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Congenital diarrhoeal disorders: advances in this evolving web of inherited enteropathies

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Abstract

Congenital diarrhoeal disorders (CDDs) represent an evolving web of rare chronic enteropathies, with a typical onset early in life. In many of these conditions, severe chronic diarrhoea represents the primary clinical manifestation, whereas in others diarrhoea is only a component of a more complex multi-organ or systemic disorder. Typically, within the first days of life, diarrhoea leads to a life-threatening condition highlighted by severe dehydration and serum electrolyte abnormalities. Thus, in the vast majority of cases appropriate therapy must be started immediately to prevent dehydration and long-term, sometimes severe, complications. The number of well-characterized disorders attributed to CDDs has gradually increased over the past several years, and many new genes have been identified and functionally related to CDDs, opening new diagnostic and therapeutic perspectives. Molecular analysis has changed the diagnostic scenario in CDDs, and led to a reduction in invasive and expensive procedures. Major advances have been made in terms of pathogenesis, enabling a better understanding not only of these rare conditions but also of more common diseases mechanisms.

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Author contributions

The authors contributed equally to all aspects in the production of this article.

Competing interests

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Introduction

Congenital diarrhoeal disorders (CDDs) are a group of rare enteropathies characterized by a heterogeneous aetiology with a typical early onset of symptoms. They are generally monogenic disorders inherited in an autosomal recessive manner.[1] CDDs are challenging to treat because of the severity of the clinical picture and the broad range of disorders in differential diagnosis.[1] Abnormal fluid transport might begin *in utero,* manifesting as maternal polyhydramnios. Then, soon after birth, patients usually present with severe diarrhoea that typically, within a few days, leads to severe dehydration and serum electrolyte imbalance. In the vast majority of cases patients require hospitalization and a prompt diagnosis.[1] The more severe forms of CDDs produce life-threatening chronic diarrhoea with massive loss of fluids and intestinal failure requiring long-term parenteral nutrition. They are associated with substantial mortality and morbidity and many patients undergo intestinal transplantation procedures.[1] Rare, mild forms with subtle clinical signs might remain undiagnosed until adulthood, by which time patients have developed irreversible complications, as observed in some patients with congenital chloride diarrhoea who develop renal dysfunction and gout as a consequence of a chronic contraction of the intravascular space.[2] Some CDDs can be treated with dietary modification, but in many cases chronic nutritional support is required. The exact prevalence of CDDs remains to be established; it differs among populations and geographical areas. A study from the Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition estimated that autoimmune enteropathy and microvillus inclusion disease (MVID) are the most common causes of CDDs.[3]

Diarrhoea can be the result of secretory and/or osmotic or inflammatory mechanisms.[4] Secretory diarrhoea is characterized by an increased electrolyte and water flux towards the intestinal lumen, resulting from either inhibition of sodium chloride (NaCl) absorption by villous enterocytes or an increase in chloride ion (Cl^-) secretion by epithelial cells in the crypts.[4] An example of a predominant secretory diarrhoea is MVID.[5] Osmotic diarrhoea is caused by the presence of nonassimilated nutrients in the gut, which drives fluid into the lumen via osmotic forces.[4] An example of a pure form of osmotic diarrhoea is glucose-galactose malabsorption, in which the unabsorbed monosaccharide reaching the colon results in diarrhoea.[6] Inflammatory diarrhoea is caused by dysregulation of the immune system leading to inflammatory infiltration and damage to the gut mucosa, as observed in autoimmune enteropathy or in immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome.

Evaluation of CDDs includes understanding the basic mechanism(s) responsible for disease. However, the increasing number of conditions included within the CDDs group—together with the fact that different conditions could be characterized by the same mechanism or that different mechanisms could overlap in the same patient—might limit this approach. Evolving knowledge of the pathogenesis of CDDs suggests the utility of a classification system based on the main pathogenetic mechanism, which could help the approach to these patients (Figure 1). This classification comprises four groups of disorders: one, defects in digestion and absorption of nutrients and electrolytes; two, defects in enterocyte structure; three, defects in enteroendocrine cell differentiation; and four, defects in intestinal immune-

related homeostasis. This Review highlights new CDD entities and advances understanding of functionally related genes that are opening new diagnostic and therapeutic perspectives.

Defects in digestion and absorption

This group includes the most abundant number of CDDs. They are conditions in which a defect in one of the main mechanisms of digestion or transport of nutrients and electrolytes leads to chronic diarrhoea. The prototypes of this group are glucose-galactose malabsorption and congenital chloride diarrhoea,[7,8] but new conditions have been described. No histological or ultrastructural defects are generally observed in these patients at the gut level (Table 1).

Familial diarrhoea syndrome

This condition has been described in 32 members of a Norwegian family, and is characterized by early-onset chronic diarrhoea and meteorism (also known as tympanites). Abdominal pain, dysmotility and IBD have been described in a subset of patients.[9] All affected members have a heterozygous missense mutation (p.Ser840Ile) in the *GUCY2C* gene, which encodes the intestinal guanylate cyclase receptor for uroguanylin, guanylin and heat-stable enterotoxins. Although this gain-of-function variant increases ligand-mediated activation of guanylate cyclase and intracellular cyclic guanosine monophosphate (cGMP) levels, basal levels are comparable to the wild-type receptor.[9] Elevated cGMP levels results in activation of protein kinase GII, leading to phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR) channel.[10] This phosphorylation leads to severe chronic secretory diarrhoea deriving from an efflux of Cl^- and water into the intestinal lumen, with reduced sodium ion (Na+) absorption owing to inhibition of the Na^+-H^+ exchanger 3 (NHE3).[11]

