# Genetic Enteropathies Linked to Epithelial Structural Abnormalities and Enteroendocrine Deficiency: A Systematic Review

\*Morgane Caralli, \*Celine Roman, \*Marie-Edith Coste, \*Bertrand Roquelaure, <sup>†§</sup>Christophe Buffat, <sup>‡§</sup>Patrice Bourgeois, <sup>‡§</sup>Catherine Badens, and <sup>\*‡</sup>Alexandre Fabre

#### ABSTRACT

**Objectives:** Congenital diarrhea and enteropathies linked to epithelial structural abnormalities constitute 3 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 boys and 135 girls).

**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 personyear; 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.

**Conclusions:** 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:** congenital diarrhea, enteroendocrine deficiencies, evolution, microvillous inclusion disease, trichohepatoenteric syndrome, tufting enteropathies

(JPGN 2021;72: 826-832)

Received September 7, 2020; accepted December 25, 2020.

- From the \*APHM, Hôpital Timone Enfants, Service de Pédiatrie Multidisciplinaire, Marseille, France, the †APHM, Hôpital de la Conception, Laboratoire de Biochimie et de Biologie Moléculaire, Marseille, France, the ‡Aix Marseille Univ, INSERM, MMG, and the §APHM Service de Génétique Médicale, Marseille, France.
- Address correspondence and reprint requests to Alexandre Fabre, APHM, Hôpital Timone Enfants, Service de Pédiatrie Multidisciplinaire, Marseille, France Aix Marseille Univ, INSERM, MMG, Marseille, France (e-mail: alexandre.fabre@ap-hm.fr).
- Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

Copyright © 2021 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.000000000003049

#### What Is Known

- Congenital diarrhea linked to epithelial structural abnormalities or enteroendocrine deficiency has considerable morbidity and mortality.
- Most published literature constitutes 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

A mong 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), trichohepatoenteric syndrome (THE; *TTC37* and *SKIV2L* mutations), microvillous inclusion disease (MVID; *MYO5B* and *STX3* mutations), and enteroendocrine deficiency (ED; *PCSK1* and *NEU-ROG3* mutations) (1,2). 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. Articles were included if they report clinical

The authors report no conflicts of interest.

data about patient with congenital diseases linked to EPCAM, SPINT2, TTC37, MYO5B, SKIV2L, STX3, NEUROG3, and PCSK1 mutations. Articles without clinical data like 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-hepatoenteric", "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 the "cited by" function for the following articles mentioned in (3-10). 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 (eg, heart, kidney, liver,

facial dysmorphy, diabetes mellitus, diabetes, choanal atresia, and obesity) were recorded. Data on nondiarrheal phenotypes linked to *MYO5B* and *STX3* defects were collected for ancillary analysis. Data table is provided as Table 1, Supplementary Digital Content, *http://links.lww.com/MPG/C211*.

#### **Statistical Analysis**

Percentile birth weight and birth height were calculated using Audipog (*https://www.audipog.net/Courbes-morpho*), and followup *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 (Prisma Flow chart in Fig. 1, Supplementary Digital Content. *http:// links.lww.com/MPG/C209* and list of included articles in Supplementary Digital References, *http://links.lww.com/MPG/C214*). In the entire cohort, there were data for 323 patients (164 boys and 135 girls). 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



**FIGURE 1.** (A) Kaplan-Meier survival curves with 95% confidence intervals for the whole cohort (n = 246), (B) Kaplan-Meier curves for parenteral dependency with 95% confidence intervals for the whole cohort (n = 149), (C) Kaplan-Meier survival curves according to the gene defect, and (D) Kaplan-Meier curves for parenteral dependency according to the gene defect.

www.jpgn.org

## 827

# Copyright © ESPGHAN and NASPGHAN. All rights reserved.



FIGURE 1. (Continued).

