STAT3 GOF mutation identified in a Hyper-IgE patient diagnosed with short stature and puberty delay

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Background:

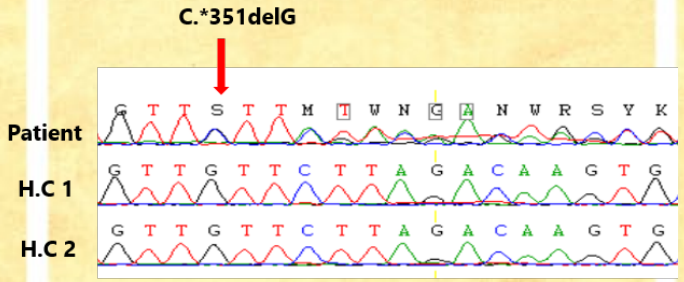
Mutations in Signal Transducer and Activator of Transcription 3 gene (STAT3) lead to different human diseases. STAT3 autosomal dominant (AD) Loss-off-function mutation lead to hyper IgE syndrome (HIES). STAT3 germline gain-off-function mutations (GOF) lead to autoimmune disease, lymphoproliferation, recurrent infection and short stature.

Purpose:

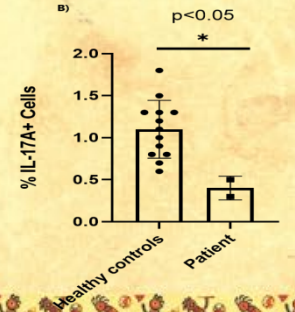
We report a 17-year-old girl with a history of recurrent lung infection leading to bronchiectasis. She has also developed vaginal yeast infection, chronic onychomycosis and oral candidiasis. Her physical examination revealed short stature, puberty delay and retained primary teeth. Laboratory findings showed elevated IgE and eosinophilia. She had a score of 53 points according to the NIH clinical HIES scoring system. The diagnosis of HIES was proposed.

Results:

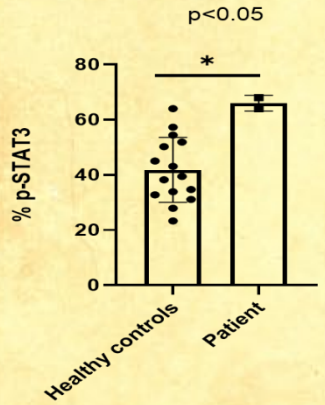
- ✓ Laboratory investigations showed normal rates of CD3, CD4, CD8, NK and CD19 cells.
- ✓ Genetic investigation by Sanger sequencing revealed a novel mutation located in the 3'UTR region (c.*351delG) of *STAT3*.



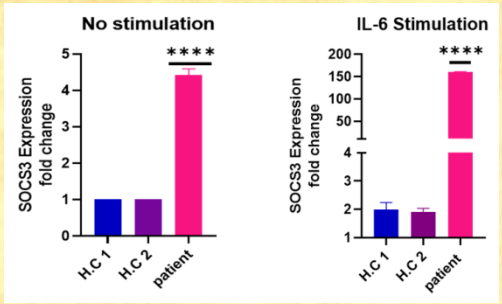
- ✓ Frequency of TH17 subset evaluated ex vivo by flow cytometry was decreased in the patient when compared to healthy controls



- ✓ STAT3 phosphorylation was slightly elevated in the patient when compared to healthy controls.



- ✓ Evaluation of SOCS3 after IL-6 stimulation by quantitative PCR, a STAT3 target gene, revealed a very high level of expression as compared to healthy controls.



Conclusion:

Herein we report a patient with overlapping clinical and biological features with the AD-HIES and the human Growth Hormone Insensitivity Syndrome. A mutation in non-conding region of STAT3 (**c.*351delG**) was identified. Interestingly, another mutation located at the same position was identified in a HIES patient. P-STAT3 and SOCS3 evaluation confirmed that this mutation is a GOF STAT3 mutation. Regarding the presence of short stature and puberty delay, we could speculate that the signaling pathway of growth hormone, involving STAT5 and STAT3 may be compromised. Indeed, STAT3 hyperactivity has been associated with STAT5 and STAT1 decreased phosphorylation .