DGAT1-deficiency-related diarrhoea

A rare null mutation in *DGAT1* (which encodes acyl CoA:diacylglycerol acyltransferases 1) has been reported in two infants, resulting in a CDD and protein losing enteropathy.[12] DGATs catalyse the final step of triglyceride synthesis. *DGAT1* is expressed ubiquitously, with highest expression in the gut. Animal models lacking *DGAT1* have delayed fat absorption with more fat reaching the distal gut. However, how DGAT1 deficiency causes diarrhoea and protein losing enteropathy is still unclear. A possible explanation could be the toxic role of excess diacylglycerols or fatty acids, which might act as bioactive signalling lipids or via a detergent-like action.[12]

Defects in enterocyte structure

Typical histological and ultrastructural hallmarks characterize this group of severe disorders that includes two main conditions: MVID,[13,14] and congenital tufting enteropathy (CTE).[15] Syndromic diarrhoea, also known as phenotypic diarrhoea or tricho-hepato-enteric syndrome (THE), is commonly included in this group, and is characterized by a wide range of histological damage[16] (Table 2). Progresses in managing patients with parenteral nutrition and intestinal transplantation have reduced the mortality rate of these conditions.

Nevertheless, advances in genetics open new perspectives in understanding their mechanisms and in the clinical approach.

Microvillus inclusion disease

The pathognomonic characteristic of MVID is loss of the apical brush border and the formation of intracellular microvillus inclusions. These microvillus inclusions are observed in ~10% of enterocytes at the villus tips, whereas normal brush borders are often present on the enterocytes in the proximal part of the villus.[17] These findings suggest that microvilli are formed initially and that stabilization of initial cell polarity might represent a future target for therapy in MVID. Most patients with early-onset MVID display inactivating mutations in myosin Vb *(MYO5B)*.[18] MYO5B works as a dynamic tether for specific RAB small GTPases (RAB8A, RAB10, and RAB11) maintaining these proteins at their appropriate subapical membrane localization. This interaction is crucial to maintain normal intestinal epithelial cell polarity, apical trafficking and microvilli growth. Alterations in this interaction, deriving from mutations in *MYO5B,* lead to a mucosa with decrements in absorptive pathways and a leaky epithelium at the villus tips, which causes alterations in both intercellular junctions and ion transport pathways necessary for adaptation through transcellular pumps and channels.[19,20] These concepts have been supported by the findings of Knowles *et al.;*[17] using a cellular model of MVID, they demonstrated that loss or mutation in *MYO5B* causes uncoupling of RABs from MYO5B with an abnormal localization of RAB8A and RAB11A throughout the cytoplasm.[17] Uncoupling of MYO5B from RAB8A promotes loss of microvilli, and a loss of interactions between RAB11A and MYO5B results in formation of microvillus inclusions.

Why MVID mutations lead to an enterocyte-specific effect as opposed to more global effects is poorly understood, given that other highly polarized epithelial tissues seem unaffected by the disease. In vertebrates, three isoforms of myosin V are recognized: MYO5A; MYO5B; and MYO5C.[21] All these isoforms can interact with RAB10 and RAB8A, but only MYO5A and MYO5B can bind to RAB11 family members.[21] One possible explanation for the severity of the intestinal features in patients with MVID is that MYO5A might compensate for the loss of MYO5B in other polarized cell types and that low levels of MYO5A in enterocytes make intestinal epithelial cells more vulnerable to loss or mutation of MYO5B.[20] Moreover, the mechanisms for establishing apical microvillar specializations might differ in different polarized epithelial cells.[20] In addition to chronic unremitting diarrhoea, patients with MVID can also develop cholestatic liver disease that worsens after intestinal transplantation. The origin of this condition has been related to altered MYO5B-RAB11A interaction, defective bile salt export pump in hepatocytes, and increased ileal bile acid absorption.[22]

Whole-exome sequencing of DNA from patients with MVID who have milder clinical phenotypes permitting partial or complete weaning from parenteral nutrition, showed homozygous truncating mutations in an apically targeted *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) named syntaxin 3 (*STX3*).[5] Syntaxin 3 acts as a regulator of protein trafficking, vesicle fusion and exocytosis, and exerts a pivotal role in cell polarity in the intestine, liver, kidney and stomach.[5] Interestingly, patients with mutations in

syntaxin 3 binding protein 2 (*STXBP2*) causing familial haemophagocytic lymphohistiocytosis type 5, have microvillus atrophy with clinical and histological findings similar to MVID.[23]

Congenital tufting enteropathy

Patients affected by CTE show typical epithelial tufts that can be present from the duodenum to the large intestine. The disorder has been linked to mutations in the epithelial cell adhesion molecule gene (*EPCAM*). The *EPCAM* expression pattern varies along the crypt-villus axis, with highest expression in the crypt epithelial and a decline in cells expressing this protein at the top of the villi. *EPCAM* does not localize to the apical membrane, but is abundant along the basolateral membranes where it regulates cellular adhesion and proliferation.[24] EpCAM is thus a pleiotropic molecule with an important role in initiation, development, maintenance, repair and in the functioning of gut epithelia. In patients with CTE, the phenotype associated with mutations of *EPCAM* gene is usually characterized by isolated diarrhoea without associated extraintestinal symptoms, except for late-onset arthritis in a subgroup of patients.[25]

