A case of Adult onset Still's Disease (AOSD) cased by a novel splicing mutation in *TNFAIP3* successfully treated with tocilizumab

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Background

TNFAIP3 encodes the NF-κB regulatory protein A20. High-penetrance heterozygous mutations in *TNFAIP3* cause a haploinsufficiency of A20, inadequate inhibition of NF-κB pathway and an autoinflammatory disorder resembling Behcet's' disease. Here we describe a patient who has a novel splicing mutation in *TNFAIP3* but presenting with AOSD.

Methods

The *TNFAIP3* variant was identified using a targeted gene panel. The mutation was confirmed using Sanger sequencing. Protein function was assessed using WB and LPS stimulation of patients PBMC

Results/Case description

32 years-old female patient presented at the age of 16 with high fever, abdominal pain, urticarial-like rash and polyarthritis. She continued to have ongoing problems with the rash, polyarthritis and ongoing systemic inflammatory response despite regular corticosteroids and DMARD's. Eventually she responded to tocilizumab. She has two children who both have episodic sterile fevers associated with pharyngitis and cervical lymphadenopathy. Her farther has history of early onset rheumatoid arthritis.

The patient was found to have a novel heterozygous variant in *TNFAIP3* c.1906C>T (Figure 1). This variant was not found in ExAC database. Further analysis shows that this single nucleotide variant at the terminal residue of *TNFAIP3* exon 6 produces an alternatively spliced mRNA resulting in *p.His636fsTer1*. Further genetic analysis of family members shows that this variant does segregate with the inflammatory clinical phenotypes. WB shows reduced expression of WT TNFAIP3 in patient's PBMC's. LPS stimulations of patient's PBMC shows significantly higher production of IL-1 and IL-8.

Conclusions

Recently 2 additional cases of A20 haploinsufficiency have been published one presenting with ALPS-like disordered, and another with complex autoimmunity. Our case adds to the expanding spectrum of clinical phenotypes associated with A20 haploinsufficiency.

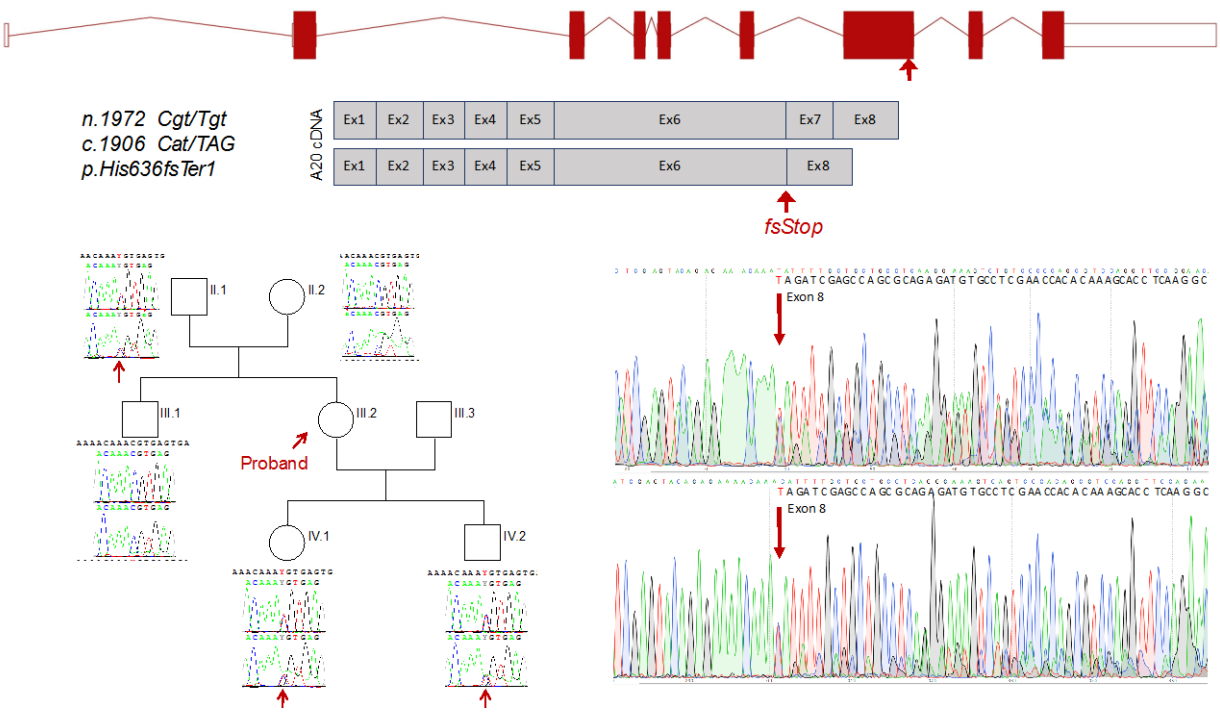

Figure 1 Mutation of the terminal nucleotide in exon 7 produces frame shift stop codon