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Inherited pancreatic exocrine insufficiency and pancreatitis: When children transition to adult care

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ABSTRACT

Hereditary pancreatitis (HP) encompasses two distinct disease groups: the first manifests as congenital exocrine pancreatic insufficiency (EPI), and the second includes hereditary forms of pancreatitis. EPI represents the ultimate expression of gland function loss. Cystic fibrosis is by far the most frequent aetiology of early-onset EPI; genetics and a growing understanding of the disease mechanisms have paved the way for innovative and personalized treatment approaches. Efforts are ongoing to further decipher the pathophysiology and explore new therapies for other causes of EPI. HP occurs in patients carrying mutations in genes encoding digestive proteases or proteins playing an important role in proper pancreatic function and homeostasis. Improved sequencing techniques have led to the discovery of several causal and disease promoting genes. Most forms of HP have a paediatric onset but complications usually manifest during adulthood. Surveillance in experienced centres is mandatory to diagnose and address these complications in a timely manner.

1. Introduction

The exocrine pancreas is comprised of acinar and ductal cells; and plays a major role in nutrient digestion. Pancreatic enzymes are synthesized in the acinar cells and stored in zymogen granules, some as inactive pro-enzymes. Enzyme release by exocytosis is mediated by neurohumoural agents (acetylcholine (Ach), cholecystokinin (CCK), secretin, vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) in response to dietary intake. Ductal cells secrete approximately 1.5–2L/day of bicarbonate-rich fluid in response to secretin stimulation. Fluid and anion secretion is primarily mediated by the cystic fibrosis transmembrane conductance regulator (CFTR). Active ductal transport of ions occurs with passive water movement into the duct lumen. This fluid flushes pancreatic enzymes into the duodenum and creates an optimal luminal pH for pancreatic enzyme function. In contact with enterocytes, trypsinogen is activated by the enterokinase in trypsin which subsequently activates the other pro-enzymes. Exocrine pancreatic function is immature at birth. Amylase secretion is almost absent in newborns, remains low in the first year of life and rises to achieve adult values at approximately 3 years of age. Lipase levels and protease activity reach 5–10% and approximately 50% of adult values at birth, respectively [1,2].

Exocrine pancreatic insufficiency (EPI) is defined as a deficient secretion of pancreatic enzymes and/or bicarbonate-rich fluid secondary to different pancreatic diseases, resulting in inadequate nutrient digestion and subsequent assimilation. Although pancreatic enzymes are involved in the digestion of carbohydrates, proteins and lipids, fat maldigestion is clinically the most relevant manifestation. The main clinical manifestations of EPI in infants are failure to thrive and fatty diarrhoea. The disturbance of exocrine function ultimately leads to deficiencies in fat-soluble vitamins, macro- and micronutrients, proteins and fat. Most aetiologies of paediatric-onset EPI are related to rare congenital diseases. Improved care of patients with hereditary exocrine pancreatic diseases has led to an increased life expectancy.

Hereditary pancreatitis is characterized by paediatric onset recurrent episodes of pancreatitis leading to mid-to long-term pancreatic dysfunction. These patients also face an increased risk of pancreatic adenocarcinoma.

The purpose of this review is to provide adult gastroenterologists insights into the aetiology, pathophysiology, evolution and points of attention in patients with paediatric-onset exocrine pancreatic diseases and hereditary pancreatitis after transition into adult care.

2. Congenital exocrine pancreatic insufficiency

Although the differential diagnosis of EPI in neonates and infants

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might seem extensive, physicians must be aware that cystic fibrosis (95%) and Shwachman-Bodian-Diamond syndrome (4%) represent by far the 2 main causes of early-onset EPI (Table 1). We will focus this review on Shwachman-Diamond and Johanson-Blizzard syndrome. The other aetiologies are either fatal during childhood or very rare.

2.1. Cystic fibrosis

Cystic fibrosis (CF) is a multisystemic, autosomal recessive inherited disorder with an estimated prevalence of 1/3000 in Caucasians. The disease is caused by mutations in cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. CF is the main cause of congenital EPI in children, representing 95% of early onset EPI aetiologies.

The authors refer to a specific chapter for further details on the disease pathophysiology, management and patient outcome of CF.