A second group of individuals with CTE characterized by mutations in *SPINT2* (which encodes kunitz-type protease inhibitor 2 [also known as hepatocyte growth factor activator inhibitor type 2, HAI-2]) have been identified. As with EpCAM, HAI-2 is a transmembrane protein.[25] This potent serine protease inhibitor is involved in epithelial regeneration, as well as in the NF-KB and transforming growth factor (TGF)-β signalling pathways. Children with *SPINT2* variants present with a syndromic form of CTE, characterized by chronic diarrhoea, associated with superficial punctate keratitis and choanal atresia, as well as other sporadic abnormalities. These different but overlapping enterocyte abnormalities suggest that the two disease-associated genes belong to distinct pathways both regulating cell adhesion and cytoskeleton dynamics leading to the CTE phenotype.[25]

Tricho-hepato-enteric syndrome

Patients with THE (also known as syndromic diarrhoea) present with chronic diarrhoea, facial dysmorphism and hair abnormalities, which might or might not be associated with other signs or symptoms, such as intrauterine growth retardation, immunodeficiency, skin abnormalities, liver disease, congenital cardiac defects and platelet anomalies.[16] Moderate to severe villus atrophy with inconstant infiltration of mononuclear cells characterizes the histological picture. THE is caused by a mutation in *TTC37* in 60% of cases and *SKIV2L* in 40% of the cases.[26] No genotype-phenotype correlation can be made either with the causative gene (*TTC37* or *SKIV2L*) or the mutation type. TTC37 (tetratricopeptide repeat protein 37; also called Ski3) is expressed in many tissues, including vascular endothelium, lung and intestine, but not in the liver.[26] TTC37 (Ski3) is a key component of the SKI complex, a multiprotein complex required for exosome-mediated RNA surveillance.[26] Subsequently, mutations in *SKIV2L* in a group of six individuals affected by typical THE syndrome, but negative for *TTC37* mutations, have been described.[27] The mutation types suggest that the disease mechanism is *SKIV2L* loss-of-function of a cytoplasmic exosome cofactor involved in various mRNA decay pathways and required for normal cell growth.[27]

The mechanism by which mRNA surveillance defects lead to various clinical symptoms needs further investigation.[16]

Defects in enteroendocrine cell differentiation

These conditions are characterized by abnormal enteroendocrine cell development or function and manifest as pure forms of congenital osmotic diarrhoea, associated or not with other systemic endocrine abnormalities. The common feature of this group of CDDs is that the genes encode either transcription factors that generate all or a subset of enteroendocrine cells, or an endopeptidase expressed in all endocrine cells, which is therefore required for the production of all active hormones (Table 3). Various knockout mouse models of each of these genes are associated with early postnatal mortality and occasionally diarrhoea.[28–30] Four genes are involved in this group of CDDs: *NEUROG3; RFX6; ARX;* and *PCSK1.*

Enteric anendocrinosis

Studies in knockout mouse models have demonstrated that neurogenin-3 (encoded by *NEUROG3;* a basic helix-loop-helix transcription factor) is required and sufficient to drive the development of enteroendocrine cells and β-cells in pancreatic islets.[31] Children with neurogenin-3 deficiency present with a severe paucity of enteroendocrine cells (enteric anendocrinosis), and also develop insulin-dependent diabetes mellitus in early childhood, but not other endocrine abnormalities.[32]

Mitchell-Riley Syndrome

Homozygous mutations of *RFX6* are associated with a complex clinical phenotype (Mitchell-Riley syndrome) highlighted by duodenal atresia, biliary abnormalities, neonatal diabetes mellitus and malabsorptive diarrhoea.[28] DNA-binding protein RFX6 (also known as regulatory factor X 6; encoded by *RFX6)* is a winged-helix transcription factor that is downstream of neurogenin-3 and is required for islet cell development and enteroendocrine cell function.[33] Unlike in children with neurogenin-3 deficiency, mutation of *RFX6* is associated with normal enteroendocrine cell number. The intestinal atresia associated with *RFX6* mutations is probably related to a not yet fully characterized role of *RFX6* in the early gut endoderm. Furthermore, although mouse studies suggest that DNA-binding protein RFX6 is exclusively expressed in enteroendocrine K-cells that express gastric inhibitory polypeptide and others hormones, it remains uncertain if this subset of cells is depleted in humans with DNA-binding protein RFX6 deficiency.[34]

Other defects of enteroendocrine cell differentiation

Mutations in the *ARX* gene—which encodes homeobox protein ARX (also known as aristaless-related homeobox), a paired homeodomain transcription factor—are associated with a complex clinical phenotype of X-linked mental retardation, seizures, lissencephaly, abnormal genitalia and occasionally congenital diarrhoea.[35] The *ARX* gene is a downstream target of neurogenin-3 and is expressed in a subset of enteroendocrine cells, including those that express cholecystokinin, secretin and glucagon.[29] More than 50% of patients with loss-of-function *ARX* mutations have a polyalanine expansion that might account for the highly

variable neurological and intestinal clinical phenotypes that are associated with this disorder.[36]

All functional hormones produced by endocrine cells, including those in the gut, are processed by a specific Ca^{2+}-dependent serine endoprotease named proprotein convertase 1/3 (PC1/3; also known as neuroendocrine convertase 1) that converts prohormones into their bioactive form.[30] Homozygote loss-of-function mutations in *PCSK1* (which encodes PC1/3) have been associated with malabsorptive diarrhoea and other endocrinopathies including adrenal insufficiency, hypothyroidism and hypogonadism.[37,38] PC1/3 is also expressed in the hypothalamic region that produces various central orexigenic hormones that control appetite, and children with mutations in *PCSK1* are extremely polyphagic. In a cohort of children with this disorder (enteric dysendocrinosis), severe failure to thrive was commonly found, and parenteral nutrition was required for the first several years of life.[39–41] Interestingly, polyphagia induced by abnormalities in central processing of components of the leptin signalling pathway results in moderate obesity beyond the first several years of life despite chronic diarrhoea. These children also develop diabetes insipidus and growth hormone deficiency, which distinguishes *PCSK1* deficiency from other enteric endocrinopathies. These findings suggest that enteric hormones might be particularly important to facilitate nutrient absorption during infancy when caloric requirement (per body weight) is at its highest.

