A Novel Variant in STAT3 in a Patient with Immune Dysregulation

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Background

- Signal transducer and activator of transcription 3 (STAT3) plays a crucial role in immune system differentiation and regulation.
- Gain-of-function mutations in STAT3 have been linked to early-onset autoimmunity and lymphoproliferation, leading to dysregulated and hyperactive immune responses[1].
- Here, we describe a previously unreported variant in the STAT3 gene in a pediatric patient with Evans syndrome.

Case Description

- A 13-year-old male with Evans syndrome diagnosed at age 3 presented to our clinic. He was receiving treatment with sirolimus.
- During this time, the patient continued to have thrombocytopenia, and developed intermittent splenomegaly and lymphadenopathy, and diffuse eczematous dermatitis. He also reported multiple hospital admissions for viral and bacterial pneumonias and frequent illness including extensive pansinusitis, mastoiditis and recurrent otitis with hearing impairment.
- The family history is significant for dad with liver failure of unknown etiology, and a sister with inflammatory bowel disease.

Diagnostic Evaluation

- CD19 491 cells/uL; 21%
- CD3 1415 cell/uL; 60%
- CD4 696 cells/uL; 29%
- CD8 645 cells/uL; 27%
- NK cells 436 cells/uL;18%
- IgM 101
- IgA 266
- IgG 955
- Norma titers to MMR, Varicella, tetanus
- Absent titers to S. Pneumoniae

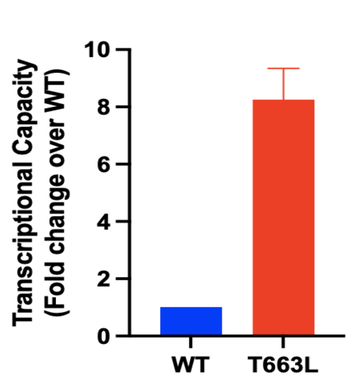
- Decreased switched memory B cells, decrease in plasmablasts and increase in transitional B cells.
- Treg subset analysis showed a normal percentage of CD4+CD25+ and a normal distribution of naïve and memory T cells.
- CT chest demonstrated ground glass appearance with areas of consolidation. There was no mediastinal adenopathy. Abdominal ultrasound with splenomegaly.

Table 1. Diagnostic evaluation (continued)

	Patient result	Reference range
CXCL9	783 pg/mL	<=647 pg/mL
sIL2R	2228.4 pg/mL	175.3-858.2 pg/mL
IL-10	6.9 pg/mL	<=2.8 pg/mL
IL-13	4.0 pg/mL	<=2.3 pg/mL

- Genetic testing for inborn errors of immunity and cytopenias panel revealed a previously unreported variant of uncertain significance: a missense mutation in exon 21 of the STAT3 gene, STAT3 (c.1987_1988delinsCT (p.Thr663Leu)), which was later confirmed to be de novo.

Functional Testing and Validation



Graph 1: Luciferase activity in patient's variant in relationship to wild type STAT3

Conclusion

- The patient's clinical presentation is consistent with STAT3 gain-of-function syndrome, characterized by autoimmune cytopenias, lymphoproliferation, dermatitis, and frequent infections. Although this exact variant has not been previously reported, a similar missense mutation, p.Thr663Ile, has been implicated in STAT3 gain-of-function syndrome.
- He was started on immunoglobulin replacement therapy every 3 weeks and continues to take sirolimus. Clinically, he is doing well with a significant decrease in infections. A JAK inhibitor is being considered.

References

1 Olbrich, Petera,b; Freeman, Alexandra F.c. STAT1 and STAT3 gain of function: clinically heterogenous immune regulatory disorders. Current Opinion in Allergy and Clinical Immunology 24(6):p 440-447, December 2024. | DOI: 10.1097/ACI.0000000000001039