

Novel STAT3 gain-of-function variant with hypogammaglobulinemia and recurrent infection phenotype

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Abstract

Signal transducer and activator of transcription 3 (STAT3) gain-of-function (GOF) syndrome is an early-onset monogenic inborn error of immunity characterized by multi-organ autoimmune disorders, growth failure and lymphoproliferation. We describe that STAT3 GOF syndrome may be presented with hypogammaglobulinemia and recurrent severe upper and lower respiratory tract infections. The patient we present here did not have multi-organ autoimmunity and lacked early-onset autoimmune manifestations. Chest CT examinations showed mild bronchiectasis with areas of non-fibrosing alveolar-interstitial disease and maldevelopment of bilateral first ribs. By using Sanger sequencing, we revealed a novel c.508G>C, p.D170H STAT3 variant affecting the coiled coil domain (CCD) of STAT3. Functional studies confirmed that p.D170H was a GOF variant as showed by increased pSTAT3 and STAT3 transcriptional activity. Our observation suggests that STAT3 GOF syndrome can manifest in early childhood with hypogammaglobulinemia and recurrent severe respiratory tract infections and may lack autoimmune manifestations. We suggest that patients with hypogammaglobulinemia and severe, recurrent infections should be screened for STAT3 variants even if autoimmune manifestations are missing.

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