Defects in intestinal immune homeostasis

Mutations in genes encoding proteins with relevant functions in intestinal immune-related homeostasis can result in early-onset chronic diarrhoea. In these CDDs, diarrhoea can derive from three main mechanisms: altered immune response against pathogens, inflammation or lack of immune regulation. Depending on the type of underlying immunological defect, the three mechanisms can variably contribute to clinical and histological manifestations. Predominant autoimmune enteropathy can be recognized in patients with genetically determined lack of specific immune regulatory mechanisms causing uncontrolled self-tissue aggression or uncontrolled inflammation (Table 4).

IPEX syndrome

IPEX syndrome is the prototype genetic autoimmune enteropathy. It is due to a mutation in the *FOXP3* gene, which is an essential transcription factor for thymic-derived regulatory T (T_{REG}) cell function.[42] $FOXP3^+$ T cells are one of the main subset of $CD4^+$ T_{REG} cells, and are able to control undesirable effector-T-cell function. *FOXP3* mutations are distributed throughout the gene and are loss-of-function. As a consequence, T_{REG} cells with mutated *FOXP3* normally differentiate in the thymus and can be detected in the peripheral blood and tissues of patients with IPEX but are unable to suppress effector T cells. The early neonatal onset and severity of IPEX enteropathy suggests that the damage is probably already established during fetal life, independent of external environmental factors, such as nutrients and gut microbiota. In addition to the intestinal architectural changes, anti-harmonin antibodies are uniquely found in IPEX and have high diagnostic value.[43] Harmonin is a scaffold protein expressed by intestinal epithelial cells, but why it is specifically targeted in patients with IPEX syndrome and not in patients with similar enteropathies and wild-type

FOXP3, still has to be clarified. However, autoantibodies against target organs are abundant in patients with IPEX, in whom T_{REG}-cell dysfunction is also associated with an increased number of autoreactive B cells owing to altered peripheral B-cell tolerance influencing the production of autoantibodies.[44]

As well as being essential for T_{REG}-cell function, FOXP3 is also transiently expressed by any activated T cells, in which it controls the cell cycle and development of T helper (T_H) cells.[45] This factor adds further complexity to the pathogenesis of IPEX, in which intrinsic impairment of the FOXP3 mutant effector-T-cell functions should be considered. Indeed, patients with IPEX manifest lymphoproliferation, a higher frequency of T_H2 over T_H1 cells and increased levels of peripheral T cells producing IL-17, a proinflammatory cytokine frequently reported in autoimmune diseases. Interestingly, mucosa lymphocyte infiltration in IPEX is predominantly by $CD4^+$ T cells, some of which express FOXP3.[44] Gut-infiltrating lymphocytes, isolated from biopsy samples of patients with IPEX and expanded *in vitro,* are enriched with IL-17-producing cells that co-express FOXP3 (L. Passerini and R. Bacchetta unpublished data). These cells could have a direct role in gut damage, whether they are activated effector T cells producing IL-17 or T_{REG} cells that, because of the FOXP3 mutation, are unstable and gain effector functions.

Lentiviral-mediated overexpression of wild-type FOXP3 successfully conveys stable regulatory function to FOXP3 mutant T cells,[44] opening new therapeutic perspectives for patients with IPEX. Several patients with IPEX have been cured with haematopoietic stem cell transplantation,[46] but this approach is preferentially feasible in children with HLA-matched donors (which are not always available). Gene correction of autologous stem cells will hopefully become an option for patients with IPEX. Other therapeutic approaches—that is, alternatives to multiple immunosuppression—could also be envisaged, aiming to re-establish tolerance in a FOXP3-independent manner. For example, IL-10 dependent type 1 regulatory T (Tr1) cells—which have an important role in peripheral regulation—can differentiate in patients with IPEX despite the presence of *FOXP3* mutation; therefore, therapeutic interventions facilitating Tr1 differentiation that could restore immunoregulation and antagonize inflammation could be envisaged. Interestingly, patients with IPEX who have their *FOXP3* mutations diagnosed late and with unusual clinical presentation, such as gastritis or nephropathy, have been reported.[47-48] Whether this different phenotype is due to the presence of hypomorphic mutation with residual protein function or due to the presence of more efficient FOXP3-independent compensatory mechanisms of tolerance remains to be clarified.

IPEX-like syndromes

These conditions are associated with mutations in genes other than *FOXP3* that are important for T_{REG}-cell maintenance, signalling and expansion.[49] Mutations in *CD25* are responsible for early-onset enteropathy resembling IPEX with autosomal recessive inheritance. Given that interleukin-2 receptor subunit alpha (also known as CD25; encoded by *CD25)* is essential not only for T_{REG}-cell function but also to mount an appropriate immune response, these patients also have an impaired ability to fight infections; the early-onset enteropathy in these patients might be due to *Cytomegalovirus* infection, concomitant

with the immune dysregulation. The majority of patients with an IPEX-like syndrome, however, lack a clear diagnosis of the underlying mechanism of their disease. In at least a group of these patients, a quantitative defect in FOXP3$^+$ T_{REG} cells is detected by measuring the peripheral percentage of the T_{REG}-specific DNA demethylated region (TSDR) of FOXP3, but the underlying gene defects still has to be determined.

