Editorial

Inflammatory bowel disease and immune defects: a spectrum of genetic variants and clinical pathogenicity

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See "Analysis of Genes Associated with Monogenic Primary Immunodeficiency Identifies Rare Variants in XIAP in Patients With Crohn's disease." by Amininejad L et al. Gastroenterology. 2018 Feb 28. pii: S0016-5085(18)30245-2.

Personalized medicine is based on the concept that predictive tests support clinical decision-making, allowing individualized interventions and improving patient outcomes. Genetic data can inform this process. Patients with inflammatory bowel disease (IBD) are more likely to have an increased burden of common genetic variants that explain a fraction of the estimated genetic IBD susceptibility [1] whereas additional common variants are associated with disease prognosis [2]. However, current genetic tests based on common variants have not yet reached the clinic because they cannot predict IBD susceptibility and disease progression with high confidence for individual patients. In contrast, a minor fraction of patients develop IBD-like intestinal inflammation due to Mendelian disorders that are caused by a single gene defect. For these patients the genetic diagnosis is of much higher predictive value because it informs treatment options that are not the standard of care in classical IBD [3]. Acknowledging this clinical need and the phenotypic overlap of the over 50 Mendelian disorders that can present with intestinal inflammation, parallel sequencing technologies can identify patients with Mendelian disorders severe IBD phenotypes early in the course of disease. Conceptually, the growing number of genetic defects associated with Mendelian disorders inform on key immune regulation checkpoints (such as IL10 signaling defects[4], CTLA4 haploinsufficiency [5] or TGFb1 deficiency[6]). In addition there are multiple genetic defects that affect bacterial recognition, antimicrobial activity or cytokine responses in phagocytes, cells that form a mucosal innate barrier by antagonizing bacteria that have translocated from the lumen into the intestinal lamina propria. An further layer of defense that can become dysregulated due to genetic defects is the intestinal epithelial barrier [3].

A fundamental question is whether subgroups of Mendelian disease-associated IBD are functionally different disorders compared to classical IBD, i.e. Crohn's disease and Ulcerative colitis. In light of the diverse pathogenic IBD mechanisms, there are shared functional pathways where different common and Mendelian genes intersect and there might even be a spectrum of functional variants on the individual gene level. A functional hierarchy within genes can range from complete loss-of-function variants (associated with Mendelian disorders) or hypomorphic variants that may confer moderate susceptibility to variants without functional effects. Beyond understanding IBD pathogenesis or the search for missing heritability, analyzing these variants has practical implications for clinical decision-making (Figure 1). So far only very few genes/loci have been described where candidate genes associated with polygenic IBD and genes of Mendelian disease associated-IBD align. Among the genes that span a variant spectrum from IBD disease susceptibility to Mendelian disease-associated IBD with high clinical impact are genes encoding the NADPH oxidase complex [7, 8]. Whereas complete loss-of-function variants in the NADPH oxidase complex affect neutrophil and macrophage antimicrobial activity and cause the primary immunodeficiency Chronic Granulomatous Disease, recent data suggest that hypomorphic variants and heterozygous variants affect the degree of reactive oxygen burst in phagocytes on a cellular level. The load of these variants collectively affects not only disease susceptibility but also Crohn's disease phenotype and severity with increased proportions of patients having perianal disease and requiring abdominal surgery [7, 8].

In this issue of Gastroenterology, Amininejad et al. investigated rare variants in 23 genes associated with Mendelian forms of IBD and immunodeficiencies [9]. In a subgroup of 660 patients with early-onset IBD and/or a familial IBD history there was an increased burden of several rare variants in X-linked inhibitor of apoptosis (XIAP). Patients with XIAP deficiency present with immunodeficiency [10, 11] including haemophagocytic lymphohistiocytosis, often triggered by Epstein-Barr virus infection, recurrent splenomegaly, tissue inflammation and dysgammaglobulinaemia. In addition to the classical X-linked inheritance pattern of XIAP deficiency that affects hemizygous males, non-random X-inactivation of *XIAP* in some females can cause variable, often milder forms of the disease (Figure 1A-C). About one third of patients develop Crohn's disease-like intestinal inflammation characterized by granulomatous transmural inflammation, fistulising disease and abscesses [10-13]. The therapeutic response of patients with XIAP-associated IBD to corticosteroids, immunomodulatory or anti-TNF therapies is poor and many require surgery [11]. In contrast, allogeneic hematopoietic stem cell transplantation (HSCT) may be curative, although this is still associated with an increased complication rate despite reduced intensity conditioning regimes [14-16]. Family counseling is important in light of the 50% risk for males within the maternal lineages of the families. The Mendelian disease XIAP deficiency is caused by complete or near complete loss of function variants (such as stop codon and frameshift mutations or deletions [11]). These genetic variants are extremely rare (among the over 86,000 alleles reported in the ExAC variant server there is only one truncating loss-of function variant reported in a female). Recent data suggest that up to 4% of males with pediatric onset Crohn's disease have rare XIAP variants suggesting a substantial enrichment in pediatric subgroups[9, 12, 13, 17]. However, not all of these reported variants are pathogenic. Variants such as XIAP p.P257A [9] and p.T470S [17] that are reported in Crohn's disease patients are far too frequent to cause a highly penetrant disease and are potential susceptibility variants. In order to distinguish between these types of variants, there is a critical need to perform comparative stimulation assays on primary monocytes in addition to measuring protein expression, both of which are accessible via quantitative flow cytometric tests [18, 19].

