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The Role of Genetics In Pediatric Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD), ulcerative colitis (UC) and unclassified IBD (IBDU), is characterized by chronic intestinal inflammation, and has a multi-factorial etiology with complex interactions between genetic and environmental factors. The genetics of IBD are believed to be common and complex with over 163 associated genetic loci. However, the genetic contribution of the majority of these common loci is small and the effect sizes are low. Although childhood onset IBD represents only 10–25% of all IBD cases, in depth research into the genetic networks of pediatric IBD has revealed exciting new developments and unsuspected pathways. Recent pediatric studies have revealed an increasing spectrum of human monogenic diseases with high effect sizes/penetrance that can present with IBD or IBD-like intestinal inflammation. A substantial proportion of patients with these genetic defects present with very early onset of intestinal inflammation, with onset of IBD at less than 10 years of age. There is also considerable overlap with primary immunodeficiencies and very early onset IBD. This review summarizes the current understanding of the genetics of pediatric inflammatory bowel disease with a focus on the very early onset population, and discusses the promising results from the effort of finding missing heritability of IBD from studying pediatric population.

Introduction

Inflammatory bowel disease (IBD) primarily includes Crohn's disease (CD) and ulcerative colitis (UC), two chronic, debilitating inflammatory disorders of the gastrointestinal tract that can lead to life threatening complications, severe impairment in quality of life, growth failure and high risk for needing surgical resections in children. The incidence of IBD peaks in late adolescents to young adults (second and third decade of life). Approximately 10–25% of incident cases of IBD occur during childhood (1). The definition of childhood or pediatric-onset IBD can be arbitrary. The age at which childhood ends and adulthood begins represents a continuum and accurate classification of pediatric phenotype is essential to determining genotype to phenotype correlation. Recently, the Paris classification was adopted (2) to sufficiently capture the dynamic features of the phenotype (change in disease location and behavior over time, growth failure), improve classification of children, and

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implement uniform standards for defining IBD phenotypes. Accordingly, age at diagnosis is used to classify IBD as very early onset (VEO - 0 to < 10 years) and early onset (EO −10 to < 17 years). VEO is characterized by a higher tendency for disease manifestation in the colon, more disease extension, and a change in disease location over time, while EO clinical characteristics are very similar to adult onset IBD.

The exact determinants of the age of onset and disease course remain largely unexplained but IBD is believed to result from a dysregulation of the immune response to the gut environmental agents housed in a genetically susceptible host. Recent genome-wide association studies (GWAS) within large IBD cohorts have identified 163 genetic loci (3). These 163 loci in total explain 13.6% of CD and 7.5% of UC total disease variance with the majority of loci contributing only a little towards the explained IBD heritability. While two GWAS focused on pediatric IBD (3, 4), they included only a small sample size with age less than 10 years old at disease onset. Clinical heterogeneity within IBD, particularly based on VEO has long been known (5–7), and recent evidence suggests that this heterogeneity is explained by different mechanism-based disease subsets (8). Growing evidence now supports that these phenotypic differences seen among the childhood onset IBD reflect variations in genetics, composition of the microbiome and perhaps environmental risk factors (10, 11). This review summarizes the current understanding of the genetics of pediatric IBD across the age spectrum with a focus on the very early onset population, and discusses the promising results from the effort of finding missing heritability of IBD from studying pediatric populations.

Decades of progress in genetic studies of IBD

There is enough evidence to support the strong contribution of genetic factors to the pathogenesis of IBD (9–16) and some of the most exciting recent developments in our understanding of the pathogenesis of IBD have been in the field of genetics.