Mutations in *STAT5B,* responsible for transactivation of the IL-2 signal from CD25 to FOXP3, have been described associated with reduced number of T_{REG} cells.[49] Children with *STAT5B* (signal transducer and activator of transcription 5b) mutation have symptoms other than enteropathy, such as growth failure and interstitial lung disease, that can help in establishing the diagnosis. Early-onset chronic or recurrent enteropathy has also been reported in patients with either loss-of-function or gain-of-function mutations in *STAT1,* which also impinges effective immunity.[50] Infections and progressive loss of T cells (both in terms of number and function, including T_{REG} cells) is reported in patients with loss-of-function mutations, whereas T_{REG}-cell instability has been suggested as a consequence of the gain-of-function variants, which is characterized by chronic mucocutaneous candidiasis.[49] A more predominant inflammatory imbalance has been described in an extended family with recurrence of lymphoproliferation, inflammation and dysmorphisms, due to mutation in *ITCH*, which encodes an ubiquitin ligase implicated in several T-cell functions.[49]

An IPEX-like disorder (characterized by diarrhoea) with profound T_{REG}-cell deficiency but a normal *FOXP3* gene sequence has been described with homozygous nonsense mutation in the *LRBA* (lipopolysaccharide-responsive and beige-like anchor) gene.[51,52] Patients with *LRBA* mutations were previously reported to have common variable immunodeficiencies phenotype and autoimmunity.[51] Analysis of other patients with LRBA deficiency clearly revealed T_{REG}-cell deficiency, decreased T_{REG}-cell markers, and impaired suppressive function of T_{REG} cells.[52]

IL-10 or IL10R deficiency

IL-10 or IL-10 receptor (IL-10R) response insufficiency is characterized by enterocolitis with ulcerative lesions in the perianal area and in the intestinal mucosa.[53] Fistula and abscesses can also be present, with recurrence requiring multiple surgical interventions. Gene mutations in either *IL10RB* or *IL10RA* (interleukin-10 receptor subunit alpha or beta) abrogate response to IL-10, causing persistent colonic inflammation.[54] Lack of STAT3 phosphorylation in response to IL-10 can be detected *in vitro* and used as a first indication of the disease cause.[55] Several anti-inflammatory drugs have been used, but pharmacological approaches only have limited efficacy. Haematopoietic stem cell transplantation has been used successfully to cure the disease.[56] Although studies of Tr1 cells in these patients have not been directly performed, these disorders illustrate the essential role of IL-10 in controlling intestinal homeostasis.[57] Interestingly, independent genome studies have demonstrated attenuated mutations in *IL-10, IL10RA, IL10RB* or in *FOXP3* in a few rare patients with IBD. This confirms the nonredundancy of both regulatory pathways in the intestine and the importance of considering genetic screening in the presence of early-onset disease.[57]

Molecular diagnostics

In the past decade, the genes responsible for most CDDs have been identified (Tables 1–4). The availability of DNA sequencing techniques, at reasonable cost, has greatly improved the diagnostic approach to these conditions through the search for DNA mutations in samples from blood cells or from amniocytes and chorionic villi (prenatal diagnosis). Molecular genetics has become helpful to obtain early and unequivocal diagnoses in patients at an age in which chronic diarrhoea might be due to a myriad of different disorders, thus permitting rapid and targeted therapeutic strategies[58] and reducing repetitive invasive and expensive procedures. Furthermore, the identification of disease-causing mutations in the affected proband along with family counselling can help to reveal asymptomatic carriers and to offer future prenatal diagnosis.[59]

Whether the type of mutation(s) can provide guidance as to the severity of the clinical phenotype is still under discussion. In selected CDDs, such as congenital chloride diarrhoea, the clinical expression is poorly related to the genotype and modifier genes might contribute to modulate the phenotype. However, genotype might predict response to therapy. For example, it has been demonstrated that specific *SLC26A3* mutations that retain at least some activity of the protein could predict a more pronounced effect of oral butyrate therapy.[60]

Although molecular genetics represents a relevant contribution to the multistep diagnostic approach to CDDs, some critical points need to be discussed. In most genes responsible for CDDs, mutations are detectable throughout the gene—with the exception of a few conditions, such as congenital chloride diarrhoea, congenital lactase deficiency, sucrose-isomaltase deficiency and MVID, in which, in some specific ethnic groups, only a few mutations are implicated owing to a founder effect.[1] This finding suggests that sequencing analysis of the whole coding region of the gene must be used to obtain a satisfactory detection rate. For most CDDs, sequencing of the whole coding region of the gene is needed to detect mutation(s) in up to 90% of affected alleles, but a few alleles remain uncharacterized. However, sequencing frequently reveals novel mutations and in some cases (for example, missense mutations) it might be difficult to be certain of their pathogenic effect, hampering our ability to provide family counselling with certainty. In these cases, international repositories of mutations might help laboratories involved in performing molecular genetics, but such databases are not available for all CDDs. Data obtained in large series of healthy individuals from the same ethnic group might help to elucidate if a genetic variant is a benign polymorphism with a high frequency in the general population. The 1000 Genomes Project[61] will address some of these concerns. More complex *in vitro* functional studies are required to assess the effect of mutations of uncertain clinical significance, but such studies are rarely performed in a routine setting.

