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**Genetics of inflammatory bowel disease from multifactorial to monogenic forms**

Bianco AM *et al*. VEO-IBD is it multifactorial or monogenic disease?

**Anna Monica Bianco, Martina Girardelli, Alberto Tommasini**

**Anna Monica Bianco, Martina Girardelli, Alberto Tommasini,** Institute for Maternal and Child Health-IRCCS “Burlo Garofolo”, 34137 Trieste, Italy

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**Correspondence to:** **Anna Monica Bianco, PhD,** Institute for Maternal and Child Health-IRCCS “Burlo Garofolo”, Via dell’Istria, 65/1, 34137 Trieste, Italy. [annamonicarosaria.bianco@burlo.trieste.it](mailto:annamonicarosaria.bianco@burlo.trieste.it)

**Telephone:** +39-403-785422

**Fax:** +39-403-785540

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**Abstract**

Inflammatory bowel disease (IBD) is a group of chronic multifactorial disorders. According to a recent study, the number of IBD association loci is increased to 201, of which 37 and 27 loci contribute specifically to the development of Crohn’s disease and ulcerative colitis respectively. Some IBD associated genes are involved in innate immunity, in the autophagy and in the inflammatory response such as *NOD2*, *ATG16L1* and *IL23R,* while other are implicated in immune mediated disease (*STAT3*) and in susceptibility to mycobacterium infection (*IL12B*). In case of very early onset of IBD (VEO-IBD) within the 6th year of age, the disease may be caused by mutations in genes responsible for severe monogenic disorders such as the primary immunodeficiency diseases. In this review we discuss how these monogenic disorders through different immune mechanisms can similarly be responsible of VEO-IBD phenotype. Moreover we would highlight how the identification of pathogenic genes by Next Generation Sequencing technologies can allow to obtain a rapid diagnosis and to apply specific therapies.

**Key words:**Inflammatory bowel disease; Primary immunodeficiency disease; Early onset; Next generation sequencing; Genome wide association studies

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**Core tip:** Genetic investigation is of fundamental importance describing inflammatory bowel disease (IBD) as a complex disease, as well as in identifying the monogenic disorders that may present with IBD-like features. Using third-generation technology should be leveraged to accelerate the screening and allow the identification of the most rare monogenic defects. Furthermore, the study of genetic variants in monogenic and in sporadic IBD could help unraveling the complex interplay between defective and compensatory immune responses, opening the way to the identification of new targets for therapy.

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**Introduction**

Inflammatory bowel disease (IBD) is the result of an unbalanced crosstalk between gut luminal content and the mucosal immune system. IBD encompasses a continuum of clinical disorders, ranging from Crohn’s disease (CD) through indeterminate colitis (IC) to ulcerative colitis (UC). In fact, some patients may present significant clinical overlap between these forms and even develop one form from another. However, there are distinctive genetic, environmental and pathogenic factors that can be involved in the three forms.

In general, CD is characterized by changes in intestinal microbiota (dysbiosis), focal translocation of bacteria across the mucosal barrier, altered mucosal response to bacterial invasion, development of chronic granulomatous inflammation, and activation of adaptive immunity as results of compensatory mechanisms to minor defects of innate immunity or autophagy. Genetic factors can involve variants of different groups of genes, leading to a leaky epithelial barrier and impaired mechanisms of phagocytosis and autophagy. Whatever is the particular combination of factors in each patient, the common result is a vicious circle of dysbiosis, granulomatous inflammation and activation of T cell immunity[1].

In contrast, a major role in UC seems to be played by dysregulation of lymphocyte immunity, with increased activation of T cells and/or reduced regulatory T cell function. Risk factors implicate a number of variants in genes associated with T cell activity and with down regulation of mucosal inflammation.

Furthermore, intermediate forms of IBD can share various clinical and genetic features with both CD and UC[2,3]. Indeterminate colitis is particularly common among subjects with very early onset in the first years of life (VEO-IBD). Indeed, patients with VEO-IBD present quite distinctive clinical features and display worse clinical course and usually poorer response to treatments compared with adult onset disease.

Although genetic factors have been associated with different forms of IBD, the diagnosis in each subject is commonly based on clinical and histopathology data, rather than genetic results. Indeed, the particular profile of common genetic variants has little consequences on the prediction of the disease course and response to treatments.

However, genetic analysis can have an important impact on clinical practice for VEO-IBD.

Monogenic disorders are believed to be very rare, but it is expected that in the severe form of earlier onset of IBD, genetic factors play a significant role in pathogenesis. In some cases, VEO-IBD can result from monogenic disorders such as primary immunodeficiency diseases (PID).