Since the human genome has been sequenced and given the development of technologies for rapid and cost-effective genome analysis, it became possible to identify IBD susceptibility loci using genotyping and the hypothesis free method of genome-wide association studies (GWAS) in CD and UC (17, 18). In all, GWAS have identified over 163 IBD loci for both CD and UC that explain only a small proportion of the inherited disease risk, mostly in Caucasians of European descent, therefore the genetics of IBD with adult-onset disease as the primary phenotype have been extensively describe (19–23). Although most investigators are fatigued and getting tired of GWAS, the GWAS efforts on IBD have revealed many unsuspected pathways and focused the IBD pathogenesis on innate immunity responses involving the integrity of the intestinal epithelial barrier, autophagy, the innate recognition and response towards the gut microbiome (17, 18, 24–26). The common pathways and genes associated with IBD revealed by GWAS are summarized in table 1.

Although GWAS have highlighted the overlap of IBD susceptibility loci with other immune-related diseases, the functional impact of most genes ascertain by GWAS is subtle or not clear, and causative loci bearing variants have not been identified.

GWAS have also outlined important observations, useful in guiding IBD studies. GWAS subscribes to the common disease-common variant model that has been the primary focus of human genomics over the last decade. Using GWAS, only a small fraction of the total heritability of IBD has been explained by identifying common alleles (with minor allele frequency > 5%) with small effect sizes. With the exception of *NOD2*, common alleles of large effect size have yet to be reported for IBD, and additional larger GWAS studies are highly unlikely to do so. Furthermore, highly penetrant variants of higher effect size are not detectable by GWAS. In addition, most GWAS studies involved mainly adult or adolescent onset IBD cases, and VEO cases were not included. The VEO group has a more severe disease course and shows positive family history for IBD, in support of higher genetic load and common genetic background (27–29). This also suggests a high likelihood that VEO cases will display Mendelian-like forms of IBD characterized by highly penetrant variants of higher effect size. The monogenetic form of VEO IBD was first confirmed by mutations in *IL10R* gene (30). In order to expand our understanding of the contribution of genetics to IBD, it is imperative to study VEO populations to ascertain low frequency variations (major allele frequency of 0.5 to 1%). Rare genetic variants have not only been predicted to vastly outnumber common variants in the human genome (31), but low frequency variants have been hypothesized to explain a substantial fraction of common complex diseases (32).

Extending the Genetic Studies into the Very Early Onset IBD Population

Causative events leading to pediatric IBD can occur any time between birth and the late teens. While the debate on an increased genetic risk at earlier age is ongoing, many studies have outlined an increased rate of family history with very early onset CD and UC (7, 33). Before GWAS, specific variants of genes were linked with early onset IBD; Variations in *IBD1* have been associated with early onset IBD (34). Variants in the *IBD5* gene have also been shown to be associate with growth indices (35) and a more severe phenotype (36). A specific variant in *NOD2* was found more often in early onset than adult CD (37). Because it is difficult to determine when inflammation begins, taking into account the time course of disease when studying pediatric IBD is important. Children constitute a population with distinct physiology and disease risks, and studying them has several advantages compare to adults: (1) the effect of environmental modifiers is minimal or orders of magnitude less (38), (2) the age-dependent gene expression is uniquely relevant, owing to the presence of an active growth phase (39–41), (3) children are more likely to have a family history of IBD than adults (33), and (4) the effect of confounders such as comorbidity and drugs is different (42–44). Consequently, the argument can be made that the disease course and manifestation in VEO cases are subject to higher genetic load (45) and common genetic background (29) as illustrated in figure 1.

Additionally, children with VEO IBD offer the opportunity to study the initial immune response and the early gut microbiome as well as change over the time, the effects of early therapeutic interventions, the natural history of the disease, and the impact of early environmental modifiers. In short, the pediatric population represents a “virgin” and fertile source of novel and helpful information to understand the triggers and pathogenic mechanisms of IBD in both children and adults alike. To have a better understanding of IBD, its risk and ultimate management, pediatric genomic studies are necessary.