Conclusions

We are observing a substantial improvement in understanding the evolving web of CDDs. Major advances have been made in terms of pathogenesis, enabling a better understanding not only of these rare conditions but also of more common diseases. Although the list of CDDs is continuously expanding, findings from both experimental models and human data are leading to improved diagnostic and therapeutic strategies (Box 1). Development of a

procedure to propagate 3D ‘enteroids’ from human intestinal stem cells is providing exciting new research perspectives for research and therapy by increasing our understanding of human intestinal pathophysiology, developmental biology and regenerative medicine.[62] A 3D culture of intestinal stem cells (organoids) derived from duodenal biopsy specimens from patients with MVID has been developed, which recapitulates most typical morphological features of the disease.[5]

Molecular genetics will further change the diagnostic scenario in CDDs. The availability of massive sequencing techniques is leading to the identification of novel disease-genes, improving our understanding of the pathophysiology of CDDs and the development of targeted therapies. Indeed, haematopoietic stem cell transplantation is becoming a valid therapeutic option for several defects in intestinal immune-related homeostasis.[63] Novel gene therapy approaches using homing endonucleases, including TALENs (transcription activator-like effector nucleases) or CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR associated protein 9), or other technologies could also be pursued.[64] Furthermore, sequencing will be extended to noncoding, regulatory regions of disease-genes such as the promoter,[65] introns and the 3’ untranslated regions,[66] increasing the detection rate of mutations and opening up the possibility of further molecular therapies.[67]

Long-term studies should be encouraged to provide more insights on the prognosis of these conditions. For example, in CTE an increased chance of weaning off parenteral nutrition with increasing age has been demonstrated—ranging from 10% chance at the age of 10 years to 40% at the age of 10–20 years.[68] This finding suggests that intestinal transplantation should be avoided if possible. Given the number of CDDs, the complexity of genotype-phenotype correlations and the need for multidisciplinary counselling to families, a strict collaboration between physicians and molecular laboratories within international networks could be useful to limit the creation of orphan diseases. Some examples of this are the MVID Patient Registry[69] (dedicated to all clinicians and scientists working in the fields of MVID and the MY05B gene), the Congenital Diarrheal Disorders website[70] and the IPEX syndrome consortium,[71] with the aim of providing rapid access to molecular analysis and other diagnostic procedures for patients with suspected CDDs.

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Box 1 |

Treatments for congenital diarrhoeal disorders

Defects in absorption and transport of nutrients and electrolytes

- Nutrition therapy (exclusion diet, special formulae)
- Substitutive therapy (salts, Zn^{2+})
- Parenteral nutrition

Defects in enterocyte structure

- Total parenteral nutrition
- Antisecretory drugs
- Intestinal transplantation

Defects in enteroendocrine cell differentiation

- Total parenteral nutrition that can be weaned beyond 2 years of age

Defects in intestinal immune-related homeostasis

- Total parenteral nutrition and hormone replacement therapy
- Immunosuppressive and immunomodulatory drugs (corticosteroids, cyclosporine, azathioprine, 6-mercaptopurine, tacrolimus, mycophenolate mofetil, sirolimus, infliximab, rituximab)
- Bone marrow transplantation

Key points

- Congenital diarrhoeal disorders (CDDs) are a group of rare inherited enteropathies with a typical onset early in the life
- These disorders are challenging clinical conditions because of the severity of the clinical picture and the broad range of diseases in differential diagnosis
- To simplify the approach to these conditions, a classification in four groups according to the main pathogenetic mechanism has been proposed
- The number of conditions included within the CDDs group has gradually increased, and many new genes have been identified, opening new diagnostic and therapeutic perspectives
- Clinically actionable molecular methods to diagnosis CDDs, and other monogenic disorders, have markedly improved in recent years
- Continued research is focused on identifying novel CDDs, and to define in detail the pathogenesis of established disorders that might provide novel therapeutic options to ameliorate morbidity and mortality

Review criteria

A literature search of the PubMed database was performed with the following search terms: “chronic diarrhea”; “congenital diarrheal disorders”; and the name of all congenital diarrheal disorders. Clinical cases, case series, reviews and research articles were analysed for this Review, with particular focus on manuscripts published in the past 5 years. Abstracts accepted for the 2014 ESPGHAN Meeting (published in the *Journal of Pediatric Gastroenterology and Nutrition*, June 2014) were also reviewed.