Several anecdotal reports showed that a number of PIDs can onset with a clinical presentation compatible with IBD. Taking into account this possibility can allow genetic confirmation and effective treatment with hematopoietic stem cell transplantation (HSCT), avoiding ineffective and dangerous treatments with immunosuppressant, biological inhibitors and even surgery. In most cases, the application of an integrated clinical, functional and genetic approach can allow the identification of some PID diagnosis, however clinical and functional signs can be unexpressed or overlooked and the correct genetic assay may be delayed. Thus, given the importance of the earliest detection of PID, we dedicated in this review a large space to the detailed description of monogenic forms of IBD. We also highlight the potential role of severe VEO-IBD.

In the first part of this review, we will discuss about the susceptibility to develop IBD followed by how the availability of improved genetic tools can impact on the early diagnostics of monogenic VEO-IBD.

In addition, the study of monogenic causes of IBD may provide significant information for a better understanding of sporadic adult onset disease. Indeed, the role of defective mucosal immunity in IBD is a fundamental unsolved question.

Increasing evidence support the idea that in most cases hyperactive intestinal inflammation can be the result of compensatory responses to the environment in presence of various immune defects. The study of genetic variants in monogenic and in sporadic IBD could help unraveling the complex interplay between defective and compensatory immune responses, opening the way to the identification of new targets for therapy.

In the second part of this review, we will discuss how defects in regulation of innate or adaptive immunity can be relevant to the pathogenesis of inflammation in IBD.

**GENES INVOLVED IN MULTIFACTORIAL SUSCEPTIBILITY IBD**

Until the last year several genome-wide associations studies (GWAS), followed by meta analysis of both principal forms of IBD (CD and UC) identified a total of 163 IBD loci: 60 loci with heterogeneous effects while the effects of the other 50 loci were not distinguishable in CD or UC. The remaining 53 loci were specific only for CD (*n =* 30) or for UC (*n =* 23) respectively. A total of 113 of the 163 IBD loci were shared with other complex traits such as immune mediated diseases and mycobacterial infection[4-6]. Recently by immunochip genotype data from both European and East Asian, Indian or Iranian cohorts implicate new 38 loci in IBD risk most of which (27 loci) contribute to both diseases (CD and UC) while of the remaining 11 loci, 7 were classified as specific to CD and 4 to UC[7].

The innate immune receptor nucleotide oligomerization domain containing 2 (*NOD2*) was the first gene associated with inflammatory bowel disease[8,9]. Three mutations (R702W, R703C and L1007fs) in the *NOD2* coding region were demonstrated to be associated with CD in Quebec affected patients that carried at least one variant[10].

In Hungarian CD patients, as well as in other countries, the three-mentioned *NOD2* variant are associated with early onset and the presence of one variant allele increases the risk for developing CD from 1.5 to 4.3 folds, while two variants alleles increase susceptibility to develop the disease from 20 to 40 folds compared with the general population [11].

The mechanisms linking *NOD2* variants to the risk of CD are not fully clear. In fact, these variants lead to loss-of-function of the protein, suggesting a link between an impaired innate immune response to bacterial infections and disease development[8,9]. In contrast, *NOD2* gain-of-function mutations, in the NATCH domain of the receptor~~,~~ are associated with Blau Syndrome (BS) and Early onset Sarcoidosis (EOS), causing a rare autosomal dominant disease characterized by a triad of symptoms (rashes, uveitis and arthritis) and onset among 3 and 4 years of age[12,13].

Another strong association with CD regards the autophagy related 16-like 1 (*ATG16L1*) gene[14,15], while interlukin-23 receptor (*IL23R*) gene, results associated with both UC and CD[16].

Few GWAS have been performed also in pediatric patients: a study identified for the first time for pediatric IBD onset the *TNFRSF6B* gene within the 20q13 and the *PSMG1* gene within the 21q22 loci[17]. In early onset cases, an association was described between *IL23R*, *STAT3*, *JAK2* and *IL12B* and CD[18,19].

Most of these genes concern the functions of innate immunity, autophagy and inflammatory cytokines production. In addition, the associations with *HNF4A* and *GNA12* point out the role of defects of epithelial barrier function[20]. Moreover Kaser *et al*[21] identified an association among hypomorphic *XBP1* variants with both IBD forms, reporting that the deletion in the intestinal epithelial cells induces spontaneous enteritis.

A study carried out on the Korean population proves the different genetics IBD among different populations. Several Korean childrens suffered from UC at the time of diagnosis showed diarrhea and hematochezia like the features in Western studies. In a particular way this study demonstrated that genetic of the IBD between the affected populations reflects the ethnic differences. In fact the *NOD2* and *ATG16L1* variants, strongly associated with IBD in western populations, were not associated in the Korean IBD patients, who conversely displayed an association with three genes (*ATG16L2*, *DUSP5* and *TBC1D1*) that aren’t associated in Western population[22].

