

Mevalonate kinase deficiency and IBD: shared genetic background

Dear editor,

We read with interest the article entitled 'Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease' written by Uhlig¹ and published by *Gut*. The study, describing the very early onset of intestinal inflammation in several orphan monogenic diseases, aimed at determining the presence of a link between the IBD-like phenotype shown by these rare diseases and the intestinal inflammation seen in typical IBD. The IBD aetiology is multifactorial: at present, genome-wide association studies have identified 163 susceptibility loci associated with an increased risk of developing IBD.² Beside these identified genetic loci that provide little contribution to explain IBD heritability, the number of monogenic diseases presenting IBD-like symptoms is however continuously increasing. These monogenic diseases usually exhibit very early onset and very severe symptoms; in addition, they are often unresponsive to common drugs (anti-inflammatory and immunosuppressive treatments, such as anti-TNF α).

Table 2 Genes and nucleotide variations (amino acid changes are reported in brackets, if present) found in homozygosity or heterozygosity in the six MKD patients analysed in our study

| Genes | Changes (nucleotide and amino acid) |
|--------------------------------|---|
| MUC4 NM_018406.6 (3q29) | c.*406C>T; c.G7702T (p.A2568S); c.A6447C (p.E2149D); c.A6409G (p.T2137A); c.A6344T (p.D2115V); c.A6265G (p.I2089V); c.A6206G (p.N2069S); c.C2834G (p.T945S) |
| KRTAP4-8 NM_031960.2 (17q21.2) | c.*468T>C; c.*442T>C; c.*258T>A; c.*198C>A; c.*94T>G; c.*30A>G, c.G502A (p.A168T); c.C451G (p.L151V); c.1dupA (p.M1fs) |
| IL23R NM_144701.2 (1p31.3) | c.T929C (p.L310P) |
| ADAM17 NM_003183.4 (2p25.1) | c.*290A>G; c.*75G>A; c.*61delA; c.-172T>C |
| RET NM_020975.4 (10q11.2) | c.*600T>A; c.*1506G>A |
| PTEN NM_001126049.1(10q23.3) | c.-1617delA; c.-1657C>G |
| IL10RA NM_001558.3 (11q23.3) | c.A1051G (p.R351G) |
| GUCY2C NM_004963.3 (12p12.3) | c.T843G (p.F281L) |
| PTPN2 NM_001207013.1(18p11.21) | c.*265G>A |
| HNFA4 NM_000457.4 (20q13.12) | c.*906A>C |

RefSeq mRNA (NM_...) and the chromosome localisation of each gene are reported.
MKD, mevalonate kinase deficiency.

In his article,¹ Uhlig reports that children with very early onset of bowel inflammation may present a different phenotype and a different genetic architecture. In particular, these children can be classified either as classical IBD patients or as patients suffering from monogenic diseases, the latter also carrying a high number of genetic variants associated with susceptibility to develop IBD. In this regard, we wish to focus the attention on six patients suffering from mevalonate kinase deficiency (MKD, OMIM #260920), diagnosed during the first year of life and followed-up at the Institute for Maternal and Child Health—IRCCS 'Burlo Garofolo' (Trieste, Italy). MKD, caused by inherited recessive mutations in the mevalonate kinase gene (MVK), is characterised by febrile attacks, often associated with abdominal pain, diarrhoea and vomiting; it can be considered as an auto-inflammatory defect predisposing to IBD-like intestinal inflammation.³⁻⁴ The six MKD patients were homozygous and/or heterozygous for missense mutations on the MVK gene (table 1).

Abdominal pain arose in all MKD patients within the first year of life, with high values of both C reactive protein and erythrocyte sedimentation rate, and very frequent episodes of diarrhoea. Patients exhibit heterogeneous phenotypes: some are more severe and respond poorly to conventional drugs, while others are mild and respond quite well to treatments (anakinra, canakinumab, etanercept), despite carrying the same MVK mutations.

We decided to further explore the hypothesis that MKD can be considered a monogenic cause of early onset pathologies with IBD-like symptoms. A whole exome sequencing analysing was carried out on the same six MKD patients followed-up at our children hospital, searching for genetic variants associated with chronic IBD. Exome enrichment was performed by TruSeq Exome Enrichment 62Mb (Illumina); sequence data were produced using Illumina HiSeq 1000 with 100-bp paired-end reads and analysed by CLC Genomics Workbench V6.5 software.

The variants (table 2) were identified in genes known to be associated with IBD

Table 1 The table illustrates MVK gene mutations with RefSeq mRNA (NM_000431.2)

| Gene | dbSNP | Change | Ref | Obs | P1 | P2 | P3 | P4 | P5 | P6 |
|-----------------------------|-------------|-------------------------------------|----------------------|-----|-----|-----|-----|-----|-----|-----|
| MVK NM_000431.2 (Chr 12) | rs104895334 | c.16_34del; p.Leu6_Gly12delinsGlyfs | CCTACTGGTGTCTGCTCCGG | C | WT | WT | WT | HET | WT | WT |
| | rs104895336 | c.G394A; p.V132I | G | A | HET | WT | WT | WT | WT | WT |
| | rs104895297 | c.C404T; p.S135L | C | T | WT | WT | HET | WT | WT | WT |
| | rs104895304 | c.T803C; p.I268T | T | C | WT | WT | WT | WT | HET | WT |
| | rs104895358 | c.G1006A; p.G336S | G | A | WT | WT | WT | WT | WT | HOM |
| | rs28934897 | c.G1129A; p.V377I | G | A | HOM | HOM | HET | HET | HET | WT |

For each mutation, the following are shown: the respective identifier (dbSNP), the nucleotide substitution and, if present, the amino acid change (Change), the reference sequence (Ref) and the one observed (Obs). For each of the six patients (P1, P2, P3, P4, P5, P6), the mutation is identified as wild-type (WT), heterozygous (HET) or homozygous (HOM).
MVK, mevalonate kinase.

from genome-wide association studies, and in genes responsible for monogenic intestinal diseases. Most of these genes encode for molecules of the innate or adaptive immunity (interleukin (IL)-23R, IL-10, IL-12B and STAT3) and for molecules which are fundamental for intestinal homeostasis (MUC4, GUCY2C, PTPN2, HNF4A and ADAM17). An extended supplementary table containing more detailed information about each patient's variants is available (<https://drive.google.com/file/d/0B6i2Abl03rZLYXEyMDRjVGgtbEE/edit?usp=sharing>.)

The different 'IBD-associated' variants, as identified in MKD patients with several combinations in both homozygous and heterozygous states, could account for the presence of abdominal symptoms and inflammation. Hence, we would like to reinforce the hypothesis of a shared genetic background between early onset IBD and MKD, which accounts for the common clinical and phenotypic features characterising the diseases.

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Contributors AM, AMB and SC conceived and designed the study; AMB and MG analysed and interpreted the data and draw tables; DV and AMB performed whole genome sequencing bioinformatic analyses; SC, AM and GK redacted the manuscript; GK and MG revised the manuscript for language and style. All authors have read and approved the final version of this manuscript.

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