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  $\pm 2\%$ ) at 12 months, 78.99% (SD  $\pm 2.79$ ) at 60 months, 75.09% (SD  $\pm 3.27\%$ ) at 120 months, and 66.93% SD ( $\pm 5.04$ ) at 228 months (Fig. 1 and Fig. 2, Supplementary Digital Content, *http://links.lww.com/MPG/* 

C210). 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.

Disease name	Gene	N	Male/ female	Alive/ death	Age at last evaluation in month	Deaths per 1000 person- years	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 weaning	Median age at parenteral nutrition weaning in month (range, n)
Tufting enteropathies	EPCAM	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)
Tufting enteropathies	SPINT2	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)
Microvillous inclusion disease	MYO5B	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, $n=3$ )
Microvillous inclusion disease	STX3	4	2/2	4/0	18 (12–72, n=3)	0	_	3/0 (100%)	-	0/3	-
Trichohepatoenteric syndrome	SKIV2L	26	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)
Trichohepatoenteric syndrome	TTC37	58	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)
Enteroendocrine deficiencies	NEUROG3	14	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)
Enteroendocrine deficiencies	PCSK1	32	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)
	Whole Cohort	323	164/135	224/57 (20.28%)	55.5 $(0-576, n=247)$	30.8	13.5 (0-228)	207/10 (95.4%)	2 (0-36, n=54)	54/130 (41.5%)	23 (3.3–276, $n = 47$ )

TABLE 1. Clinical information of the patients analyzed for the whole cohort and according to the gene defect

Data are presented as the median, range, and number of cases. IT = intestinal transplantation.



**FIGURE 2**. Dotplot and median. (A) Gestational term in weeks according to the gene defect, (B) birthweight in percentile according to the gene defect, (C) birth length in percentile according to the gene defect, (D) last-recorded weight by *z*-score according to the gene defect, (E) last-recorded length by *z*-score according to the gene defect (graph done with PlotsOfData *https://huygens.science.uva.nl/PlotsOfData/*).

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, Supplementary Digital Content,

*http://links.lww.com/MPG/C212* and Figure 2 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 ED, 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 2 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 Table 2, Supplementary Digital Content, *http://links.lww.com/MPG/C212* and Fig. 2). 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 NEU-ROG3). 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) (Table 3, Supplementary Digital Content, http://links.lww.com/MPG/C213).

We evaluated the clinical characteristics of the patients with regard to the 10 following data: 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 data 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 data per patient ( $\rho$  -0.3399; 95% confidence interval [CI] -0.5197 to -0.1313], P = 0.0019).

We proceeded to pair comparison between the different syndromes. The statistically significant findings were:

- 1. The sex ratio differed statistically between PCSK1 ED and SPINT2 TE or TTC37 THE (2.56 vs 0.66, P = 0.0136 or 0.87, P = 0.0264, respectively).
- 2. 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.
- 3. TTC37 patients required parenteral nutrition less often than patients with ECPAM TE (75% vs 100%, P = 2.39E-05) or patients with MYO5B MVID (75% vs 100%, P = 0.0035).
- 4. 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 vs 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.

- 5. The gestational term was shorter for patients with MYO5B MVID versus PCSK1 ED (36 vs 41 weeks, P = 0.0045), SKIV2L THE versus PCSK1 ED (36 vs 41 weeks, P = 0.0065), TTC37 THE versus EPCAM TE or PCSK1 ED (35.7 vs 40 weeks, P = 0.0231, and vs 41 weeks, P = 0.0001, respectively).
- 6. The birth weight was lower for patients with: SKIV2L THE versus those with EPCAM TE, MYO5B MVID, and PCSK1 ED (0.39th vs 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 vs 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 vs 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 boys and 3 girls) 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 MYO58B PFIC (p=0.051).

There were 3 patients with an *STX3*-related syndrome with congenital cataract associated with intellectual disability, but no diarrhea was described; however, very few clinical data were available in these reports.