Recently, new technologies allow expanding the possibility of genetic analysis in IBD~~.~~ Indeed, Whole Exome Sequencing studies (WES) performed the identification of further genetic association with CD, including missense mutations in the PR domain-containing 1 (*PRDM1*), that encodes a transcription factor expressed by T and B cells, and a common variation in Nuclear domain 10 protein 52 (*NDP52*), an adaptor protein that acts in selective autophagy of intracellular bacteria[23].

In addition, Xu *et al*[24] discovered in Chinese patients by WES novel genetic variants in the *DLG1* gene involved in cell proliferation, T cell polarity and T cell receptor signalling, as a susceptibility gene for CD.

**MONOGENICS FORMS IN EARLY ONSET IBD**

EO-IBD is defined by the onset of disease within the 6th year of age. This group includes neonatal IBD (first 28 d of age), Infant and toddler onset IBD (younger than 2 years, VEO-IBD), and early childhood groups[25].

In VEO-IBD, the disease tend to be much more severe and much more difficult to control with conventional therapies, compared with adult-onset IBD. Increasing evidence suggest a stronger genetic contribution to these forms compared with adults. Indeed some patients with VEO-IBD may have developed intestinal inflammation as part of a monogenic disease, usually a PID. In fact, these cases may account, at least in part, for the phenomenon of missing heritability in IBD, which is the inability to explain all the genetic contribution to IBD based solely on the additive effect of common risk gene variants[26]. Overall, at least 58 genes can play a role in VEO-IBD (Table 1), in addition to those associated with susceptibility to multifactorial IBD. Most of these genes are the cause of very rare monogenic disorders that can present with clinical and histopatological features similar to IBD. The different diseases associated with early onset IBD-like symptoms have been recently reviewed elsewhere[27]. Distinguishing monogenic forms among VEO-IBD is a crucial importance to allow the best treatment. A panel of candidate genes used for the analysis of VEO-IBD can allow a timing diagnosis and an effective cure in many patients, as well as an epidemiologic definition of the real impact of PIDs in this field.

However, it is worth noting that most cases of VEO-IBD can still recognize a multifactorial origin, as suggested by the evidence of the increased incidence of early onset cases of IBD in recent decades, reaching 4.37 per 100000 children[25].

Below we discuss how monogenic disorders involving different immune mechanisms can similarly be responsible for VEO-IBD.

***Hyper and autoinflammatory disorders***

A chronic or episodic inflammatory disease of the intestine can occur as part of a complex clinical picture in subjects affected by several autoinflammatory disorders.

Mevalonate kinase deficiency (MKD) is an autosomal recessive disease caused by mutations in the *MVK* gene and it is characterized by febrile attacks associated with diarrhea, vomiting and abdominal pain. The occurrence of abdominal pain and diarrhea, sometimes with blood and mucus, together with leukocytosis, chronic anemia and increased CRP could raise the suspicion of IBD[28]. In most cases intestinal inflammation occurs only during febrile flares, yet the use of glucocorticoids can hidden the typical periodicity of the disease, reducing the severity but increasing the frequency of symptoms, thus making more difficult the diagnosis[29]. In some cases, patients with MKD may present with VEO-IBD with the characteristics of indeterminate colitis. Of note, treatment with anti-IL-1 agents can allow relieving inflammatory colitis as well as other febrile and inflammatory features typical of the disease[30-32].

IBD can be also more frequent and severe in patients with MEFV mutations. Identification of MEFV can allow diagnosis of Familial Mediterranean Fever and effective treatment with colchicine [33,34].

Recently, a de novo missense mutation (S707T) in the *PLCG2* has been detected by the exome analysis in two patients suffering from an autosomal dominant inflammatory disorder with severe enterocolitis and mild immunodeficiency, even if it is not clear whether gut inflammation is facilitated by the hyper-inflammatory defect or by the immunodeficiency[35].

Familial cold autoinflammatory syndrome-2, a systemic auto-inflammatory disease caused by heterozygous mutations in the *NLRP12* gene can present abdominal pain vomiting and buccal aphthous ulcers together with cold-induced fever[36] and in some cases hypogammaglobulinemia[37].

Familial cold autoinflammatory syndrome 4 is an autosomal dominant disease caused by heterozygous mutation in the *NLRC4* gene and characterized by intermittent episodes of rash, arthralgia, and fever after exposure to cold[38]. Recently a family was reported with a syndrome featuring neonatal onset enterocolitis, in which the father and two respective sons carried a missense mutation (p.V341A) in the *NLRC4* gene. It has also been shown that this mutation, functionally associated with gain of function, cosegregates in the family with the disease[39].