2.2. Shwachman Bodian Diamond Syndrome and related syndromes

Shwachman Bodian Diamond Syndrome (SDS) is a rare inherited multisystemic disease first described by Nezelof in 1961 as a congenital form of lipomatosis with EPI and leukopenia [5]; nevertheless, the syndrome was ultimately named after physicians Harry Shwachman, Martin Bodian and Louis Diamond in 1964 [6]. In 2003 Boocock identified biallelic mutations in the *SBDS* gene in 90% of SDS children [7]. The gene encodes a protein that plays an essential role in ribosome biogenesis. More recently, mutations in other genes (*EFL1* [8], *DNAJC21* [9,10], *SRP54* [11,12] and *eIF6* [13]) coding for ribosomal proteins have been found in the remaining 10% SDS individuals. Ribosome synthesis is a complex and highly conserved process requiring the coordinated expression, assembly and removal of a large number of ribosomal proteins, ribosomal RNAs and small nuclear RNA molecules. The process is initiated in the nucleus, and early subunits are then exported to the cytoplasm where subunit maturation and assembly are completed [14,15]. SBDS was shown to function as a cofactor for elongation factor-like GTPase 1 (EFL1) by releasing eukaryotic initiation factor 6 (eIF6) from the 60S ribosomal subunit, enabling 80S ribosome formation during the final cytoplasmic step of ribosomal biogenesis [8]. All described *SBDS* mutations are hypomorphic; null mutants are lethal. Similarly, studies in yeast have shown that DNAJC21 is involved in removing auxiliary factors from the S60 ribosomal subunit [9,10]. Overall, it seems that impaired maturation of the large ribosomal subunit secondary to mutations in one of these 4 genes leads to SDS. Finally, *SRP54* encodes for a ribosomal GTPase that mediates the cotranslational targeting of newly synthetized nascent secretory and membrane proteins from the ribosome to the endoplasmic reticulum (ER) [11,12]. The authors also showed that *SRP54* knockdown in granulocytes led to increased ER stress and autophagy. It remains to be further clarified how mutations affecting such ubiquitous protein synthesis and targeting mechanisms can lead to precise organ abnormalities.

Table 1
Aetiologies of exocrine pancreatic dysfunction in infancy.

	Gene mutation	Inheritance	OMIM	Estimated prevalence at birth in Caucasian populations
Cystic fibrosis	*CFTR*	AR	219700	1/3000
Shwachman-Diamond syndrome	*SBDS* (90%)	AR	260400	1/76,000 [3]
	EFL1	AR	617538	
	DNAJC21	AR	617048	
	SRP54	AD	604857	
	eIF6	AD?	602912	
Pearson syndrome	mtDNA deletion	(mt)	557000	unknown
Johanson-Blizzard syndrome	*UBR1*	AR	243800	1/250,000 [4]
Shteyer syndrome	*COX4I2*	AR	607976	Exceptional
Pancreatic agenesia/hypoplasia				
Pancreatic hypoplasia	*PDX1*	AR	600733	Exceptional
Pancreatic and cerebellar agenesis	*PTF1A*	AR	607194	Exceptional
Pancreatic agenesis and congenital heart defects	*GATA6*	(AD)	601656	Exceptional
Isolated enzyme deficiency				
Lipase	*PNLIP*	AR	246600	Exceptional

AD: autosomal dominant; AR: autosomal recessive; mt: mitochondrial genetic transmission, OMIM: Reference in the Online Mendelian Inheritance in Humans catalogue.

2.2.1. Disease features

2.2.1.1. Shwachman Bodian Diamond Syndrome type 1 (SDS1). Clinically, SDS1 is characterized by the association of exocrine pancreatic dysfunction, variable degrees of haematologic abnormalities, skeletal anomalies and short stature (Table 2) [16].

Pancreatic disease – A vast majority (90%) of SDS patients present with EPI within the first year of life. Pathologically, the pancreas of SDS patients is small. The acinar cells are lost and replaced by connective tissue and adipocytes while the ductal cells and Langerhans islets are preserved. Residual acinar cells contain only a few zymogen granules [17]. Fatty loose stools, failure to thrive and liposoluble vitamin deficiency are the main clinical features that lead to EPI diagnosis, generally before 6–12 months of age. On ultrasound imaging, the pancreas appears small and hyperechoic, suggestive of fatty infiltration. A modest improvement in exocrine function can be seen in later childhood in approximately 50% of patients. Pancreatic ductal function is preserved in SDS. In this context, it is hypothesized that exocrine function improvement is due to the physiologic maturation of pancreatic enzyme secretion with age [18]. Patients becoming pancreatic sufficient (PS) no longer require pancreatic enzyme supplementation. Regular pancreatic function testing is therefore warranted. Distinguishing PI from PS patients may be challenging, as most pancreatic function tests lack sensitivity or specificity or may be affected by enzyme supplementation. Serum immunoreactive trypsinogen may circumvent these limitations; the concentration of trypsinogen in PI is low (<50 μg/L, normal values 140–400 μg/L) but rise above 50 μg/L in PS patients, sometimes reaching normal values [19].

Haematologic disease – Neutropenia is seen in almost all SDS children. Nevertheless, it can either be persistent or cyclic and range from normal to severe. Normochromic normo- or macrocytic anaemia and thrombopenia are slightly less frequent and usually remain asymptomatic. Severe pancytopenia is rare. Bone marrow aspirates show varying degrees of cell hypoplasia, myeloid maturation arrest and increased fat deposition. SDS children, especially boys, are more prone to develop myelodysplasia and malignancies. SDS-related leukaemias have a poor prognosis as they are less responsive to standard chemotherapy protocols; however, bone marrow transplantation has been shown to improve the outcome [20].

Skeletal abnormalities and short stature – SDS children may have a low or normal birth height. Despite adequate nutrient intake and normal growth velocity, most children will remain below or around the 3rd percentile for height. Characteristic skeletal anomalies in SDS include a short stature, delayed appearance of secondary ossification centres, thoracic dystrophy and metaphyseal dysplasia affecting primarily the long bones [21] (Fig. 1).

