STAT3 GAIN OF FUNCTION MUTATION PRESENTING AS LYMPHOPROLIFERATIVE SYNDROME

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INTRODUCTION

Signal transducer and activator of transcription 3 (STAT3) is an important transcription factor that play a role in multiple cellular functions including proliferation and differentiation (1). Mutation of the *STAT3* gene can manifest in the form of loss of function (LOF) or gain of function (GOF). *STAT3* LOF give rise to hyper-immunoglobulin E syndromes which is characterized by recurrent lung and skin infection with raised immunoglobulin E. On the contrary, the clinical manifestations of *STAT3* GOF is very broad, involving hematological, gastrointestinal, musculoskeletal and pulmonary systems (3).
In this paper, we utilized whole exome sequencing approach to elucidate the genetic etiology of a child with *STAT3* GOF mutation.

CASE HISTORY

- Our index case started having recurrent pneumonia since the age of 2 months.
- At 11 months of age, he was noted to have failure to thrive, hepatosplenomegaly and generalized lymphadenopathy. Bone marrow examination showed no evidence of leukemia. Preliminary immunologic assessment showed raised immunoglobulin levels and elevated lymphocyte subsets.
- At 15 months, progressive pancytopenia was noted. Genetic studies for autoimmune lymphoproliferative syndrome (ALPS) was negative.
- Patient had multiple hospital admissions over the subsequent years due to various reasons including anemia, pneumonia and recurrent febrile episodes.
- Blood sample was sent for WES to establish a genetic diagnosis.

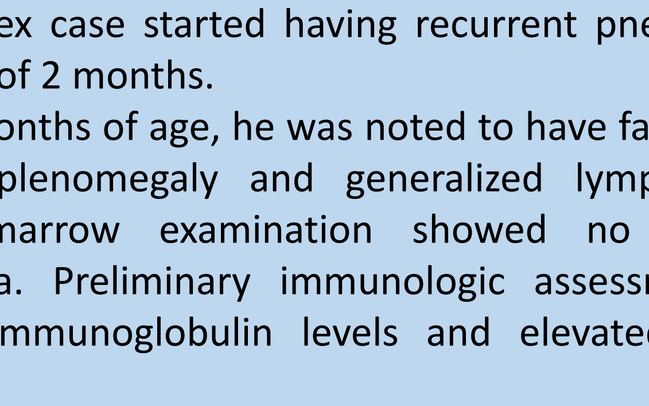
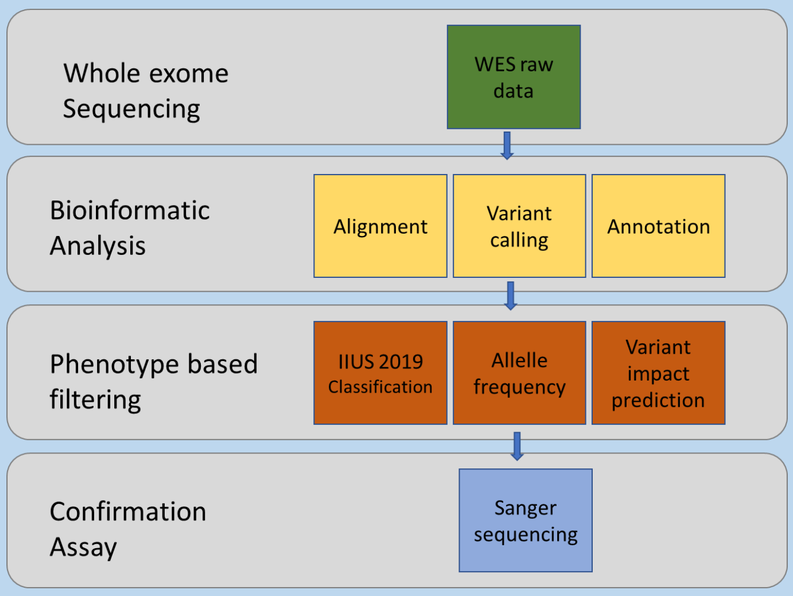
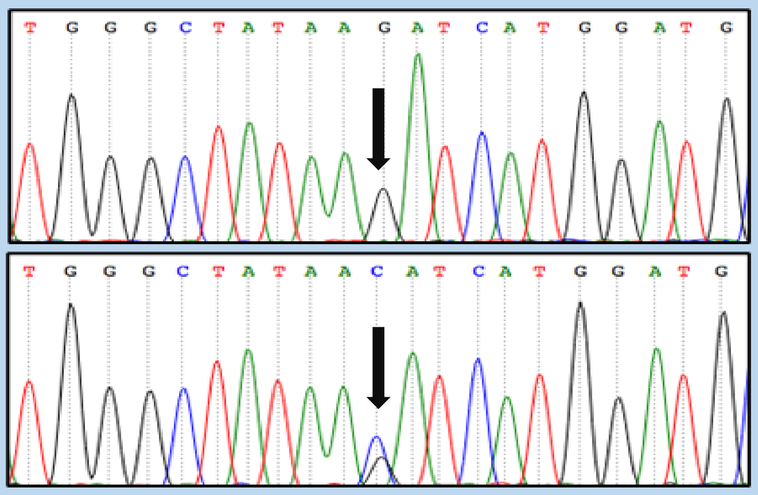


Figure 1: Family pedigree of the affected family

DIAGNOSTIC PROCESS



RESULTS AND DISCUSSION



- WES confirmed a c.G1974C (p.K658N) mutation in *STAT3*
- Similar mutation has been reported in patients with early-onset multiorgan autoimmune disease (4).
- The similarity of clinical features between ALPS and *STAT3* GOF may cause diagnostic challenges in health setting with limited diagnostic capability.

CONCLUSION

WES has assisted in establishing a definitive diagnosis which could have been missed using targeted panel sequencing

References

1. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. The New England journal of medicine. 2013 Jan 10;368(2):161–70.
2. Forbes LR, Milner J, Haddad E. Signal transducer and activator of transcription 3: a year in review. *Curr Opin Hematol*. 2016;23(1):23-27.
3. Gonzalez-Mancera MS, Johnson B, Mirsaeidi M. *STAT3* gain-of-function mutation in a patient with pulmonary *Mycobacterium abscessus* infection. Respir Med Case Rep. 2020 Jun 12;30:101125.
4. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Allen HL, De Franco E, et. Al. Activating germline mutations in *STAT3* cause early-onset multi-organ autoimmune disease. Nat Genet. 2014 Aug;46(8):812-814.