Canna *et al*[40] report a de novo missense substitution (p.T337S) on NLRC4 NBD domain that causes early onset recurrent fever flares and macrophage activation syndrome (MAS).

***Defect of cytotoxicity and hyperinflammation***

The association of inflammatory enterocolitis with MAS can be found also in subjects with XIAP mutations, as described by Worthey[41]. Indeed, XIAP deficiency, already associated with X-linked lymphoproliferative syndrome-2 (XLP2), can be the cause of Crohn’s like features in the absence of MAS[42]. In particular, Zeissig *et al*[43] identified *XIAP* private variants in absence of symptoms related to XLP2 in a cohort of German boys with early onset CD. Of note, macrophage activation in subjects with XIAP deficiency is a compensatory phenomenon sustained by Interferon-g production by lymphocytes and natural killer cells with impaired antiviral capacity, thus it is not of autoinflammatory origin. Similarly, the development of Crohn’s-like disease seem to be due to a deficiency rather than to an excess of *XIAP* function, leading to defective activation of *NOD2* in monocytes. In contrast to lymphohistiocytosis, IBD has been reported also in female subjects heterozygous for *XIAP* mutations[44].

Inflammatory colitis has been reported also in anecdotal cases of subjects with X-linked lymphoproliferative syndrome, although in this case the mechanisms are unknown[45].

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease characterized by typical syndromic features including albinism, hemorrhagic diathesis, and pigmented reticuloendothelial cells. The HPS patients with specific mutations in the respective genes (*HPS-1*, *HPS-4*, *HPS-6*) have major organ involvement including also severe granulomatous colitis with pathologic features suggestive of CD[46-50].

***Immune regulation and dysregulation disorders (innate and adaptive immune responses)***

Autoimmune enteropathy is part of the X-linked immune dysregulation, polyendocrinopathy, enteropathy disease (IPEX) and it is caused by *FOXP3* gene mutations. Although the disorder has distinctive features making it well distinguishable from IBD, mutation in FOXP3 have been recently associated with very-early IBD phenotype[51].

Autoimmune enteropathy has been described, albeit more rarely, also in the autoimmune polyendocrinopathy syndrome type[52].

In recent years, several studies highlighted the causative role of the immunoregulatory cytokine *IL-10* and of its receptor *IL10R* in the early onset IBD[53-62] and the genetic analysis of *IL-10*, *IL10RA*, *IL10RB* has became routinely in patients who developed the first symptoms within the 3 months of life, regardless of parents’ consanguinity[63].

***Defects in phagocyte bacterial killing and neutropenia***

Neutrophil defects are often associated with intestinal inflammation. In particular, subjects with glycogen storage disease-type 1b (*GSD-1b*) show neutrophil dysfunction and run increased risk of developing Crohn’s Disease-like IBD[64-66].

In a similar manner, subjects with defect of *G6PC3*, often develop CD-like inflammation, which is also associated with persistent T cell lymphopenia[67].

Other neutrophil defects associate with early onset IBD include Leukocyte Adhesion Deficiency-1 (LAD-1, *ITGB2* mutated), which can be associated with chronic ileocolitis[68], early onset ulcerative colitis and a non-specific Crohn’s like colitis[69] as well as with bacterial infections.

However, the best-characterized defect of phagocytes associated with VEO-IBD is Chronic Granulomatous disease (CGD), both in its X-linked and autosomal recessive forms. Severe infections by catalase positive bacteria and fungi are usually prominent clinical features, however, cases presenting first with intestinal inflammation, often in the first months of life, are not rare, in particular among subjects with autosomal recessive CGD[70-73]. IBD in subjects with CGD reproduces the clinicopathological features of CD[74]. Recently, Dhillon *et al*[75] found some variants in heterozygosis in NADPH complex genes not leading to appreciable immunodeficiency, yet associated with susceptibility to VEO-IBD. Actually, the pathogenesis of inflammation in CGD could also be attributed to a deficiency of autophagy, leading to autoinflammatory response dominated by IL-1 release[76].

***T and B lymphocyte selection and activation defects***

Intestinal inflammation is a common feature in several PID affecting adaptive immunity.

Wiskott Aldrich Syndrome, an X-linked PID due to mutation in WASP protein, can often present with neonatal or infantile hemorrhagic and inflammatory colitis that can occur before other typical signs such as dermatitis and infections[77,78]. Thrombocytopenia with small platelets and in some cases also hypogammaglobulinemia usually with normal/high-IgA can help addressing the correct diagnosis[79].

