We present 2 brothers, born to consanguineous (second cousin) parents, with persistent, moderate neutropaenia secondary to a previously undiagnosed mutation in the CSF3R gene. 

Methods: Patient A is a 13-year old boy who was referred with a history of recurrent knee swelling. His father described that, from an early age, whenever he had a viral illness he developed marked swelling of his knee which settled spontaneously over a few days. In between episodes he remained completely well and fully active. Growth was normal and there was no history of recurrent or unusual infections. USS & MRI confirmed the presence of large effusions in the knees during these episodes. On examination A had clinical evidence of synovitis in his right knee which settled spontaneously over 3 weeks. However a few months later his arthritis subsequently extended to involve his other knee, both hips, elbow and shoulder. He was treated with Etanercept with good clinical response. Patient H is the younger brother of A. He was diagnosed with severe eczema at age 3 which needed treatment with topical steroids & tacrolimus, along with oral montelukast, to control. He subsequently developed vernal keratoconjunctivitis which required high-dose cyclosporine & steroid eye-drops to control.

Initial Investigations: Both A and H had been noted from an early age to have neutropaenia. This was initially noted during admission for a viral illness but repeat samples over several years showed persistent neutropaenia (Patient A 0.27 – 0.94, patient H 0.9 – 1.1). Patient A also had markedly raised ESR (range 27 – 120mm/hr) noted during episodes of arthritis. All other investigations were reported as normal.

Results: Whole exome sequencing of patient A revealed a novel homozygous single nucleotide variant c.909C>A affecting exon 8 of the CSF3R gene on Chr. 1. This was confirmed by Sanger sequencing, and the same homozygous mutation was found in patient H. CSF3R encodes the receptor for Granulocyte Colony Stimulating Factor (G-CSF). This receptor consists of an extracellular Ig-like domain, a cytokine receptor homology domain, 3 fibronectin domains, a trans-membrane domain, and a cytoplasmic domain that couples to Janus Kinases for signal transduction. The c.909C>A variant leads to a premature stop codon, p.Tyr303*. Residue Y303 is located in the 2nd extracellular fibronectin type III domain. Truncation thereafter leads to a protein that, if expressed at all, would lack its trans-membrane and cytoplasmic domains. Homozygous Y303X is thus predicted to be a null mutation.

Conclusion: G-CSF is a crucial cytokine that induces proliferation, differentiation, & survival of myeloid progenitors. This variant has not, to our knowledge, been previously described. It is compatible with low level neutrophil production, as in our patients, which may be boosted by GM-CSF, but not G-CSF. Other recessive loss-of-function mutations in CSF3R have been found in patients with severe congenital neutropaenia. These patients are, unsurprisingly, refractory to rhG-CSF treatment. It is not clear how this mutation is linked to autoimmunity in these 2 boys. Theoretically both G-CSF, which is likely to be circulating in high concentrations, and GM-CSF, which may be increased to stimulate neutrophil production, have been shown to have pro-inflammatory effects, and indeed are potential targets for future treatment modalities in autoimmune diseases.

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