2.2.1.2. SDS type 2 and SDS-like syndromes. Shwachman Bodian Diamond type 2 (SDS2) is caused by mutations in *EFL1*, while patients with Shwachman Bodian Diamond-like (SDS-like) syndromes carry mutations

Table 2
Clinical features of Shwachman Bodian Diamond syndrome.

	SDS1
Pancreatic	Exocrine pancreatic dysfunction (PI/PS)
Haematologic	Neutropenia (persistent, cyclic)
	Leukopenia
	Altered chemotaxis
	Anaemia
	Thrombopenia
	Increased foetal haemoglobin
	Pancytopenia
	Aplastic anaemia
	- Blood malignancies:
	Myelodysplasia
	Acute myeloid leukaemia
	Acute lymphoblastic leukaemia
	Juvenile myelomonocytic leukaemia
Skeletal	Metaphyseal dysostosis
	Long bone tubulation
	Short stature
	Thoracic anomalies
	- narrow thorax – severe thorax dystrophy
	- costochondral thickening
	- short, horizontalized ribs
	Polydactyly, syndactyly, clinodactyly
	Osteopenia
Other	
++	Immunodeficiency
	Recurrent (life-threatening) viral, bacterial and fungal infections
++	Poor appetite
	Feeding difficulties
++	Hepatomegaly
	Elevated liver enzymes
	On histology:
	Steatosis
	Inflammatory cell infiltrates
	Fibrosis
++	Renal tubular dysfunction
	Urine tract anomalies
++	Developmental delay
	Cognitive and behaviour problems
+	Dental abnormalities
	Dysplastic teeth
	Enamel defects
	Delayed tooth eruption
+	Ichthyosis
(+)	Cleft palate
(+)	Endocardial fibrosis
(+)	Diabetes mellitus
(+)	Eye anomalies
	- strabismus
	- coloboma
	- punctate keratitis

The frequency of clinical features is rated from ++ (frequent) to (+) (rare); PI: pancreatic insufficient; PS: pancreatic sufficient; SDS1: Shwachman Diamond Syndrome type 1.

in either *DNAJC21*, *SRP54* or *eIF6*. Clinical features associated with SDS2 and SDS-like syndromes are summarized in Table 3.

2.2.2. Management

The gastrointestinal management of SDS1, SDS2 and SDS-like children is mainly supportive. Once EPI is diagnosed, pancreatic enzyme replacement therapy and liposoluble vitamin supplements should be initiated, and dietary advice should be given to the child and the parents. As the exocrine function may improve, regular assessment of pancreatic function is recommended. Haematologic follow-up and infection management are mandatory in these patients [16]. The potential development of more targeted therapies relies on further advancements to decipher the precise molecular mechanisms of ribosome maturation that are affected by SBDS(-related) mutations.

2.2.3. Outcome

Long-term survival of SDS1 patients was studied by Cesaro et *al.* [24] in an Italian cohort and was 95.7% (95%CI 89.9–98.2) at 10years and 87.4% (95%CI 75.3–93.8) at 20years. Early mortality was attributed to severe infections and haematologic malignancies. Survival beyond 30 years is poorly investigated. Two patients were reported with pancreatic cancer at young ages (24y and 38y, respectively) raising caution about the increased risk for this type of tumour in young SDS adults [25,26]. The outcome of SDS2 and SDS-like patients is unclear.

2.3. Johanson-Blizzard syndrome

Johanson-Blizzard syndrome (JBS) is a very rare multisystemic autosomal recessive disorder initially inadvertently described as "an example of trypsinogen deficiency" by Morris and Fisher in 1967 [27]. In 1971, Johanson and Blizzard delineated the syndrome phenotype which includes EPI, hypo- or aplastic nasal alae, oligodontia, hearing impairment, mental retardation and short stature [28]. In 2005, the disease was found to be caused by homozygous or compound heterozygous mutations in the ubiquitin-protein ligase E3 component *N*-recognin 1 (*UBR1*) gene [29]. *UBR1* encodes one of at least four E3 ubiquitin ligases of the *N*-end rule pathway that recognize and ubiquinate destabilizing *N*-terminal residues of proteins to facilitate their degradation by the proteasome. It is hypothesized that altered UBR1 function is responsible for the accumulation of unfolded proteins in the ER, causing ER stress. The precise pathophysiologic link between specific deficient protein degradation and the clinical spectrum of JBS remains to be further deciphered [4,30,31].

2.3.1. Clinical features

The phenotype of JBS patients is largely but not solely predicted by the mutation found in individuals. Indeed, patients carrying mutations leading to protein loss of function have more severe phenotypes than those with hypomorphic mutations [32].

Pancreatic disease – A constant feature in JBS patients is EPI, which is most frequently present from birth and persistent over time. On histopathology, the pancreas shows progressive acinar cell loss during foetal period, replaced by connective tissue, inflammatory infiltrates and blood vessels. Ductal cells and Langerhans islets seem preserved. The residual acinar cells contain normal amounts of zymogen granules, although zymogen exocytosis in response to neurohumoural stimuli is impaired. In the pancreas, the *N*-end rule pathway may thus also be involved in zymogen vesicle trafficking and exocytosis [29]. These observations corroborate previous quantitative pancreatic function tests showing, in relation to the total acinar secretion, normal fluid and anion outputs but severely reduced enzyme secretion [33].