Severe combined immunodeficiency (SCID) is often followed by enteropathy and failure to thrive, even before infections. In some cases a low lymphocyte count per age can raise the suspicion of SCID. However, in other cases with hypomorphic mutations in SCID associated genes, such as *DCLRE1C*, *RAG1*, *RAG2*, *LIG4*, *ADA*, *IL2RG*, *CD3G*, *ZAP70* and *LCK*, lymphocyte count can be normal due to the development of dysfunctional lymphocytes[25,80-84]. Rarely, a leaky SCID may present for years with IBD only, in the absence of severe infections. The presence of other signs such as severe eczematous rash should raise the suspicion of a SCID[81,85].

In all these cases only the analysis of lymphocyte subsets, and in particular of recent thymic emigrants (or the molecular measure of T cell receptor excision circles) can assist the correct diagnosis[86].

Common variable immunodeficiency (CVID) is also associated with intestinal inflammation, but the disease rarely occurs in the first years of life[87,88]. The development of IBD seems to be favorished by dysregulation of T-cells derived cytokines[89].

Although the CVID is a polygenic disease, there are a low percentage of cases due to specific genetic defects such as *LRBA*, *ICOS* and *IL-21*, which may often present with earlier onset in life.

In particular, deficiency of the LPS-responsive beige-like anchor (*LRBA*) gene has been found in patients affected by CVID with early onset hypogammaglobulinemia, inflammatory bowel disease and autoimmune cytopenia[88,90]. Serwas *et al*[91] recently identified a new missense mutation in the *LRBA* gene in a young girl with severe early IBD-like disease without other manifestations of immunodeficiency.

Other forms of CVID associated with IBD include deficiencies of *ICOS* gene, *CTLA-4*, programmed cell-death-1 (PD-1), *IL-21*, *TNFRSF13B* and *COG6*[92-95].

IBD-like phenotype was observed also in patients with hyper-IgM syndrome resulting from defects in the CD40 ligand[96,97], AID genes[98] and in subjects with agammaglobulinemia due to defects in *BTK*[99,100] or *PIK3R1*[101].

***Disorders of apoptosis***

Several cellular mechanisms such as the embryonic development, cell differentiation and the elimination from the intestine and from other body parts are regulated by the caspases that are cysteine proteases. Caspase dysfunction has been associated with IBD, in particular CASP-8 is involved in the inflammation of the mucosa and controls in the CD patients the necroptosis of the Paneth cells and the death of the epithelial cells[102].

***Well defined syndromes associated with early onset IBD***

The multiple intestinal atresia (MIA) combined with SCID, is caused by mutations in the *TTC7A* gene[103]. Recently MIA was reported in different families with a very early onset form of apoptotic enterocolitis[104,105].

Another immunodeficiency associated with low numbers of B cells and immunoglobulins is the Tricho Hepato Enteric Syndrome, a syndromic diarrhea usually associated with mutations in the *TTC37* or in the *SKIV2L* gene[106-108].

X-linked anhidrotic ectodermal dysplasia with immunodeficiency, caused by hypomorphic mutations in the nuclear factor-kB essential modulator (*NEMO*), is associated both with epithelial and immune defects. A part from syndromic features of ectodermal dysplasia and susceptibility to infection from various pathogens, patients often present severe chronic colitis, which in some cases has been reported to worsen after HSCT, probably depending on the engraftment of donor immune cells on the background of defective host epithelial cells [109,110].

Other syndromes with early onset chronic diarrhea intestinal inflammation comprise defects of *GUCY2C*, an intestinal receptor for the heat stable bacterial enterotoxins[111], *ITCH*, involved in the ubiquitin-editing protein complex[112], and *MASP2* which is an important bactericidal factor[113].

***Defects affecting the integrity of intestinal barrier***

Mutations in the type VII collagen gene (*COL7A1*) induced the dystrophic epidermolysis bullosa, a genodermatosis. IBD can develop both from mutations in *COL7A1* and from acquired defects in this protein due to autoimmunity[27,114].

Other molecules involved in the intestinal barrier include *ADAM17A*, which has been associated to an autosomal neonatal recessive syndrome characterized by inflammatory skin and bowel disease [115].

Recessive mutations in *KIND1/FERMT1* gene are responsible for Kindler syndrome, characterized by skin blistering, poikiloderma, photosensitivity and sometimes UC-like gastrointestinal symptoms and haemorrhagic diarrhea[116].

EO-IBD can be observed also in patients with EGFR deficiency, together with skin disease[117,118].

More complex is probably the pathogenesis of IBD in Loeys-Dietz syndrome, an autosomal disease caused by mutations in the *TGFBR1* and *TGFBR2* genes that encode respectively for the receptor type 1 and 2 of the transforming growth factor β (TGF- β)[119].

