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EDITORIAL

Special issue: the genetics of early onset inflammatory bowel disease (IBD) and diarrheal disorders

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Inflammatory bowel diseases (IBD) and diarrheal disorders are debilitating conditions affecting millions of people worldwide. As a whole, these disorders are defined by intestinal inflammation or dysfunction due to complex interactions between rare and common genomic variations, epigenetic changes, the microbiome, and environmental effects (Nambu et al. 2021; Noble et al. 2023).

Although generally rare, a key subgroup of the above are the monogenic IBD and diarrheal disorders, mainly defined by an early onset, a severe disease course, and with a higher likelihood to be refractory to conventional treatment options (Kelsen et al. 2020). Understanding the genetics underlying these disorders is essential for defining the diagnosis, the prognosis, thus ending the diagnostic odyssey, and lead the way for targeted therapies. Moreover, getting to a diagnosis enables the family to make informed family planning decisions, including prenatal and preimplantation genetic diagnoses.

Advances in sequencing technologies and biological platforms continuously contribute to our understanding of the molecular genetics and pathophysiology underlying early onset IBD (EOIBD) and diarrheal disorders, making significant progress in both diagnostics and therapeutics. To date, nearly 100 genes and over 200 genetic loci have been associated with isolated or syndromic diarrheal disorders, manifesting with IBD-like symptoms and other gastrointestinal or extra-intestinal findings (Nambu et al. 2021; Kammermeier et al. 2023; Noble et al. 2023). Studies have shown that up to 40% of patients with disease onset before the age of 6 years receive a genetic diagnosis, and the diagnostic rates reduce significantly as the age of onset increases (Charbit-Henrion et al. 2018; Lega et al. 2019; Uhlig et al. 2021). Indeed, several groups of international experts continuously work to define modalities and provide guidelines to improve diagnosis and guide therapeutic approaches (Uhlig et al. 2021; Kammermeier et al. 2023).

In this Special Issue of Human Genetics, we assembled a collection of Review articles and Original Investigations by leading clinicians and scientists working in the field of monogenic gastrointestinal diseases. This issue highlights the importance of genetics to understand the pathophysiology of early onset and multifactorial IBD, and underscores the need for multidisciplinary approaches that integrate multiple disciplines, including genetics, gastroenterology, and immunology, to improve diagnosis and guide treatment.

Monogenic IBD is often associated with primary immunodeficiencies, which represent at least 20% of EOIBD patients (Kelsen et al. 2019; Uhlig et al. 2021). In this Special Issue, Azabdaftari et al. provide a historic timeline review from publication of the first case reports of patients with likely monogenic IBD, to gene discovery and the current standard of care. They give a systematic overview of EOIBD genes and disorders, focusing on immunological defects while following a taxonomy model to integrate phenotypes and disease pathways (Azabdaftari et al. 2022).

While immunological aspects of EOIBD are broadly studied, other mechanisms of disease should not be overlooked. Two reviews in this issue focus on non-immunological congenital diarrheas and enteropathies (CoDEs). Babcock et al. comprehensively review the genetic, clinical, and therapeutic aspects of intestinal epithelial disorders. These disorders lead to intestinal barrier disruption, alterations in fluid and electrolyte transport, and tissue development and regeneration defects, and have limited therapeutic options, mostly relying on intensive fluid and nutritional management (Babcock et al. 2022). Other categories of CoDEs include protein-losing and autoimmune

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enteropathies, which are reviewed in this issue by Stallard and colleagues. They provide insight into the key genetic and pathophysiological defects which are involved in these phenotypes (Stallard et al. 2023).

In line with these Review articles, three Original Investigations explore different aspects of three congenital diarrheal disorders. Kurolap et al. describe a highly prevalent pathogenic *CD55* variant in the Bukharan Jewish population, which leads to heterogeneous disease severity, from asymptomatic to fulminant protein-losing enteropathy, often misdiagnosed as IBD (Kurolap et al. 2022). This wide phenotypic spectrum likely results from the leaky nature of the splice-altering variant and should be noted by gastroenterologists seeing patients of Bukharan descent with unresolved gastrointestinal issues of various degrees, in view of the available treatment with the terminal complement inhibitor eculizumab (Kurolap et al. 2017; Ozen et al. 2021).

Marek-Yagel et al. describe the first single-nucleotide coding variant in *PERCC1*, leading to an autosomal recessive congenital enteropathy, which to date, has been associated only with deletions in the regulatory region flanking the *PERCC1* open reading frame (Oz-Levi et al. 2019; Marek-Yagel et al. 2022). Importantly, the *PERCC1* coding region is not targeted by most exome capture kits, and therefore cannot be diagnosed through exome sequencing. This could explain some of the cases who currently remain undiagnosed and should raise awareness among physicians to order direct gene sequencing if they have high levels of suspicion that the patient might have *PERCC1*-related retractable diarrhea.

Kiparissi et al. suggest a phenotype expansion to *PMM2*-related hyperinsulinism-polycystic kidney disease, to include self-limiting EOIBD with gastric antral foveolar hyperplasia (Kiparissi et al. 2023). Although only three patients have been observed with this unique IBD phenotype, it might represent an underdiagnosed feature of the disease that does not require special interventions.

Finally, the discussion of IBD genetics cannot be complete without touching the polygenic or multifactorial IBD. As mentioned above, over 200 genetic loci have been associated with IBD, but these explain only up to 25% of the observed heritability. In this issue, Jans and Cleynen extensively review the history of non-monogenic IBD genetics, including twin studies, linkage analyses, sequencing studies, GWAS and polygenic risk scores, touching upon discoveries made, remaining gaps, and how these findings helped better understand the IBD pathogenesis (Jans and Cleynen 2023).

We thank all authors who contributed their expertise and novel findings, and made this Special Issue possible. We hope the publications in this issue will serve as a valuable resource for those working in this field to better understand and manage these challenging conditions.

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