Facial features and cognitive impairment – A characteristic finding in JBS is abnormal nasal alae development ranging from mild wing hypoplasia to aplasia. Definitive dentition anomalies including oligo- or hypodontia, are also a constant feature. Severe JBS forms are further associated with facial clefting (cleft palate, cleft lip, lateral facial clefts), microcephaly, low set ears and sensorineural hearing loss. Finally, abnormal frontal hair implantation, a prominent forehead, lacrimal duct anomalies, lid coloboma and congenital cataract may complete the craniofacial phenotype. Children with JBS often have mild to severe developmental delay and intellectual disability, but normal intelligence can be seen in patients with milder phenotypes.

Additionally, less common clinical features in JBS patients are summarized in Table 4 [32,34.]

2.3.2. Management

The management of JBS is symptomatic, including enzyme and liposoluble vitamin supplementation.

2.3.3. Outcome

Historically, many JBS patients died from complications related to EPI, malnutrition and hormone deficiencies. Currently, JBS patients managed adequately survive into adulthood.

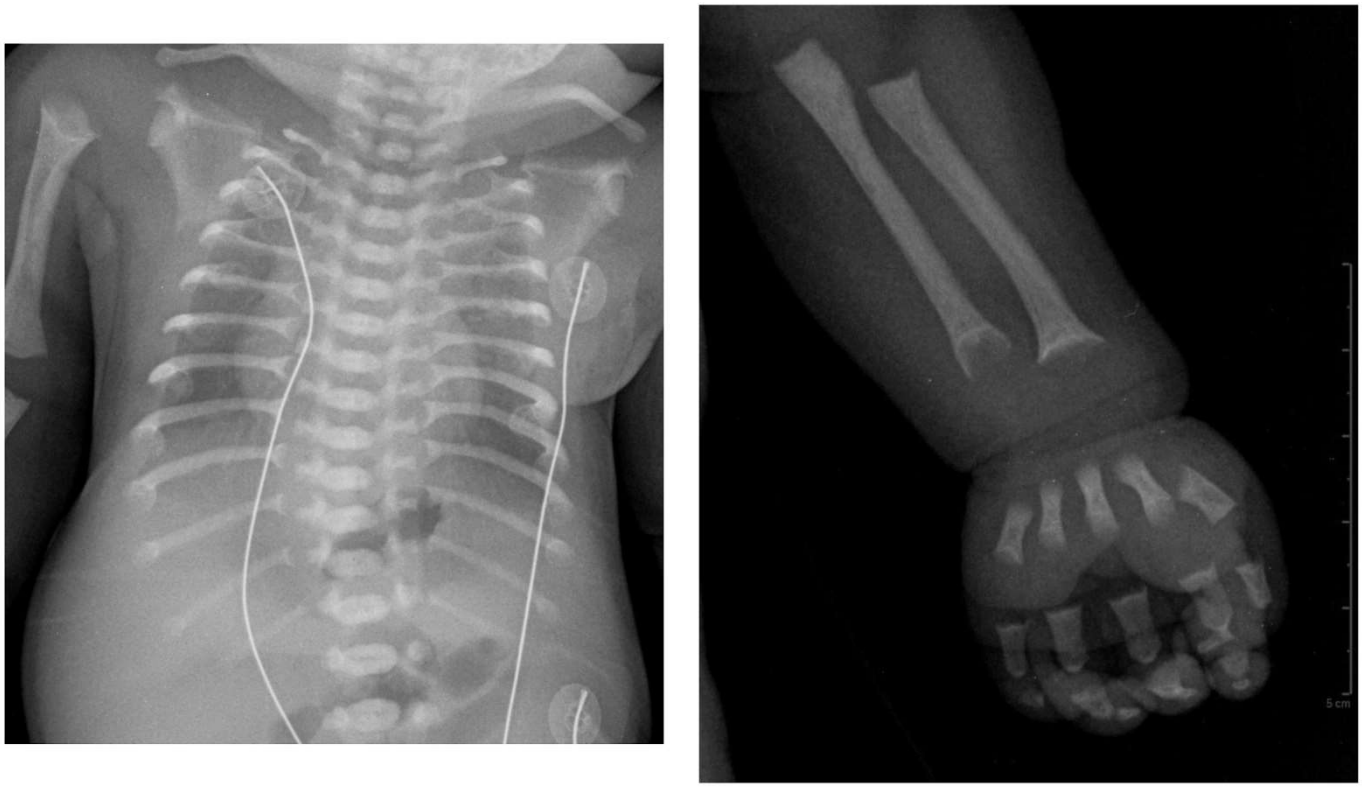

Fig. 1. Skeletal anomalies in a patient with Shwachman-Bodian-Diamond syndrome.
A. Narrow thorax, horizontalized ribs, high set clavicles, hypoplastic lungs. B. Long bones metaphyseal dysostosis.