**CONCLUSION**

When we are faced with a patient with symptoms related to chronic inflammatory bowel disease, it is essential to consider first both the age of onset and the severity of symptoms just to find out whether the patient is suffering from classical multifactorial IBD or if we are facing a severe clinical case, potentially caused by a monogenic form, as which characterized by a more severe phenotype and resistant to traditional therapies. This first classification is critical to guide genetic investigation. The identification of monogenic forms, that are quite rare, can have high impact on the therapeutic options, with particular reference to hematopoietic stem cell transplantation. Thus, in case with early onset and severe or atypical features, the genetic research should be directed toward the identification of a mendelian form of the disease. Target sequencing of multiple candidate genes can be accomplished with technologies such as the ION TORRENT, which are now available in many laboratories. The target sequencing must be designed to analyze all those genes that up to that time have been identified associated with a particular phenotype with severe early onset. In cases with high suspicion of a mendelian cause, but with normal target sequencing results, a more complete and sensitive analysis can be performed by comparison of the patients’ whole exome sequence with that of their parents and/or relatives[120].

When a monogenic disorder underlying intestinal inflammation is detected, we should discard the diagnosis of IBD and refer to IBD-like inflammation. This is easy and correct when we are dealing with well-defined PID, such as Wiskott Aldrich disease or crohnic granulomatous disease. The distinction is much more tricky when we found other immune defects, such as those involving XIAP or LRBA.

An easy distinction could be based on the functional consequences of the genetic defect. It has been proposed that cases with lack of immunity should be indicated as PID, whilst the diagnosis of IBD should be reserved to cases with hyper-response of innate and adaptive immunity. However, it has been argued that excessive or defective immune responses can lead to similar inflammatory disorders, highlighting the importance of a proper functioning of immunity for intestinal homeostasis[121]. What makes even more complicated the clinical picture, is the fact that, a continuum may exist between severe defect, leading to both infections and inflammation signs, and mild defect, presenting only inflammatory signs.

Molecular genetics can help distinguishing inborn defects with excessive or defective immunity but, even more importantly, allow to discriminate defects expressed only in hematopoietic-derived cells from ~~or~~ defect with an important role also in intestinal epithelium. In the first case (*e.g*., in subjects with neutropenias, Wiskott Aldrich disease and chronic granulomatous disease) HSCT is able to cure both the immunodeficiency and gut inflammation; in the second case (*e.g*., defects of *NEMO*, *NOD2*) HSCT can be ineffective. More difficult is to predict the success of HSCT in other disorders in which the genetic defect can be important both in hematopoietic-derived cells and epithelia.

In brief, inflammatory bowel disease can be the result of different genetic mechanisms leading to common inflammatory phenotypes and requiring similar treatments. VEO-IBD is often resistant to conventional treatment.

Finding the molecular cause in single individuals could open the way to the development of novel and more specific therapeutic approaches.