In summary, clinicians should be aware that monogenic diseases may "masquerade" as classical IBD especially in young patients with severe clinical presentation and familial disease. In addition there is increasing evidence that rare hypomorphic variants in some Mendelian disease-associated IBD genes contribute to the variant burden in patients with early onset IBD. Functional validation steps in clinically approved laboratories are required to characterize the genetic variants, assess the degree of protein function defect and to inform a probabilistic interdisciplinary diagnostic and decision-making process. The example of XIAP and Chronic Granulomatous disease variants illustrate the complex considerations required to ensure that patients with Mendelian disorders are not missed (and that patients with hypomorphic variants are not over-treated). It is likely that future diagnostic strategies for Mendelian disorders with high but not complete IBD penetrance and variable phenotype need to implement the impact of additional genetic susceptibility variants in a di-, oligo- or polygenic context [20] as well as environmental factors such as the microbiota composition and microbial metabolic activity.

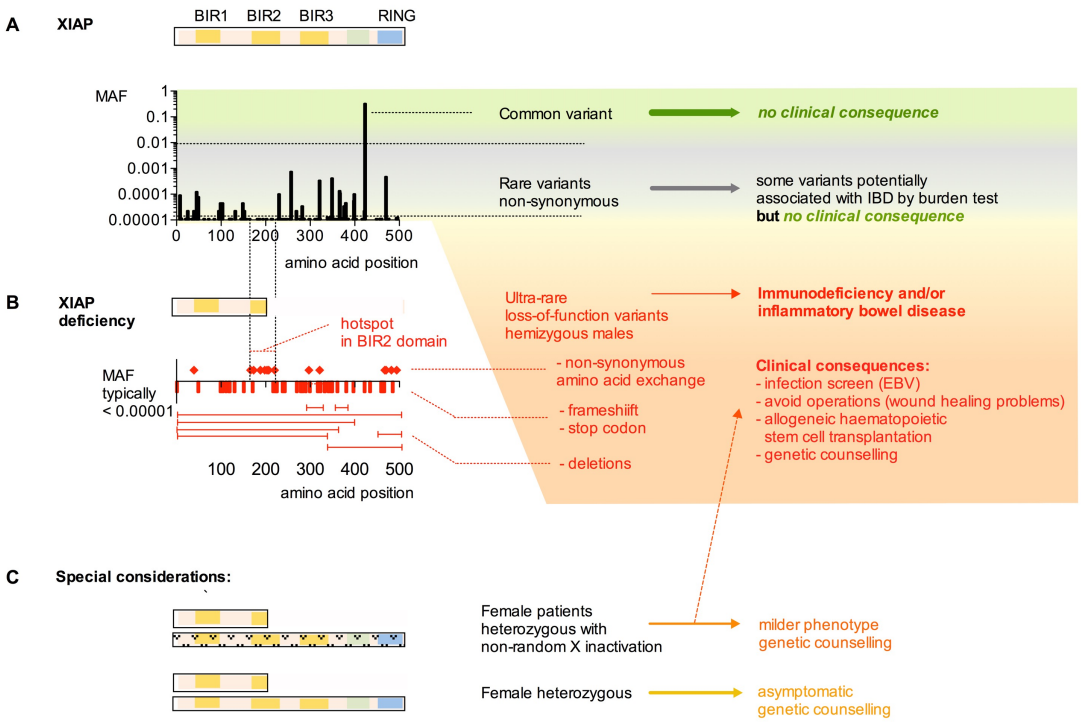

Figure 1: The expanding genetic variant spectrum in *XIAP*.
A The protein domain structure of XIAP with its three 'baculovirus inhibitor of apoptosis protein repeat' (BIR) domains and the ring domain are shown. Genetic non-synonymous variants and their minor allele frequency (MAF) in the Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org) dataset are indicated. The common XIAP variant p.Q423P is neither associated with IBD nor immune dysfunction and has no clinical consequence. Some of the rare variants with minor allele frequency between 0.00001 and 0.01 show reduced activity and are statistically associated with IBD due to their variant burden but have largely no clinical implications.
B Ultra-rare hemizygous functional variants (stop codon, frameshift, deletions or non-synonymous amino acid variants in particular affecting the BIR2 domain) with complete or near complete loss-of-function cause immunodeficiency and intestinal inflammation in male individuals (variant data derived from[11]). Those patients require an interdisciplinary clinical follow up that is different for the standard of IBD care as well as genetic counseling.
C Females with heterozygous pathogenic variants are largely non-affected carriers. Due to non-random X-inactivation of the wild type *XIAP* allele, mild clinical presentations are not infrequent and severe phenotypes have been described. Genetic counseling is required as well as a clinical follow up dependent on individual cellular protein function and on disease progression.

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