Table 3
Clinical features of Shwachman Bodian Diamond type 2 and SDS-like syndromes.

	EFL1 (SDS2)	*DNAJC21*	*SRP54*	*eIF6*
Reported cases (n =)	4	15	23	1
Reference(s)	[8]	[9,10,22,23]	[11,12]	[13]
Exocrine pancreatic dysfunction	Yes (4/4)	Yes (8/15)	Yes (14/23)	Yes (1/1)
Haematologic features	Yes	Yes	Yes	Yes
Skeletal anomalies	Yes	Yes	Yes	Yes
Specific characteristics – dissimilar to SDS1	Myopia Arched palate	Retinal abnormalities Cirrhosis Hypermobile joints Hip dysplasia Cryptorchidism	–	–

SDS2: Shwachman Bodian Diamond type 2.

3. Hereditary pancreatitis

Hereditary pancreatitis (HP) is a rare disorder characterized by early onset recurrent episodes of pancreatitis. The disease is caused by mutations in genes coding for a wide variety of proteins, including pancreatic pro-enzymes, their inhibitors, anion pumps responsible for pancreatic ductal fluid production or calcium homeostasis.

A positive family history of pancreatitis is suggestive of an inherited aetiology but is not mandatory.

Most hereditary forms of pancreatitis reveal themselves during the first two decades of life, but some will only manifest later in life. HP is usually diagnosed after recurrent episodes of pancreatitis. Patients present with at least 2 of the following: 1) abdominal pain suggestive for pancreatitis 2) raised amylase/lipase levels above 3x upper limit of norm; and 3) positive imaging findings for pancreatitis [35,36].

HP significantly predisposes patients to endocrine and exocrine dysfunction as well as to pancreatic cancer.

3.1. Aetiologies of hereditary pancreatitis

HP aetiologies can be classified into 3 groups based on their pathogenic mechanism: trypsin-dependent, misfolding-dependent and/or ductal cell-related causes (Table 5).

3.1.1. Hereditary pancreatitis related to trypsin-dependent mechanisms

3.1.1.1. PRSS1. In 1996, Whitcomb et *al.* mapped the *PRSS1* gene on the long arm of chromosome 7. *PRSS1* encodes cationic trypsinogen protease 1, a pro-enzyme that is activated in trypsin by enteropeptidase in the duodenum. Trypsin then further activates the other pancreatic enzymes. Premature, intrapancreatic cleavage of trypsinogen induces zymogen activation in the pancreas, parenchyma autodigestion, inflammation and pancreatic injury. Several physiological mechanisms prevent intrapancreatic enzyme activation. The serine protease inhibitor (SPINK1) inactivates trypsin, while chymotrypsin C (CTRC) and cathepsin L degrade trypsinogen [45–47].

The 3 most frequent gene mutations are R122H, N29I and A16V. Depending on the location of the genetic defect, *PRSS1* mutation leads to a protein gain of function by favouring trypsinogen autoactivation, preventing CTRC-dependent degradation (e.g. p.N29I, p.V39A, p. R122C, p.R122H) or increasing CTRC-in/dependent trypsinogen autoactivation (e.g. p.A16V, p.N29I) [48].

HP related to *PRSS1* is an autosomal dominant disorder with incomplete (80%) penetrance.

The first episode of pancreatitis related to *PRSS1* mutation occurs at a mean age of 10–12years [49,50].

3.1.1.2. SPINK1. *SPINK1* (serine protease inhibitor Kazal-1) is located

Table 4
Clinical features in Johanson-Blizzard syndrome.

	JBS
Pancreatic	Exocrine pancreatic dysfunction (PI » PS)
Cranio-facial	Nasal alae hypoplasia/aplasia
	Scalp defects/aplasia cutis
	Dental anomalies
	Microcephaly
	Lacrimal duct anomalies
	Lid coloboma
	Congenital cataract
	Absent superior puncta
	Abnormal frontal hair
	Low set ears
	Facial bone defects
	Cleft palate, cleft lip, facial clefts
	Sensorineural hearing loss
Other	
++	Short stature
++	Developmental delay
	Intellectual disability
+	Hypothyroidism
+	Congenital heart disease
	- Ventricular septum defect
	- Atrial septum defect
	- Patent ductus arteriosus
	- Myxomatous mitral valve
	- Dextrocardia
	- Cardiomyopathy
+	Anorectal anomalies
	- Imperforate anus
+	Genitourinary defects
	- Vesicoureteral reflux
	- Hypospadias
	- Duplex of uterine and vagina
	- Prostate aplasia
	- Micropenis
(+)	Kidney anomalies
(+)	Diabetes mellitus
	Hypopituitarism
(+)	Café au lait spots
(+)	Raised liver enzymes
	Cholestasis
(+)	Sacral hiatus

Frequency of clinical features is rated from ++ (frequent) to (+) (rare); PI: pancreatic insufficient; PS: pancreatic sufficient.

Table 5
Genes involved in hereditary pancreatitis.

