVID notamment le recours à une nutrition parentérale à long terme. Bien que de nombreux cas aient été rapportés dans la littérature, les données sur la morbi-mortalité n'ont pas été clairement établies du fait de la rareté de ces maladies. **Méthodes :** Nous avons effectué une revue systématique de tous les cas publiés depuis le 13 Janvier 2019 et avons récupéré 86 articles décrivant 323 patients . La recherche a été effectuée dans Medline (PubMed) et Google scholar. Une analyse statistique a été réalisée à l'aide de biostatgv(<https://biostatgv.sentiweb.fr/>). **Résultats :** Le taux de mortalité était de 20,28%, avec un âge médian au décès de 13,5 mois, dans la moitié des cas le décès était dû à des infections. La nutrition parentérale était nécessaire chez 95,4% des patients et le sevrage de la nutrition parentérale a été réalisé chez 29,35% des patients à un âge médian de 23 mois. **Conclusion :** Dans cette étude, nous avons recueilli des données publiées sur 323 patients atteints de huit entéropathies congénitales différentes. Ceci a permis de mieux décrire l'histoire naturelle de ces maladies et de dégager quelques nouvelles caractéristiques cliniques

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**JURY : Président : Professeur ELENGA Narcisse**

**Juges : Pr FABRE Alexandre (directeur de thèse)**

**: Pr GELU-SIMEON Moana**

**: Dr ROSENTHAL Jean-Marc**

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CARALLI Morgane

Sujet de la thèse : Histoire Naturelle des diarrhées congénitales génétiques, revue systématique de la littérature

Thèse : Médecine - Université des Antilles

Année 2020

Numéro d'identification : 2020ANTI0608

MOTS-CLES : diarrhées congénitales, nutrition parentérale, MUO5B, NEUROG3, EpCAM, SKIV2L, SPINT 2, TTC37 , STX3

<http://anneau.bnf.fr> ou <http://www.hon.ch/honselect>

RESUME :

Introduction : Les diarrhées congénitales et les entéropathies liées à des anomalies de la structure épithéliale comprennent trois entités rares différentes : La dysplasie épithéliale intestinale, aussi appelée entéropathie en touffes (TE) liée aux mutations EPCAM et SPINT2 ; La maladie des inclusions microvillositaires (MVID) liée aux mutations MYO5B et STX3 ; Le syndrome tricho-hépto-entérique (THE) lié aux mutations TTC37 et SKIV2L. Les entéropathies auto-immune liées aux mutations PCSK1 et NEUROG3 partagent des caractéristiques cliniques communes avec la TE, le THE ou la MVID notamment le recours à une nutrition parentérale à long terme. Bien que de nombreux cas aient été rapportés dans la littérature, les données sur la morbi-mortalité n'ont pas été clairement établies du fait de la rareté de ces maladies.

Méthodes : Nous avons effectué une revue systématique de tous les cas publiés depuis le 13 Janvier 2019 et avons récupéré 86 articles décrivant 323 patients . La recherche a été effectuée dans Medline (PubMed) et Google scholar. Une analyse statistique a été réalisée à l'aide de biostatgv(<https://biostatgv.sentiweb.fr/>).

Résultats : Le taux de mortalité était de 20,28%, avec un âge médian au décès de 13,5 mois, dans la moitié des cas le décès était dû à des infections. La nutrition parentérale était nécessaire chez 95,4% des patients et le sevrage de la nutrition parentérale a été réalisé chez 29,35% des patients à un âge médian de 23 mois.

Conclusion : Dans cette étude, nous avons recueilli des données publiées sur 323 patients atteints de huit entéropathies congénitales différentes. Ceci a permis de mieux décrire l'histoire naturelle de ces maladies et de dégager quelques nouvelles caractéristiques cliniques

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