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

Meriem Ben-Ali¹, Roukaya Yaakoubi¹, Imen Ben-Mustapha¹, Najla Mekki¹, Amel Benchida², Mohamed-Ridha Barbouche¹

Abstract

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

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.

STAT3 phosphorylation was slightly elevated. The percentage of TH17 cells was reduced as assessed by flow cytometry. No STAT3 mutations were found in coding exons by targeted Sanger sequencing. Interestingly, we identified a rare mutation located in the 3'UTR region (c.*351delG). In order to assess the functional effect of this mutation, we evaluate the induction of SOCS3 by quantitative PCR, a STAT3 target gene, and found very high level of expression as compared to healthy controls. This result suggests that this mutation is a STAT3-GOF mutation.

Short stature and puberty delay are predominant features in STAT3-GOF disorder. There are multiple differential diagnoses for STAT3-GOF syndrome due to overlapping clinical and immunologic features with other disorders which makes the diagnosis more challenging. Early onset diabetes or growth failure should raise suspicion.