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**Table 1 Genes involved in the phenotype of monogenic very early onset of inflammatory bowel disease**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Hyper and autoinflammatory disorders** | | | | | | | |
| **Gene** | **Inheritance** | **Chr** | **OMIM** | **Disease** | **Clinical Features IBD-like** | **Treatment** | **Reference** |
| MVK | AR | 12q24 | #260920 | Mevalonate kinase deficiency | Abdominal pain, Diarrhea, Vomiting | Anakinra | [28,30,31,32] |
| MEFV | AR | 16p13 | #134610 #249100 | Familial Mediterranean Fever | Diarrhea, abdominal pain, mucus in the stool, peritonitis | Colchicine | [33,34] |
| PLCG2 | AD | 16q23 | #614878 | Autoinflammation, antibody deficiency, and immune dysregulation syndrome | Bloody diarrhoea, UC, enterocolitis |  | [35] |
| NLRP12 | AD | 19q13 | #611762 | Familial cold autoinflammatory  syndrome 2 | Abdominal pain | Anakinra | [37] |
| NLRC4 | AD | 2p22 | #616050 | Autoinflammation with infantile enterocolitis | Neonatal-onset enterocolitis | Anakinra | [38-40] |
| **Immune regulation and dysregulation disorders (innate and adaptive immune responses)** | | | | | | | |
| XIAP | XL | Xq25 | #300635 | X-linked lymphoproliferative syndrome 2 | Perianal abscesses | HSCT | [41-44] |
| STXBP2 | AR | 19p13 | #613101 | Familial haemophagocytic lymphohistiocytosis type 5 | IDB-like colitis | HSCT | [45] |
| HPS1 | AR | 10q23 | #203300 | Hermansky Pudlak syndrome  (type 1, 4 and 6) | IBD, UC, Granulomatous colitis | Platelet transfusion | [46-50] |
| HPS4 | 22q12 | #614073 | Granulomatous colitis | Anakinra  Infliximab  subtotal colectomy |
| HPS6 | 10q24 | #614075 | Gastrointestinal symptoms, granulomatous colitis, imperforate anus, gluteal flap repairs |
| FOXP3 | XL | Xp11 | #304790 | Immunodysregulation, polyendocrinopathy and enteropathy | Intractable diarrhea, total or subtotal intestinal villous atrophy, enteropathy | HSCT | [51] |
| AIRE | AR/AD | 21q22 | #240300 | Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy | Malabsorption, diarrhea,  chronic atrophic gastritis | No specific treatment is available | [52] |
| IL10 |  | 1q32 | \*124092 | IL-10 Signaling defects | Severe early-onset enterocolitis | HSCT | [53-63] |
| IL10RA | AR | 11q23 | #613148 | Inflammatory Bowel Disease-28, early onset | Early onset enterocolitis,  enteric fistula, perianal abscesses |
| IL10RB | AR | 21q22 | #612567 | Inflammatory Bowel Disease-25, early onset | Early onset enterocolitis,  perianal abscesses, enterocutaneous and rectovaginal fistula |
| **Defects in phagocyte bacterial killing and neutropenia** | | | | | | | |
| SLC37A4 GSD-1b | AR | 11q23 | #232220 | Glycogen storage disease 1b | Perioral and perianal lesions, ileitis, colitis, CD-like, protuberant abdomen | Granulocyte colony stimulating factor, prophylactic oral iron | [64-66] |
| G6PC3 | AR | 17q21 | #612541 | Severe Congenital neutropenia 4 | Diarrhea, colitis, abdominal pain, perianal fistula or abscess, CD-like, oral aphthous ulceration | Granulocyte colony stimulating factor | [67] |
| ITGB2 | AR | 21q22 | #116920 | Leucocyte adhesion  deficiency 1 | CD-like with discontinuosus stomatitis, ileocolitis, perianal and rectal abscess, fistulas, adhesion, strictures | HSCT | [70,71] |
| NCF1 | AR/XL | 7q11 | #233700 | Chronic granulomatous disease | Colitis, perirectal abscess | HSCT | [70-75] |
| NCF2 | AR | 1q25 | #233710 | Perirectal abscesses due to immunodeficiency |
| NCF4 | AR | 22q12 | #613960 | Chronic granulomatous colitis, diarrhea perianal infections, erosions and ulceration of the gastric fundus and colonic mucosa, multiple small granulomata on colonic biopsy. |
| CYBA | AR | 16q24 | #233690 | Perirectal abscesses due to immunodeficiency |
| CYBB | XL | Xp11 | #306400 | Gastrointestinal perirectal abscesses due to immunodeficiency, enteritis and colitis |
| **T and B lymphocyte selection activation defects** | | | | | | | |
| WAS | XL | Xp11 | #301000 | Wiskott-Aldrich Syndrome | Diarrhea, hematemesis and melena  IBD, UC like, colonic inflammation with crypt abscess | HSCT/  transfusion of autologous genetically modified | [77-79] |
| DCLRE1C | AR | 10p13 | #603554 #602450 | Omenn Syndrome;  Athabascan-type severe combined immunodeficiency | Chronic diarrhea | HSCT | [25,80-82,85,86] |
| RAG1 | AR | 11p12 | ~~4~~  #603554 | Omenn Syndrome |
| RAG2 | AR |
| LIG4 | AR | 13q33 | #606593 | LIG4 Syndrome | Protracted diarrhea~~,~~  ~~failure to thrive~~ | HSCT |
