

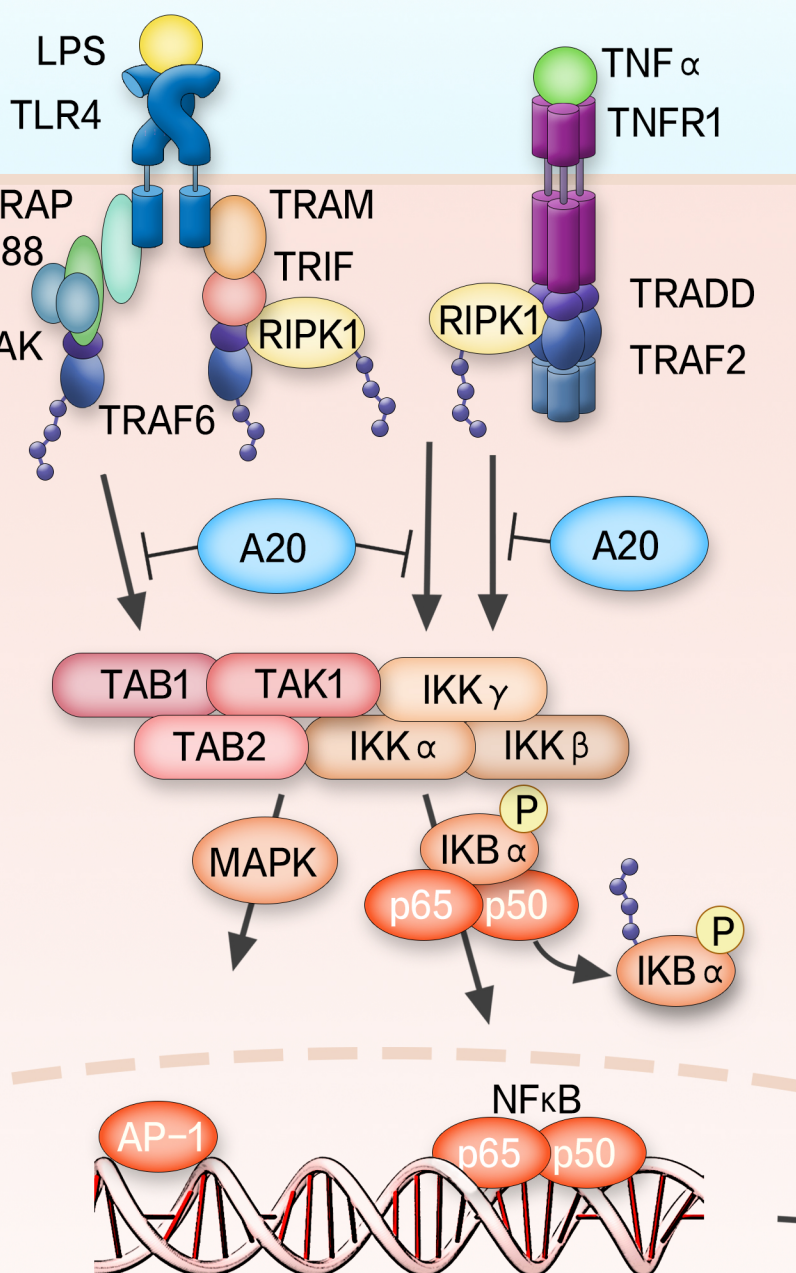
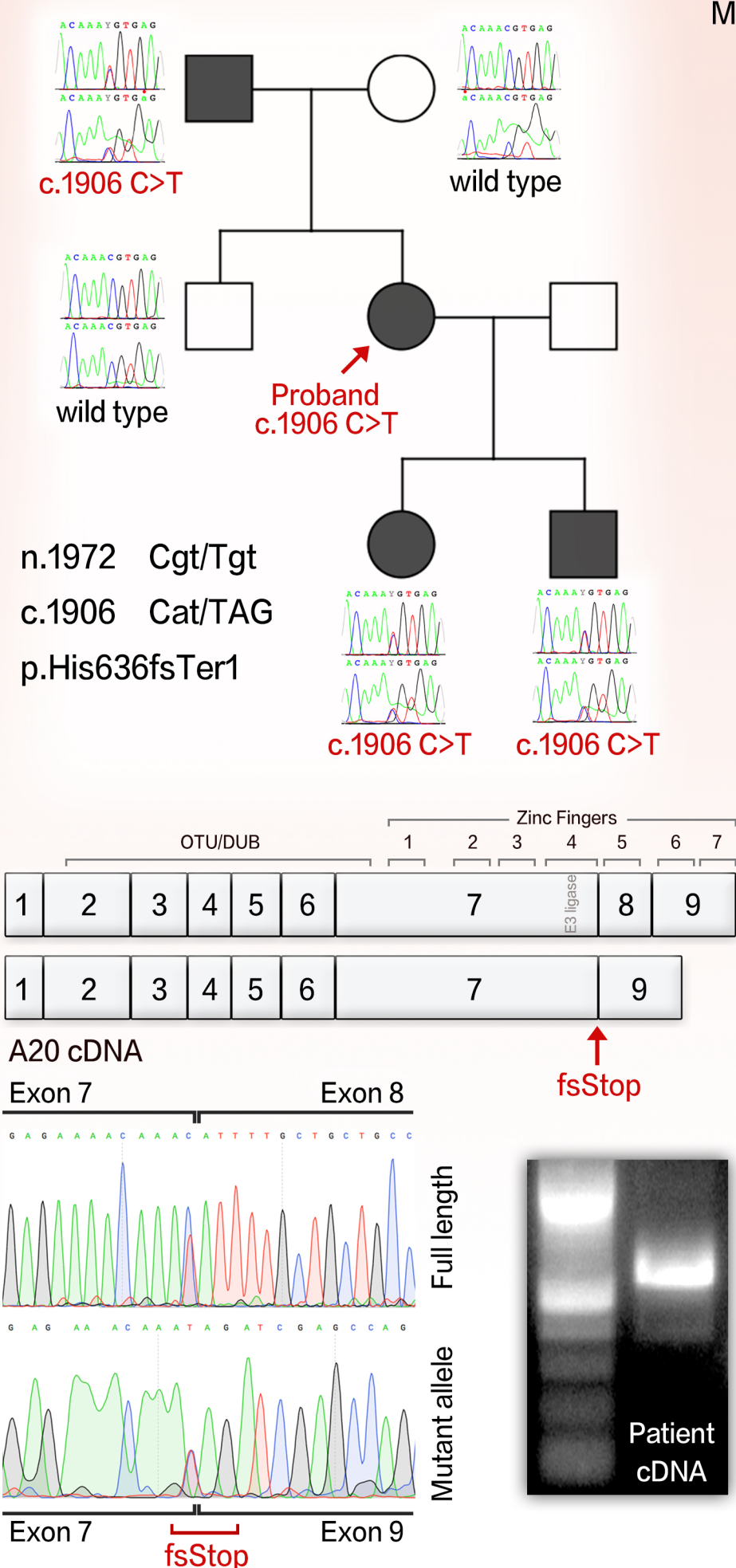
A case of Adult onset Still's Disease (AOSD) caused by a novel splicing mutation in *TNFAIP3* successfully treated with tocilizumab

