

**Genomics identifies XIAP deficiency in an adult IBD patient:
the clinical and health care impact**

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Author contributions

NB, PK, FP, SK, ST and HU contributed to study setup and patient recruitment. MQ, RW, ECS, SP, TS, KG, CA and HHU performed genetic or functional analysis. All authors discussed data and contributed to the manuscript.

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Dear editors:

In some patients with extreme phenotypes of Inflammatory Bowel Disease (IBD) (in particular in those with infantile or very early onset IBD less than 6 year of onset, non-responsiveness to therapy, or extraintestinal manifestations) Mendelian forms of IBD have been described¹. To identify patients with Mendelian disease associated IBD in a cohort with age at diagnosis between 7 to 40 years of age, we screened for 59 Mendelian forms of IBD by exome sequencing across 503 IBD patients with severe disease, as indicated by need for intestinal surgery and/or therapy progression to biologics (Supplementary material). This enriched the group of patients towards those with a diagnosis of Crohn's disease (CD) (73% CD, 26% ulcerative colitis (UC; among those 30% with a history of acute severe UC), 1% inflammatory bowel disease unclassified (IBDu). Due to the selection criteria, rates of surgery and exposure to biological anti-TNF therapy (in particular adalimumab and infliximab) were higher compared to the overall Oxford IBD cohort (67% *versus* 26%; 74% *versus* 27%, respectively; $p < 0.05$), reflecting the enrichment of patients with acute severe UC and Crohn's-associated fistulising disease, abscesses, or strictures.

We identified one patient with XIAP deficiency. The patient originally presented at age 11 with diarrhoea, abdominal pain, weight loss and perianal disease. Inflammatory and penetrating disease necessitated multiple resections of the colon and small bowel over the following 30 years. During the clinical course he required multiple hospital admissions totalling more than 1000 days in hospital for treatment of recurrent inflammation, fistulation and perianal disease, needing multiple operations (Figure 1A and B). Response to classical immunomodulator and biologic therapies was insufficient to control the disease. The outcome was a high jejunostomy with less than 100 cm of small bowel remaining. Due to short gut syndrome and intestinal failure he has been dependent on parenteral nutrition for 8 years. At age 41, whilst being considered for completion enterectomy and small bowel transplantation, our exome sequencing identified a mutation in *XIAP* (X linked inhibitor of apoptosis). The mutation c.145C>T (NM_001167.3) results in a stop codon p.R49* leading to a truncated protein, which completely abrogates XIAP protein expression and NOD2 signalling (Figure 1C-E). The genetic diagnosis of XIAP deficiency meant that small bowel transplantation was deferred until after haematopoietic allogeneic stem cell transplantation, which is currently under discussion.

XIAP deficiency is a recognised Mendelian disorder causing IBD, with many patients presenting with CD-like granulomatous intestinal inflammation²⁻⁵. There is an increased

increased burden of rare coding *XIAP* variants in IBD patients without immunodeficiency phenotype⁶. Not all variants described cause a complete loss of the XIAP protein function.

The XIAP deficient patient identified here illustrate the exceptional clinical impact that a genetic diagnosis provides. It illustrates the magnitude of health care utilisation by patients with Mendelian disorders, the potential to seek curative approaches such as allogeneic hematopoietic stem cell transplantation and the opportunity to prevent suffering or unnecessary procedures that collectively have major implications for health care. In the case of the XIAP-deficient patient alone, over the 4-year period between 2013 to 2017, hospital-related costs exceeded £400,000, excluding the costs associated with home parental nutrition at £70,000 per year and a potential small bowel transplant which would have been likely fatal in the setting of XIAP deficiency (UK cost £250,000).

Our study has several implications: clearly, the number of patients needed to screen to identify one patient with a Mendelian disorder is high. The diagnostic yield of Mendelian disorders in this older population was low compared to patients with infantile IBD. However, the clinical consequences and opportunities of finding such diagnoses for the individual patient are enormous; even if established at an adult age with decades of delay. In the case of XIAP deficiency, where a proportion of patients present with a dominant IBD phenotype rather than an immunodeficiency phenotype, genomic screening with subsequent functional validation¹⁴ is the diagnostic approach of choice. The costs of genomic-screening (either *via* targeted panel sequencing or *via* exome/genome sequencing and initial virtual panel analysis) in patients with a severe IBD phenotype represent only a fraction of the health care costs of those patients and is therefore justified. Since an early, precise genetic diagnosis may avoid decades of disease progression, failing therapies and debilitation, early screening of patients for known disease causing highly penetrant variants might be rational and even cost-effective but – as in many other disorders⁸ – there is need for a formal analysis of healthcare utilisation including cost-benefits in different disease stages.

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Figure 1: Clinical and functional characteristics of XIAP deficient patient with Mendelian disorder-associated IBD.

A Clinical course of XIAP deficient patient (symptoms, hospitalisation, operations)

B Perianal disease and histology.

C Sanger sequencing of the patient with hemizygous XIAP c.145C>T in comparison to control.

D Absent XIAP protein expression in CD4+ and CD8+ T cells in the patient with XIAP p.R49* as indicated by FACS.

E Absent muramyl dipeptide (MDP) response but normal responsiveness to LPS in the patient with XIAP p.R49* as indicated by FACS.