Gene mutation	Inheritance	OMIM	Estimated risk of CP
Trypsin-dependent mechanisms			
PRSS1	AD	167800	x4.7 p.R122H [37]
SPINK1	AD/AR	608189	x10 p.N34S [38]
CTRC	AR/AD	601405	x5 average [39,40]
Misfolding-dependent mechanism			
PRSS1	AD	167800	
CPA1	Sporadic (AD)	114850	x25-80 [41]
CEL/CEL-HYB	AD	114840	x5.2[42]
Ductal cell-related mechanisms			
CFTR	AR	602421	x1.5-16 [43,44]
CLDN2	X-linked	300520	–
TRPV6	AD/AR	–	–
CaSR	AD	601199	–
AP2S1	AD	602242	–

AD: Autosomal dominant; AR: autosomal recessive; OMIM: Reference in the Online Mendelian Inheritance in Humans catalogue; CP: Chronic pancreatitis.

on chromosome 5 and encodes the pancreatic secretory trypsin inhibitor (PTSI). Functional analysis has shown that most mutations lead to protein loss of function. The pathogenic mechanisms associated with N34S, the most prevalent *SPINK1* mutation, remain to be deciphered.

The link between *SPINK1* mutations and HP was first suggested by Witt *et al.* [51]. At least one mutation in *SPINK1* (c.27delC) is transmitted in an autosomal dominant manner [52]. However, in most cases, HP is seen in patients presenting with two *SPINK1* mutations. Additionally, HP can occur in patients with a heterozygous *SPINK1* mutations and a mutation in another pancreatitis-related gene (*CTRC*, *CFTR* [44,53]) or presenting with environmental (tobacco, alcohol) risk factors for pancreatitis. Approximately 2% of the healthy general population harbour a heterozygous *SPINK1* mutation. Overall, *SPINK1* is considered a disease modifier rather than a causal mutation [54].

In a French cohort [55], the first bouts of hereditary pancreatitis related to *SPINK1* occurred at a median age of 20.1years. *SPINK1*-related pancreatitis was significantly more associated with recurrent episodes of pancreatitis than idiopathic pancreatitis. The *SPINK1* p.N34S variant was estimated to increase the chronic pancreatitis risk by 9.7-fold in a European/North American population [38].

3.1.1.3. CTRC. The role of *CTRC* in hereditary pancreatitis was first described by Rosendahl *et al.* [56]. *CTRC* encodes chymotrypsin C, a trypsin-degrading enzyme. Mutations in *CTRC* cause protein loss of function by various mechanisms. *CTRC* secretion may be defective (p.A73T), the enzyme is inactive (p.K247_R254del) or its activity is reduced (p.V235I), CTRC degradation by trypsin is increased (p.R254W) or *CTRC* mRNA expression is decreased (p.G60=). Although most variants are sporadic, familial inheritance has been reported. *CTRC* mutations are considered disease modifiers rather than disease causing. CTRC p.G60= was estimated to increase chronic pancreatitis risk by 2.5-fold in heterozygous and by a 10-fold in homozygous patients [39,40].

3.1.2. Hereditary pancreatitis related to protein misfolding

Proteins fold into their native configuration and undergo post-translational modifications in the endoplasmic reticulum (ER). Mutation-induced misfolding of pancreatic proteins may cause ER stress by altered Ca2+ homeostasis and the accumulation of protein aggregates in the ER.

3.1.2.1. PRSS1. Rare *PRSS1* (such as p.R116C, p.C139S) variants impair trypsinogen folding causing intracellular protein retention [57].

3.1.2.2. CPA1. In 2013, *CPA1*, encoding the carboxypeptidase A1, was shown to be a causal gene for early-onset pancreatitis [41]. CPA1 mutations induce protein misfolding, which results in defective carboxypeptidase secretion, intracellular retention and ER stress. Mutations are expected to increase the risk for CP by 25-80-fold compared to a control population [41].

3.1.2.3. CEL mutations and the CEL-HYB allele. Mutations in *CEL*, a gene encoding carboxyl ester lipase, cause maturity onset diabetes of the young type 8 (MODY8) and are, in some patients, associated with exocrine pancreatic insufficiency [58]. Nonallelic homologous recombination of *CEL* with its adjacent pseudogene *CELP* has recently been recognized as a genetic risk factor for pancreatitis [42]. The hybrid protein remains stuck in the ER, causing ER stress.

3.1.3. Genes affecting ductal cell fluid production/composition

3.1.3.1. CFTR. The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, located on chromosome 7, codes for a cAMP-responsive chloride channel at the apical surface of secreting epithelia [59,60]. The CFTR protein also interacts with other membrane proteins to maintain epithelial tight junctions and barriers to fluid movements, regulates the activity of other anion channels and is responsible for maintaining an adequate internal pH of some intracellular organelles [61]. More than 2000 *CFTR* mutations have been described to date. The most frequent, occurring at least on 1 allele in >65% CF patients, is a 3-base-pair deletion causing the loss of a phenylalanine at position 508 of the protein (F508del). *CFTR* mutations have been classified into 6

categories based on their predominant effect on CFTR function or processing. Class I mutations regroup non-sense, frameshift or splicing mutations resulting in absent CFTR synthesis while class V and VI variants lead to reduced synthesis or decreased stability of the CFTR protein, respectively [62,63]. Mild alleles have a dominant effect over more severe alleles. As the functional impact of many mutations is still unknown and as some mutations probably have overlapping molecular effects, scores have been developed to predict the disease severity. The pancreatic insufficiency prevalence (PIP) score correlates the CFTR genotype with exocrine pancreatic function. Patients with severe *CFTR* mutations (Class I-III) have cystic fibrosis (CF), are usually pancreatic insufficient and have PIP scores of 1; while individuals with mild genotypes may have cystic fibrosis or CF-like disease, are pancreatic sufficient (PS) and have PIP scores <0.25. These patients, as they have a certain functional acinar reserve, are more prone to develop pancreatitis later in life [64].

