A dominantly-inherited Behcet-like disorder caused by haploinsufficiency of the TNFAIP3/A20 protein

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A dominantly-inherited Behcet-like disorder caused by haploinsufficiency of the TNFAIP3/A20 protein

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Introduction
TNFAIP3 encodes the anti-inflammatory A20 protein that functions as a potent negative regulator of NFκB signaling and the NLRP3 inflammasome. Low penetrance common variants of TNFAIP3 have been associated with a number of autoimmune diseases. Here we report 5 high penetrance dominantly-inherited frameshift and nonsense TNFAIP3 mutations in 11 patients with early-onset systemic inflammation, arthralgia/arthritis, oral and genital ulcers, and ocular inflammation.

Objectives
To identify a possible genetic cause of dominantly-inherited early-onset systemic inflammatory disease.

Patients and methods
We performed exome sequencing in 3 families, candidate gene screening in 2 families, and targeted sequencing of 384 Turkish and 384 Japanese patients. We utilized immunoblotting, cytokine profiling, immunostaining, immunofluorescence, real-time PCR, and flow cytometry to study abnormalities in patients’ immune cells.

Results
Four TNFAIP3 mutations were located in the N-terminal OTU domain of A20 and generated truncated proteins of similar length, while the fifth mutation was a truncating frameshift and nonsense TNFAIP3 mutations in 11 patients with early-onset systemic inflammation, arthralgia/arthritis, oral and genital ulcers, and ocular inflammation.

Conclusion
Truncating TNFAIP3 mutations cause haploinsufficiency of the A20 protein, with upregulation of the NFκB signaling pathway, NLRP3 inflammasome activation, and overproduction of proinflammatory cytokines. Targeted therapies with biologics that inhibit these cytokines may be effective in these patients. This is the first report of a human disease caused by high penetrance germline mutations in TNFAIP3.

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