Genetic Studies in Pediatric Onset IBD: Progress

Investigation of the genetic determinants of pediatric IBD has been motivated by the rapid rise in incidence of pediatric-onset IBD in the world, yet data is lacking in VEO and non-European populations. In an attempt to explore their specific implication in children, many established GWAS loci ascertained in adults do not distinguish early from later onset CD (46). Because of the many challenges to performing genomic studies in pediatric populations (47), little effort has been dedicated to identifying IBD genes exclusively in the pediatric-onset IBD population. The need to first identify and characterize the right population as a prerequisite to pediatric IBD studies, led the Crohn's and Colitis Foundation of America (CCFA) to launch the "Challenges in Pediatric IBD" initiative in 2005 (48). Two pediatric GWAS studies (3, 4) identified novel loci (*TNFRSF6B, IL27*) genes, but they are not exclusive to pediatric onset, as they have been replicated in GWAS meta-analysis from adult studies.

The failure of GWAS loci to distinguish early onset from adult IBD can lead to various conclusions: (1) the similarity in effect of established loci between early and late onset highlight similarity in the overall pathogenicity, or (2) the matching of the IBD phenotype in GWAS interfered with the identification of loci unique to early or late onset IBD. On the other hand, the difficulty associated with the identification of early-onset specific loci by GWAS, suggest that differences in phenotypic characteristics between early and late onset could be driven by variants that are not detectable using GWAS. Therefore, the need to understand the molecular pathogenesis of VEO requires a population with unique or narrow phenotypes and a methodology/technology capable of complementing GWAS beyond the common disease–common variant hypothesis

Sequencing in IBD Genetic Studies: Progress

Variants that code for protein are more likely to have greater penetrance and are amenable to functional experimentation. Such variants are usually of low to rare frequency and have not only been predicted to vastly outnumber common variants in the human genome (31), but are also hypothesized to explain a substantial fraction of common complex diseases (32). Sequencing is the method of choice to ascertain low frequency to rare variants that have effect sizes higher than those shown by GWAS (figure 2).

An estimated 85% of high effect mutations reside in 1% of the human genome, representing the entire protein coding sequence known as the exome (49). Sequencing of all protein coding regions quickly became a practical method to identify functionally relevant variants. Targeted sequencing represents a hypothesis driven approach to ascertain disease-causing variant in GWAS loci. With rapid advances and decreasing cost of next generation sequencing (NGS) technologies, whole exome sequencing (WES) has become more cost effective than gene panel or multi-gene sequencing to find functional variants in the protein coding regions of the genome. WES represents a hypothesis free and unbiased way of surveying the entire genome for variants (known or novel) that GWAS failed to reveal. Targeted sequencing and WES have been successfully applied to detect causal variants in many genes associated with IBD by GWAS (table 2).

The first application of WES to a VEO case revealed a rare mutation affecting regulatory function of the *XIAP* gene in a child who presented at 15 months with intractable IBD (66). Since then, WES has successfully identified rare functional variants in novel genes implicated in the pathogenesis of VEO (*FOXP3* (67), *IL10RB* (30, 56) and *XIAP* (66) genes) or even adult (*GSDMB* (54) and *NDP5*2 genes (61)) IBD. WES is therefore the most current cost effective technology capable of exposing low to intermediate frequency variants that may have higher effect size than the weaker associations reported by common GWAS variants.

Both targeted sequencing and WES have advance our understanding of IBD by (1) confirming already known IBD risk variants detected by GWAS, (2) showing that previously known loci may harbor rare risk variants with high effect undetected by GWAS, and (3) identifying novel risk and disease causing variants and genes. Studies have shown that VEO cases of IBD experience a distinct and more severe disease course, and show positive family history for IBD. Therefore, the ascertainment of genetic causal variants in VEO IBD cases, clearly lends support to the expectation of higher genetic load or common familial genetic background (27–29). This is reminiscent of Mendelian diseases characterized by highly penetrant variants of higher effect size.