3.1.3.2. CLDN2. *CLDN2* encodes the claudine-2 protein, a component of the tight junction [65]. The pathophysiologic mechanism by which variants in *CLDN2* cause pancreatitis remains to be further studied.

Dysregulation of calcium homeostasis. Impaired calcium homeostasis has been described to play a role in pancreatitis development.

3.1.3.3. TRVP6. *TRVP6* (transient receptor potential cation channel subfamily V member 6 gene) encodes an epithelial calcium channel [66]. The mechanisms underlying the development of pancreatitis in patients with *TRVP6* variants remain unclear. It is hypothesized that impaired Ca2+ uptake by the ductal cells may increase intraluminal Ca2+ levels and activate zymogens. Of note, 20% carry a compound heterozygous mutation in *SPINK1*.

3.1.3.4. CaSR and AP2S1. Calcium sensing receptor (*CaSR*) and adaptor-related protein complex 2 σ1 subunit (*AP2S1*) mutations lead to decreased sensitivity of the calcium sensor receptor to ionized calcium or altered receptor signal transduction; ultimately resulting in hypercalcaemia. A French study described an overrepresentation of rare CaSR mutations in a CP cohort [67]. Only a fraction of patients harbouring mutations in these genes will develop pancreatitis, and most of them carry a second heterozygous variant in *SPINK1*. Furthermore, pancreatitis could be abrogated by Ca2+-lowering medication in patients with compound heterozygous *CaSR* or *AP2S1/SPINK1* mutations [68,69]. Additional studies are necessary to strengthen the role of CaSR and AP2S1 in the pathogenesis of pancreatitis.

In summary, multiple causal and disease modifier genes have been discovered to date in individuals with early-onset pancreatitis. Physicians need to be aware that HP is a complex genetic disease, that often involves multiple genes. The impacts of multiple genetic mutations sum to give rise to pancreatitis with an earlier onset and an increasing degree of severity.

3.2. Management and long-term outcome

The management of patients with HP is no different from that of patients with other aetiologies of pancreatitis [70]. In the acute phase, the treatment of mild to moderate pancreatitis is based on fasting to rest the pancreas and intravenous hydration using isotonic crystalloid solutions. In the case of severe pancreatitis, early aggressive intravenous fluid resuscitation during the first 12–24 h is of critical importance [71]. Another essential factor in managing acute pancreatitis is to administer analgesics to relieve pain. The prophylactic use of antibiotics should be avoided; antimicrobial agents should be reserved for patients with a proven infection. Early ERCP is only recommended in case of concomitant acute cholangitis due to biliary obstruction, which is rare in HP patients [72].

The diagnosis of chronic pancreatitis (CP) is based on (repetitive) documented bouts of pancreatitis and/or persistent abnormalities of the gland on imaging and/or exocrine or endocrine pancreatic dysfunction [73]. The management of CP consists of treating the pain and correcting the functional deficiencies. Patients should also be counselled to avoid additional exposure to environmental risk factors for pancreatitis such as alcohol and smoking [74].

Pain in CP is addressed medically with analgesics, following the WHO guidelines for pain management. In cases of unsuccessful analgesic therapy, endoscopy or surgery should be attempted to alleviate any pancreatic duct obstruction (stones, stenosis) and thereby the pain [70]. The genetic nature of HP suggests a higher risk of pancreatitis recurrence than other causes of CP. Total pancreatectomy with islet autotransplantation (TPIAT) has been well described as a more definitive therapeutic option for paediatric and adult patients with HP unresponsive to medical, endoscopic or conventional surgical approaches [75]. Dietary counselling should be offered to patients with proven exocrine pancreatic insufficiency in addition to supplements of fat-soluble vitamins and pancreatic enzymes. Diabetic patients should be addressed to the endocrinologist.

Studies analysing the long-term outcome of HP patients have been hampered by small cohort sizes, the wide spectrum of mutations (compound heterozygous, *trans*-heterozygous mutations) and difficulties evaluating the additional impact of confounding factors such as smoking and alcohol consumption. Nevertheless, HP predisposes patients to an increased risk for exo- and endocrine pancreatic insufficiency as well as pancreatic cancer. Lifelong patient surveillance is therefore mandatory to detect threatening complications early.

The risk of pancreatic dysfunction increases significantly with advancing age and is influenced by the patient's genotype. Few large cohort studies have reported functional outcomes for patients carrying mutations in PRSS1 and SPINK1 (Table 6). The long-term evolution of patients with other gene mutations remains more elusive.