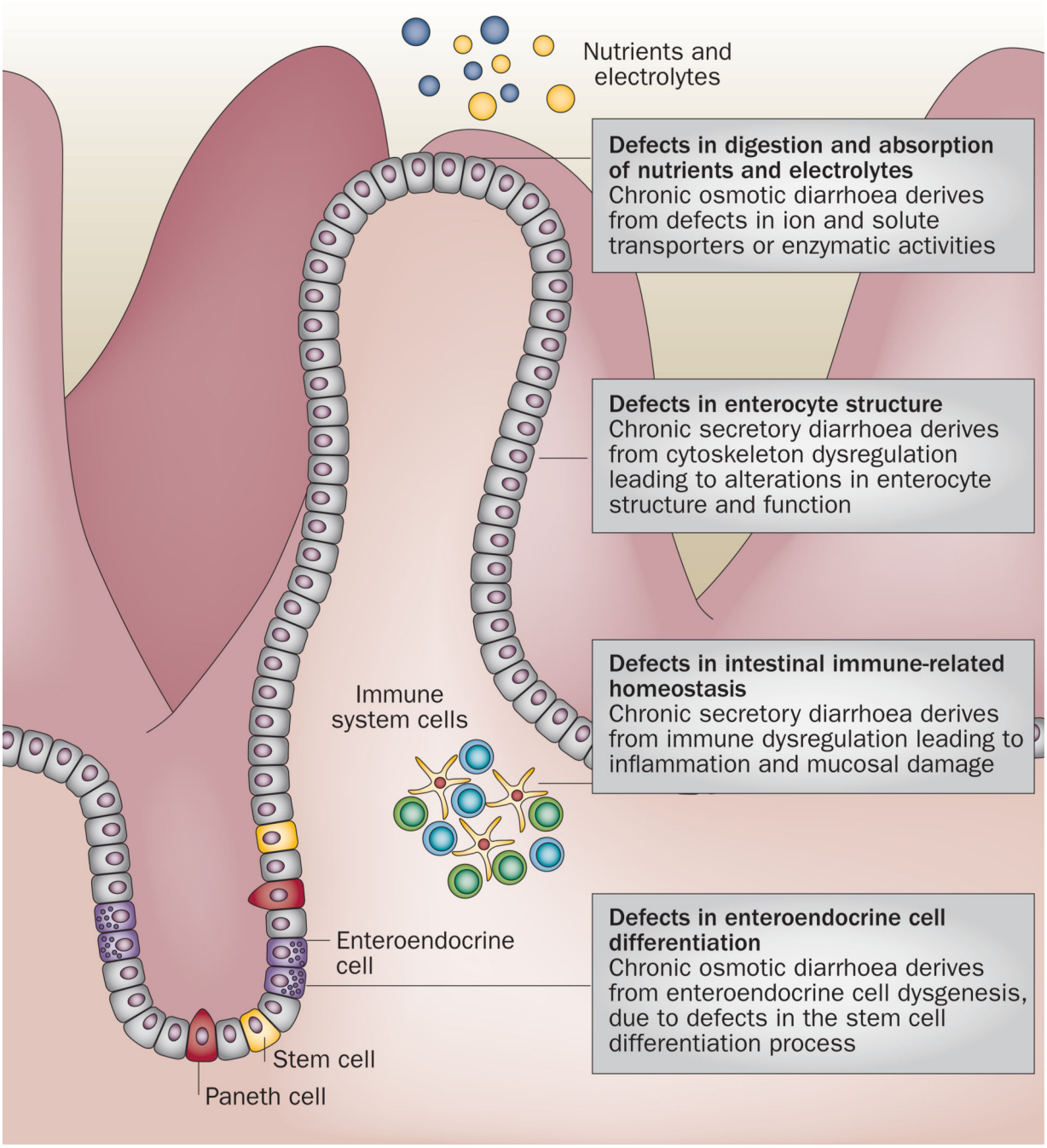

Figure 1 |.
The evolving knowledge in congenital diarrhoeal disorders pathogenesis suggests a new classification that could help the therapeutic approach to these conditions.

Table 1 |

Defects in absorption and transport of nutrients and electrolytes: genetics and epidemiology

Disease	Inheritance and incidence	Gene (OMIM number)	Impaired biological activity causing diarrhoea and involved protein
Abetalipoproteinaemia	AR 150 cases described	*MTTP* (157147)	Impaired microsomal triglyceride transfer protein activity, lower synthesis of VLDL and reduced absorption of lipids
Acrodermatitis enteropathica	AR 1:500,000	*SLC39A4* (607059)	Impaired duodenal and jejunum Zn^{2+} transport by solute carrier family 39 member 42
Chylomicron retention disease	AR 40 cases described	*SAR1B* (607690)	Impaired chylomicron transport within enterocytes owing to the altered activity of a small GTPase
Congenital chloride diarrhoea	AR Common in Finland, Poland, Persian Gulf; few hundred cases in other ethnic groups	*SLC26A3* (126650)	Impaired ileal and colonic Cl^-/HCO_3^- exchange owing to the impaired activity of solute carrier family 26 member 3
Congenital lactase deficiency	AR 1:60,000 in Finland; few hundred cases in other ethnic groups	*LCT* (603202)	Reduced brush border Lactase-phlorizin hydrolase activity
Congenital sodium diarrhoea *	AR Few cases described	*SPINT2** (605124)	Impaired jejunal Na^+/H^+ exchange due to the reduced activity of serine peptidase inhibitor Kunitz type 2
Diarrhoea associated DGAT1 mutation	AR One Ashkenazi family described	*DGAT1* (604900)	Impaired activity of diacylglycerol acyltransferase 1; unknown effect
Enterokinase deficiency	AR Few cases described	*TMPRSS15* (606635)	Impaired activation of trypsinogen by transmembrane protease serine 15
Familial diarrhoea syndrome	AR One family described	*GLUCY2C* (601330)	Increased activity of guanylate cyclase 2C enhances levels of cGMP, hyperactivating intestinal cystic fibrosis transmembrane conductance regulator
Fanconi–Bickel syndrome	AR Few hundred cases described	*SLC2A2* (138160)	Impaired activity of solute carrier family 2 member 2 (facilitative glucose carrier) in hepatocytes, pancreatic beta cells and enterocytes
Glucose–galactose malabsorption	AR Few hundred cases described	*SLC5A1* (182380)	Impaired sodium-coupled enterocyte absorption of glucose and galactose due to reduced activity of solute carrier family 5 member 1
Hypobetalipoproteinaemia	Autosomal co-dominant 1:1,000–1:3,000	*ApoB* (107730)	Impaired apolipoprotein B structure and stability and consequent reduced absorption of lipids
Lysinuric protein intolerance	AR Few hundred cases described	*SLC7A7* (603593)	Impaired amino acid transport due to altered light chain of the solute carrier family 7 member 7
Maltase–glucoamylase deficiency	AR Few cases described	*MGAM* (154360)	Reduced maltase–glucoamylase activity (which might be combined with the deficient activity of other brush border enzymes)
Primary bile acid diarrhoea ≠	AR Few cases described	*SLC10A2* (601295)	Reduced enterohepatic reabsorption of bile acids by solute carrier family 10 member 2
Sucrase-isomaltase deficiency	AR 1:5,000; higher in Greenland, Alaska and Canada	*SI* (609845)	Reduced brush border sucrase and/or isomaltase activity