Monogenetic Disorders and Association with Very Early Onset IBD

The distinct and more severe disease phenotypes seen in VEO cases are associated with difficulty in classifying VEO IBD as CD or UC. The rates of unclassified IBD (IBD-U) or indeterminate colitis (IC) are higher in young children (34% in children under 2 years and 21% in children under 7 years) as opposed to adults (6%) (68). The specific VEO phenotypes often include manifestation of known monogenic diseases and the first case of the Mendelian form of VEO IBD was confirmed as a mutation in the *IL10R* gene (30) that underlined an association of IBD with primary immunodeficiency. Recently, a novel *FOXP3* mutation was also identified in a two-generation family with early onset phenotypes similar to IBD (67), thus lending support to the manifestation of Mendelian disease in IBD cases. Many monogenic disease genes have been shown to confer overlapping pathology with IBD (known as IBD-like pathogenesis) and are seen more frequently in VEO cases (69). These diseases represent potential targets for identifying additional VEO heritability using exome sequencing. A list of genes underlying monogenic conditions is detailed in table 3. This confirms previous reports that single gene disorders also predispose to complex disorders (70, 71) and suggest that many Mendelian and complex disorders could share genetic architecture, where Mendelian loci may contain common variants with low effect size (detectable by GWAS) characterized by incomplete penetrance. Such common variants are capable of modifier functions and likely contribute to complex diseases alongside Mendelian, high effect size variants (detectable mainly by sequencing).

Future

To dissect the complete spectrum of variations that underlie IBD, VEO populations with IBD and Mendelian comorbidity should also be considered because IBD and Mendelian diseases often share phenotypes but involve variants that belong to different part of the

spectrum within the same loci. In GWAS, not only are subjects with Mendelian disorders typically excluded by design but also variants that underlie Mendelian forms of VEO IBD are undetected. Substantial IBD heritability remains to be elucidated and it is unlikely that the expansion of GWAS with larger size cohorts will yield any additional missing heritability. It is clear by now that Mendelian loci contain variants that predispose to complex disease such as IBD and this makes next generation resequencing the ideal choice to comprehensively test such a hypothesis.

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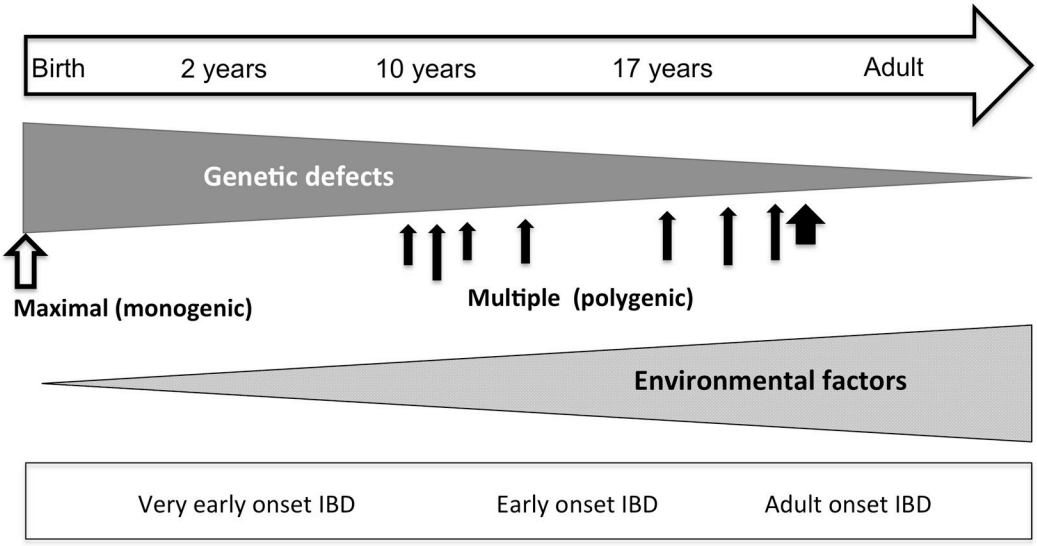