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TNFAIP3 encodes the NF- κ B regulatory protein A20. High-penetrance heterozygous germline mutations in *TNFAIP3* have been recently described to cause a novel systemic autoinflammatory disorder due to haploinsufficiency of A20 and inadequate inhibition of NF- κ B pathway.^{1,2} The majority of patients have presented with Behcet's disease-like phenotype characterised by recurrent oro-genital ulcers, uveitis and arthralgia. Here we describe a patient who presented with AOSD but found to have a novel splicing mutation in *TNFAIP3* causing A20 haploinsufficiency

Gene variant

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



Clinical Features

32 year old female presented at age 16

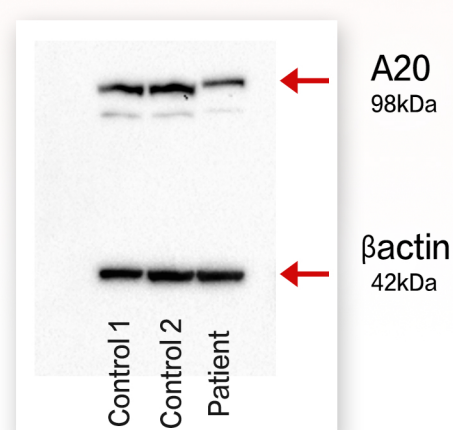
- Ongoing systemic inflammatory response
- Continued urticarial-like rash
- Resolved abdominal pain
- Large joint polyarthrititis
- High fever

Corticosteroids in combination with DMARD's
– Failed to respond
IL-6 inhibition (tocilizumab)
– Excellent response

Both children have episodic sterile fevers associated with pharyngitis and cervical lymphadenopathy.
Farther has a history of early onset rheumatoid arthritis.