[*] Analysis of the intestinal brush border membrane of affected patients revealed that the condition is caused by a functional defect in one of the Na^+/H^+ exchangers localized to the apical membrane of small intestinal epithelial cells. However, no mutations were detected in the genes encoding any of the Na+/H+ exchangers identified so far (NHE1, NHE2, NHE3, and NHE5)[72]

[≠] In adults, an alteration of the normal regulatory mechanisms in the synthesis of bile acids, mediated by fibroblast growth factor 19 (FGF-19), has been found as a main cause of bile acid diarrhoea.[73]

Abbreviation: AR, autosomal recessive.

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Table 2 |

Defects in enterocyte structure: genetics and epidemiology

Disease	Inheritance and incidence	Gene (OMIM number)	Impaired biological activity causing diarrhoea and involved protein
Congenital tufting enteropathy *	AR 1:50,000–100,000; higher among Arabians	*EPCAM* (185535)	Defective activity of epithelial cell adhesion molecule causes the altered cell–cell adhesion
	12 patients described	*SPINT2* (605124)	Impaired activity of serine peptidase inhibitor Kunitz type 2, which is involved in epithelial regeneration
Microvillous inclusion disease	AR Few cases described; higher frequency among Navajo	*MYO5B* (606540)	Reduced activity of myosin 5B causes abnormal recycling of endosomes
	AR Two patients described	*STX3* (600876)	Impaired activity of syntaxin 3, which is involved in membrane fusion of apical vesicles
Trichohepatoenteric syndrome (syndromic diarrhoea)	AR Few cases described	*TTC37* (614589)	Impaired synthesis or localization of brush border transporters due to the reduced activity of tetra-trico-peptide repeat domain 37
	AR Few cases described	*SKIV2L* (600478)	Unknown mechanism due to the impaired activity of SKI2W helicase

* Congenital tufting enteropathy associated with an *EPCAM* mutation is characterized by only intestinal involvement, whereas a mutation in *SPINT2* leads to a syndromic form with dysmorphic features, woolly hair, small birth weight and immune deficiency and diarrhoea with high sodium content in the stools.

Abbreviation: AR, autosomal recessive.

Table 3 |

Defects in enteroendocrine cell differentiation: genetics and epidemiology

Disease	Inheritance and incidence	Gene (OMIM number)	Impaired biological activity causing diarrhoea and involved protein
Enteric anendocrinosis	AR Few cases described	*NEUROG3* (604882)	Altered neurogenin-3, which regulates the development of gut epithelial cells into endocrine cells
Mitchell–Riley Syndrome	AR Few cases described	*RFX6* (612659)	Reduced activity of regulatory factor X6 involved in pancreatic morphogenesis and development
Proprotein convertase 1/3 deficiency	AR Few cases described	*PCSK1* (162150)	Reduced activity of proprotein convertase 1/3 involved in the activation of prohormones produced by enteroendocrine cells
X-linked lissencephaly and MR	X-linked Few hundred cases described	*ARX* (300382)	Impaired activity of aristaless related homeobox transcriptional factor, which regulates enteroendocrine cell development

Abbreviation: AR, autosomal recessive.

Table 4 |

Defects in intestinal immune-related homeostasis: genetics and epidemiology

Disease	Inheritance and incidence	Gene (OMIM number)	Impaired biological activity causing diarrhoea and involved protein
Early onset enteropathy with colitis	AR Few cases described	*IL10* (124092)	Altered IL-10 or its receptor subunits involved in the control of intestinal microbial stimulations
		IL10RA (146933)	
		IL10RB (123889)	
IPEX syndrome	X-linked Few hundred cases described	*FOXP3* (300292)	Impaired activity of forkhead box P3 involved in the development of $CD4^+CD25^+$ T_{REG} cells
IPEX-like disorders	AR Few cases described	*CD25* (147730)	Impaired synthesis of α chain of IL-2 receptor on T_{REG} cells
	AR Few cases described	*STAT5B* (604260)	Impaired activity of signal transducer and activator of transcription 5b involved in IL-2 signalling in T_{REG} cells
	AD Few cases described	*STAT1* (600555)	Enhanced or reduced activity of signal transducer and activator of transcription 1 causes the reprograming of T_{REG}cells into T_H1-like cells
	AR One family described	*ITCH* (606409)	Altered activity of ITCHY E3 ubiquitin ligase implicated in the development of T_{REG} cells
	AR Three families described	*LRBA* (606453)	Impaired activity of lipopolysaccharide-responsive beige-like anchor protein stimulates apoptosis of T_{REG} cells

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked; T_H1, type 1 T helper cell; T_{REG}, regulatory T cell.

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