Figure 1.
Genetics and environmental contribution to IBD from birth to adulthood

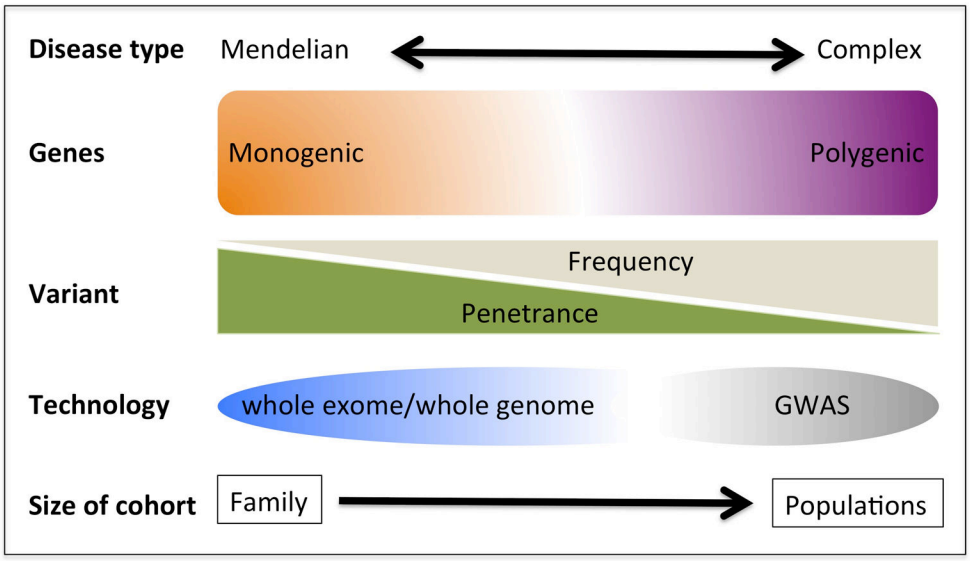

Figure 2.
Identification of disease associated or disease causing genomic variations

Table 1

IBD loci found by GWAS segregate into networks and pathways (21, 24)

Pathways	Genes
Cellular responses	
Autophagy	*ATG16L1, IRGM, NOD2, LRRK2, CUL2, PARK7, DAP*
Apoptosis/necroptosis	*FASLG, THADA, DAP, PUS10, MST1*
ER stress	*CPEB4, ORMDL3, SERINC3, XBP1*
Carbohydrate metabolism	*GCKR, SLC2A4RG*
Oxidative stress	*PRDX5, BACH2, ADO, GPX4, GPX1, SLC22A4, LRRK2, NOD2, CARD9, HSPA6, DLD, PARK7, UTS2, PEX13*
Intracellular logistics	*VAMP3, KIF21B, TTLL8, FGFR1OP, CEP72, TPPP*
Inflammatory response	*PTPN2, PTPN22*
Cell migration	*ARPC2, LSP1, AAMP*
Viral response	*IFIH1*
IBD-related processes	
Epithelial barrier	*GNA12, HNF4A, CDH1, ERRFI1, MUC19, ITLN1*
Restitution	*REL, PTGER4, NKX2-3, STAT3, ERRFI1, HNF4A, PLA2G2A/E*
Solute transport	*SLC9A4, SLC22A5, SLC22A4, AQP12A/B, SLC9A3, SLC26A3*
Paneth cells	*ITLN1, NOD2, ATG16L1, XBP1*
Innate mucosal defense	*NOD2, ITLN1, CARD9, REL, SLC11A1, FCGR2A/B*
NF-κB	*REL, TNFAIP3, NFKB1*
Ubiquitylation	*UBE2L3*
Immune cell recruitment	*CCL11/CCL2/CCL7/CCL8, CCR6, IL8RA/IL8RB, MST1*
Antigen presentation	*ERAP2, LNPEP, DENND1B*
IL-23/TH17	*IL23R, IL12B, JAK2, TYK2, STAT3, STAT4, ICOSLG, IL21, TNFSF15, IL27*
T-cell regulation	*NDFIP1, TNFSF8, TAGAP, IL2, IL2RA, TNFRSF9, PIM3, IL7R, IL12B, IL23R, PRDM1, ICOSLG, TNFSF8, IFNG, IL21*
B-cell regulation	*IL5, IKZF1, BACH2, IL7R, IRF5, IRF8*
Immune tolerance	*IL10, IL27, SBNO2, CREM, IL1R1/IL1R2, NOD2*
Other	*ZMIZ1, YDJC, TAGAP, IL18RAP*