Pancreatic cancer is a dreaded complication of HP, with a cumulative incidence ranging from 7.2 to 53.5% at 70years (Table 7). The variability among studies may be explained by referral bias, variable inclusion of patients with milder phenotypes and improved prevention of other risk factors such as alcohol or smoking over time, which positively impacts outcomes. The increased susceptibility to pancreatic cancer in HP patients has led to the development of surveillance guidelines [72]. Patients with HP should be screened for pancreatic adenocarcinoma and followed-up in experienced centres. Annual surveillance is recommended to start at 50y or 10y before the onset age of pancreatic cancer in a family member. Imaging modalities of choice are either magnetic resonance imaging or endoscopic ultrasound. Cystic lesions observed during follow-up screening should be further evaluated by an experienced multidisciplinary team.

4. Summary

Early onset exocrine pancreatic insufficiency rarely occurs in children and is almost invariably associated with generalized inherited disorders. Over the last decades, early recognition and management have led to significant survival improvement; many patients now reach adulthood. Cystic fibrosis represents by far the primary cause of EPI (95%). Recent advances in human genome sequencing and editing as well as in techniques to study disease mechanisms have provided an unprecedented opportunity to increase our understanding of rare diseases. Unravelling pathophysiologic mechanisms has also paved the way for the development of novel therapies. The *CFTR* gene was discovered 30 years ago, and recently, research has led to the development of different channel modulators that can significantly impact different organ functions and quality of life. Studies are ongoing to further address the impact of these molecules on acinar reserve and more broadly, pancreatic function. In the meantime, major efforts have improved our knowledge of the complex mechanisms underlying

Table 6
Risk for exocrine and endocrine pancreatic insufficiency in patients with hereditary pancreatitis.

Exocrine pancreatic insufficiency													
Study		Population	Patient (n =)	Exo PI	Age at Exo PI (y)	Time to Exo PI (y)	Cumulative incidence of Exo PI (%)						
							10y	20y	30y	40y	50y	60y	70y
Rebours [49]	HP	France	200	67/200 (34%)	29 (1–76)	–	0	15	35	53	67	79	92
	PRSS1	France	135	50/135 (37%)	30 (1–76)	–	0	9	27	48	64	77	93
Masamune [76]	HP	Japan	271	54/139 (39%)	–	42 (38–46)	3	16	29	45	57	69	–
	PRSS1	Japan	71			35 (26–44)							
	SPINK1	Japan	41			42 (28–57)							
	Other	Japan	32			53							
Zou [77]	HP	China	535	93/535 (17%)	39	–	7	32	51	72	91	98	99
Muller [55]	SPINK1	France/UK	209	77/209 (37%)	50 (45–55)	–	–	5	15	28	52	–	–
Endocrine pancreatic insufficiency													
Rebours [49]	HP	France	200	51/200 (26%)	38 (14–76)	–	0	15	35	53	67	79	92
	PRSS1	France	135	38/135 (28%)	37 (14–76)	–	0	9	27	48	64	77	93
Masamune [76]	HP	Japan	271	30/139 (22%)	–	58 (52–64)	2	6	13	29	36	53	–
	PRSS1	Japan	71			42 (36–48)							
	SPINK1	Japan	41			61 (40–82)							
	Other	Japan	32			58 (28–88)							
Zou [77]	HP	China	535	122/535 (23%)	39	–	2	22	39	59	83	96	99
Muller [55]	SPINK1	France/UK	209	36/209 (17%)	69 (56–81)	38 (33–42)	–	–	8	13	26	43	–

Endo PI: endocrine pancreatic insufficiency; ExoPI: exocrine pancreatic insufficiency; HP: hereditary pancreatitis; y: years.

Table 7
Risk for pancreatic adenocarcinoma in patients with hereditary pancreatitis.

Study		Population	Patient (n =)	PDAC/PCancer	Age at PDAC/PCancer	Cumulative incidence of cancer (%)			
						30y	40y	50y	60y
Rebours [49]	HP	France	200	10/200 (5%)	55 (39–78)	–	10	18,7	53,5
Masamune [76]	HP	Japan	271	7/158 (4,4%)	45 (30–65)	3	7	11	23
Muller [55]	SPINK1	France/UK	209	7/107 (3,3%)	60	–	1	12	28

HP: hereditary pancreatitis; PCancer: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma.

ribosome biogenesis and its clinical phenotype translation. Until more targeted treatments are conceived, the cornerstones of EPI management are enzyme replacement therapy, liposoluble vitamin supplementation and nutritional support.

Thanks to the development and broader use of DNA sequencing techniques, HP is increasingly recognized in patients with early-onset disease. The clinical presentation and acute episode management is similar to other pancreatitis aetiologies; nevertheless, those patients are at increased risk for exocrine and endocrine dysfunction as well as pancreatic cancer. Physicians need to be aware of these specificities, as follow-up of these patients is mandatory to detect these life-threatening complications early.

Declaration of competing interest

The author has no potential conflict of interest.

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