### DISCUSSION

In this review, we gathered published data from 323 patients with 8 different congenital enteropathies. Altogether, these data confirm the high morbidity and mortality encountered in these diseases, with 20.28% of the described patients 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 MIVD and SPINT2 TE. Furthermore, the reports indicated some specific links like immune deficiency and facial dysmorphism in TTC37 and SKIV2L THE, 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 Pépin (11) et al in 2018. A puzzling feature of PCSK1 ED is the sex ratio with a nearly 3 times higher incidence in male patients than in female patients (P = 0.07), although we cannot rule out a stochastic effect.

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 NEU-ROG3 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 nondigestive features that were clearly linked to the disease. Currently, there are 2 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 (12) in 2010. Recently, Overeem et al (13) in 2019 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 1 article with an atypical phenotype. For example, in TTC37 THE, the last-recorded height was based on data from 11 patients; however, 7 of these patients were from a report by Fabre et al (14) in 2018, 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 (notably using the details about mutations); 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 (eg, 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.

**Acknowledgments:** We would like to thank Editage (*www.editage.com*) for English language editing and we thank Paul Guerry (Green Grow Scientific) for the computing Figure 1.

#### REFERENCES

- Thiagarajah JR, Kamin DS, Acra S, et al., PediCODE Consortium. Advances in evaluation of chronic diarrhea in infants. *Gastroenterology* 2018;154:2045–59.
- Canani RB, Castaldo G, Bacchetta R, et al. Congenital diarrhoeal disorders: advances in this evolving web of inherited enteropathies. *Nat Rev Gastroenterol Hepatol* 2015;12:293–302.
- 3. Wang J, Cortina G, Wu SV, et al. Mutant neurogenin-3 in congenital malabsorptive diarrhea. *N Engl J Med* 2006;355:270–80.
- Sivagnanam M, Mueller JL, Lee H, et al. Identification of EpCAM as the gene for congenital tufting enteropathy. *Gastroenterology* 2008;135: 429–537.
- Müller T, Hess MW, Schiefermeier N, et al. MYO5B mutations cause microvillus inclusion disease and disrupt epithelial cell polarity. *Nat Genet* 2008;40:1163–5.
- Heinz-Erian P, Müller T, Krabichler B, et al. Mutations in SPINT2 cause a syndromic form of congenital sodium diarrhea. *Am J Hum Genet* 2009;84:188–96.
- Hartley JL, Zachos NC, Dawood B, et al. Mutations in TTC37 cause trichohepatoenteric syndrome (phenotypic diarrhea of infancy). *Gastroenterology* 2010;138:2388–98.
- Fabre A, Charroux B, Martinez-Vinson C, et al. SKIV2L mutations cause syndromic diarrhea, or trichohepatoenteric syndrome. *Am J Hum Genet* 2012;90:689–92.
- Jackson RS, Creemers JW, Farooqi IS, et al. Small-intestinal dysfunction accompanies the complex endocrinopathy of human proprotein convertase 1 deficiency. *J Clin Invest* 2003;112:1550–60.
- Wiegerinck CL, Janecke AR, Schneeberger K, et al. Loss of syntaxin 3 causes variant microvillus inclusion disease. *Gastroenterology* 2014; 147:65–8.
- Pépin L, Colin E, Tessarech M, et al. A new case of PCSK1 pathogenic variant with congenital proprotein convertase 1/3 deficiency and literature review. *J Clin Endocrinol Metab* 2019;104:985–93.
- Girard M, Lacaille F, Verkarre V, et al. MYO5B and bile salt export pump contribute to cholestatic liver disorder in microvillous inclusion disease. *Hepatology* 2014;60:301–10.
- Overeem AW, Li Q, Qiu YL, et al. A molecular mechanism underlying genotype-specific intrahepatic cholestasis resulting from MYO5B mutations. *Hepatology* 2019;72:213–29.
- 14. Fabre A, Petit LM, Hansen LF, et al. A new mutation in the C-terminal end of TTC37 leading to a mild form of syndromic diarrhea/tricho-hepato-enteric syndrome in seven patients from two families. *Am J Med Genet A* 2018;176:727–32.