NLRP3 inflammsome IL-1 β
IL-8, IL-17A, TNF α , IL-10, IL-6
Other pro-inflammatory cytokines

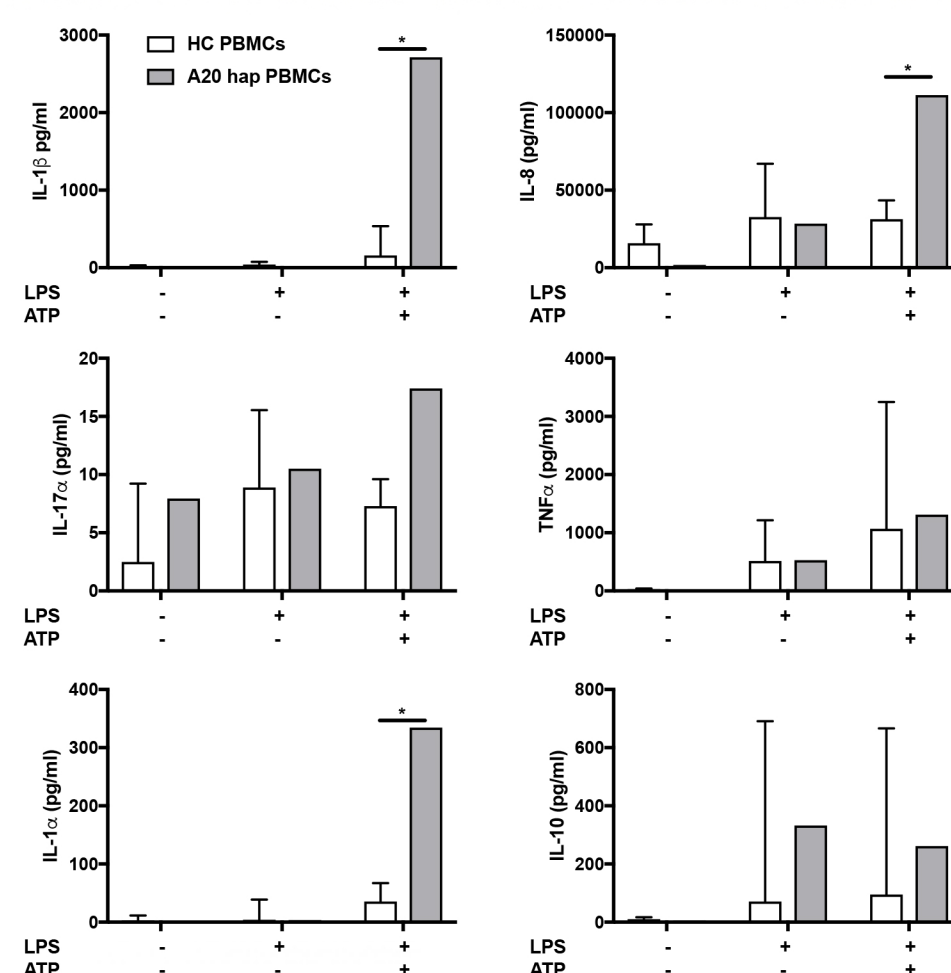
Protein expression



A20 haploinsufficiency in patient derived PBMCs is consistent with other reported cases of disease due to haploinsufficiency.^{1,2}

Cytokine response

Patient PMBCs were assessed for response to LPS & ATP. Cytokine secretion was measured with Meso Scale MSD. Flow cytometry of LPS & TNF α treated patient PBMCs also produced increased p65. (not shown).



Conclusion

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

1. Zhou Q et al. (2016) Loss-of-function mutations in *TNFAIP3* leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. Nat Genet.
2. Aksentjevich I and Zhou Q (2017) NF- κ B Pathway in Autoinflammatory Diseases: Dysregulation of Protein Modifications by Ubiquitin Defines a New Category of Autoinflammatory Diseases. Front. Immunol.

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