Table 2

GWAS loci sequenced to identify rare causative variants associated with IBD (genes in bold apply to very early onset studies)

Gene symbol	Description	Ref.
ADAM17	Disintegrin and metalloproteinase domain-containing protein 17	(50)
IL10	Interleukin 10	(51)
NCF2	Neutrophil cytosolic factor 2	(52)
C1orf106	Chromosome 1 open reading frame 106	
CARD9	Caspase recruitment domain family, member 9	
CUL2	Cullin 2	(53)
IL18RAP	Interleukin 18 receptor accessory protein	
MUC19	Mucin 19, oligomeric	
PTPN22	Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)	
BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	
ERAP2	Endoplasmic reticulum aminopeptidase 2	(54)
IL10	Interleukin 10	
SEC16A	SEC16 homolog A (S. cerevisiae)	
HEATR3	HEAT repeat containing 3	(55)
IL10RA	Interleukin-10 receptor alpha subunit	(28, 56, 57)
IL23R	Interleukin 23 receptor	(58)
LRBA	LPS-responsive vesicle trafficking, beach and anchor containing	(59)
# NCF4	Neutrophil cytosolic factor 4	(60)
PRDM1	PR domain containing 1, with Zinc finger domain	(61)
RNF186	Ring finger protein 186	(62)
SLC22A4	Solute carrier family 22 (organic cation/ergothioneine transporter), member 4	(63)
TNFRSF6B	Tumor necrosis factor receptor superfamily, member 6b, decoy	(64)
TTC7A	tetratricopeptide repeat domain 7	(65)

Table 3

Monogenic genes associated with IBD-like presentation. Modified from Uhlig et al. (69)

Function	Gene	Associated conditions
Epithelial barrier and epithelial response defects	*COL7A1*	Dystrophic epidermolysis bullosa
	FERMT1	Kindler syndrome
	IKBKG	*X linked ectodermal dysplasia and immunodeficiency*
	ADAM17	*ADAM-17 deficiency*
	GUCY2C	*Familial diarrhoea*
Neutropenia and defects in phagocyte bacterial killing	*CYBB, CYBA, NCF1, NCF2, NCF4*	*Chronic granulomatous disease*
	SLC37A4	*Glycogen storage disease type 1b*
	G6PC3	*Congenital neutropenia*
	ITGB2	*Leucocyte adhesion deficiency 1*
Hyper- and autoinflammation	*MVK*	*Mevalonate kinase deficiency*
	PLCG2	*Phospholipase Cγ2 defects*
	MEFV	*Familial Mediterranean fever*
	STXBP2	*Familial haemophagocytic lymphohistiocytosis type 5*
	XIAP	*X linked lymphoproliferative syndrome 2*
	SH2D1A	*X linked lymphoproliferative syndrome 1*
	HPS1, HPS4, HPS6	*Hermansky–Pudlak syndrome*
	ICOS	*Common variable immunodeficiency type 1*
	LRBA	*Common variable immunodeficiency type 8*
	BTK, PIK3R1	*Agammaglobulinaemia*
	CD40LG, AICDA	*Hyper-IgM syndrome*
	WAS	*Wiskott–Aldrich syndrome*
	DCLRE1C	*Omenn syndrome*
	DOCK8	Hyper IgE syndrome
	SKIV2L, TTC37	Trichohepatoenteric syndrome
	PTEN	*PTEN hamartoma tumour syndrome*
Regulatory T cells and immune regulation	*FOXP3, IL2RA*	*X linked immune dysregulation, polyendocrinopathy, enteropathy*
	IL10RA, IL10RB, IL10	*IL-10 signalling defects*
Defects in intestinal innervation	*RET*	Hirschsprung's disease