| ADA | AR | 20q13 | #102700 | Partial adenosine deaminase deficiency | Enzyme replacement therapy using frozen irradiated red blood cells/ HSCT |
| IL2RG | XL | Xq13 | #300400  #312863 | Severe Combined Immunodeficiency;  Moderate Immunodeficiency | HSCT |
| CD3G | AR | 11q23 | #615607 | Immunodeficiency 17 | Diarrhea autoimune, gastroenteritis,  recurrent, enteropathy | HSCT |
| ZAP70 | AR | 2q11 | #269840 | Selective T-cell defect | Diarrhea | HSCT |
| LCK | AR | 1p35 | #615758 | Immunodeficiency 22 | Darrhea autoimmune, panniculite | HSCT | [83,84] |
| LRBA | AR | 4q31 | #614700 | Common variable immunodeficiency 8 | Colitis, IBD | Ig replacement therapy/HSCT | [88,90,91] |
| ICOS | AR | 2q33 | #607594 | Common variable immunodeficiency 1 | Early onset gastrointestinal tract infections, enteritis, recurrent diarrhea | Ig replacement therapy/HSCT | [92] |
| IL21 | AR | 4q27 | # 615767 | IL-21 deficiency | Early onset IBD | Ig replacement therapy/HSCT | [93] |
| CTLA-4 | AD | 2q33 | #616100 | Autoimmune lymphoproliferative  syndrome type V | Early onset IBD and autoimmunity | No specific treatment is available | [122] |
| TNFRSF13B | AR/AD | 17p11 | #240500 | TACI deficiency | Enteritis, recurrent diarrhea | Ig replacement therapy/HSCT | [94] |
| COG6 | AR | 13q14 | #614576 | Congenital disorder of glycosylation, type III | Anal anteposition, recurrent diarrhea, IBD | No specific treatment is available | [123] |
| BTK | XL | Xq22 | #300755 #307200 | Agammaglobulinemia. Isolates growth hormone deficiency type III | Diarrhea | Ig replacement therapy/HSCT | [99,100] |
| PIK3R1 | AR | 5q13 | #615214 | Agammaglobulinemia 7 | Recurrent gastroenteritis | [101] |
| CD40LG | XL | Xq26 | #308230 | Immunodeficiency  with hyper-IgM type I | Diarrhea | [96,97] |
| AICDA | AR | 12p13 | #605258 | Immunodeficiency  with hyper-IgM type II | Gastrointestinal tract infections | [98] |
| **Disorder of apoptosis** | | | | | | | |
| CASP8 | AR | 2q33 | #607271 | Caspease 8 deficiency | chronic diarrhea | No specific treatment is available | [102] |
| ITCH | AR | 20q11 | #613385 | Autoimmune disease,  multisystem with facial dysmorphism | Enteropathy, chronic diarrhea, malabsorption, gastrostomy tube feeding | Immunosuppressive treatment | [112] |
| MASP2 | AR | 1p36 | #613791 | MASP2 deficiency | IBD, UC-like | [113] |
| **WELL defined syndromes associated with EO-IBD** | | | | | | | |
| TTC7A | AR | 2p21 | #243150 | Multiple intestinal atresia | Multiple areas of atresia along the small and large intestines,  Intestinal malrotation Intraluminal calcification,  bowel distention  Mucous membrane ulceration | Surgery | [103-105] |
| TTC37 | AR | 5q15 | #222470 | Trico hepato enteric syndrome | Diarrhea, severe villous atrophy | Parenteral nutrition  Ig supplementation | [107,108] |
| SKIV2L | AR | 6p21 | #614602 | Trico hepato enteric syndrome 2 | Diarrhea, colitis,  severe and intractable villous atrophy | [106] |
| NEMO/  IKBKG | XL | Xq28 | \*300248 | X-linked ectodermal dysplasia and immunodeficinecy | CD-like colitis, villous atrophy, recurrent digestive tract infections, intractable diarrhea and recurrent ulcerations | HSCT | [109,110] |
| GUCY2C | AD | 12p13 | #614616 | Familial Diarrhea | Early onset chronic diarrhea, IBD, CD, small-bowel obstruction, esophagitis, irritable bowel syndrome, ileal inflammation, abdominal pain | Parenteral nutrition | [111] |
| **Defects affecting the integrity of intestinal barrier** | | | | | | | |
| COL7A1 | AR | 3p21 | #226600 | Dystrophic epidermolysis bullosa | Gastrointestinal complications, diarrhea, colitis, esophageal blisters strictures,  anal blisters, constipation | Immunomyeloablative chemotherapy and allogenic HSCT | [114] |
| ADAM17 | AR | 2p25 | #614328 | Neonatal inflammatory skin and bowel disease 1 | Perioral and perianal erythemas with fissuring, diarrhea, malabsorption, plasma cell duodenitis crypt hyperplasia, villous atrophy | EGFR Ligands | [115] |
| FERMT1/KIND1 | AR | 20p12 | #173650 | Kindley syndrome | Intestinal involvement with haemorrhagic diarrhoea, UC | No specific treatment is available | [116] |
| EGFR | AR | 7p11 | #616069 | Neonatal inflammatory skin and bowel disease 2 | Diarrhea | No specific treatment is available | [117;118] |
| TGFBR1 | AD | 9q22 | #609192 | Loeys-Dietz syndrome, type 1 | Gastrointestinal disorders, | Medication and  preventative surgery | [119] |
| TGFBR2 | AD | 3p24 | #610168 | Loeys-Dietz syndrome, type 2 |

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; HSCT: Hematopoietic stem cell transplantation.