

Letter to the Editor

Challenges of genetic counseling in patients with autosomal dominant diseases, such as the hyper-IgE syndrome (STAT3-HIES)

To the Editor:

Heterozygous mutations in the transcription factor signal transducer and activator of transcription 3 (*STAT3*) cause autosomal dominant hyper-IgE syndrome (HIES), which presents with *Staphylococcus aureus* skin abscesses, pneumonias with pneumatocele formation, mucocutaneous candidiasis, and eczema with increased serum IgE levels.¹⁻³ Here we report a family with 3 children affected by autosomal dominant HIES, suggesting genetic inheritance (Fig 1). Grandparents and both mothers (individuals I.1 and I.3) do not show any clinical findings of STAT3-HIES. The common father (subject I.2) of the 3 children is healthy except for mild atopic periorbital eczema since childhood. He has normal serum IgE levels (11.3 IU/mL), had 1 sinusitis, and had a tonsillectomy because of chronic inflammation.

The index patient is the 10-year-old daughter (individual II.1) of I.1 and I.2, who was born 2 weeks preterm after an unremarkable pregnancy. At 5 months of age, she started experiencing eczematous dermatitis, which spread from the head to the shoulders. She had recurrent oral and diaper dermatitis, otitis media, urinary tract infections, bronchitis, and pneumonia, some of which required intravenous antibiotic treatment. At 4 years of age, she was started on prophylactic antibiotic treatment with cefuroxime. Failure to shed primary teeth, increased serum IgE levels (9.716 IU/mL; value for age, <90 IU/mL), onychomycosis, recurrent bacterial infections of the skin and airways, hyperextensible joints, and characteristic facies were additional findings indicative of STAT3-HIES. Genomic analysis was completed at the age of 6 years, and the heterozygous *STAT3* hotspot mutation R382Q was identified. Radiography at 10 years of age revealed scoliosis of the lumbar and thoracic spine, with no signs of pneumatoceles or bronchiectasis.

The 6-year-old son (individual II.2.) of subjects I.2 and I.3 was born at full term after an unremarkable pregnancy. He had a newborn rash and started experiencing recurrent *Staphylococcus aureus* infections all over his skin. At 1 year of age, he had an abscess at the foreskin requiring surgery and intravenous antibiotic treatment. At the age of 5 years, persistent oral thrush required treatment with amphotericin B. He has no history of pathologic bone fractures, scoliosis, or hyperextensible joints, as seen in patients with STAT3-HIES, but has contractures of the tendons of 3 fingers. He has an increased serum IgE level (738 IU/mL at age 5 years; value for age, <90 IU/mL).

His 4-year-old brother (individual II.3) presented with eczema and recurrent respiratory tract infections beginning in early infancy. Recurrent otitis media required antibiotic treatment until the placement of tympanostomy tubes. Antibiotic prophylaxis was started at 3.5 years of age. Despite recurrent respiratory tract infections, he has not developed chronic lung changes, such as pneumatoceles. Scoliosis of the cervical spine was confirmed by means of chest radiography. His serum IgE level is increased (266 IU/mL at age 4 years; value for age, <60 IU/mL).

To confirm STAT3-HIES, sequencing of the gene *STAT3* was performed by using the Sanger technique with genomic DNA

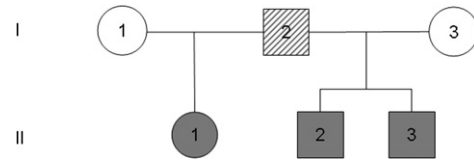


FIG 1. Pedigree of the family. The index patient (subject II.1), as well as her 2 half brothers (individuals II.2 and II.3), are shown as *solid symbols*, which indicate affected subjects. *Open symbols* present unaffected subjects with the wild-type sequence (individuals I.1 and I.3), whereas the *striped symbol* reflects the mosaicism of individual I.2. *Squares* indicate male subjects, and *circles* indicate female individuals.

(gDNA) extracted from peripheral blood, as described previously.⁴ The heterozygous mutation c.1145G>A, p.R382Q in exon 13 of the *STAT3* gene, was found in the 3 children (Fig 2), whereas the parents (individuals I.1, I.2, and I.3) had the wild-type sequence for exon 13.

Because it did not seem likely that all 3 children had independent and sporadic identical mutations, gDNA from the semen and oral mucosa of individual I.2 was extracted with a Biorobot EZ1 forensic card (Qiagen, Hilden, Germany).⁵ The mutation was not found in the oral mucosa gDNA, but the heterozygous R382Q mutation of the gene *STAT3* was identified in the genetic material extracted from the semen (Fig 2).

To show the functional consequence of the identified *STAT3* mutation, peripheral mononuclear cells were stimulated with phorbol 12-myristate 13-acetate/ionomycin to assess the T_H17 cell numbers, as previously described.⁴ T_H17 cell counts are known to be significantly decreased in patients with STAT3-HIES,^{4,6} and indeed, they were diminished in subjects II.1, II.2, and II.3 (0.03%, 0.07%, and 0.15% T_H17 cells of CD4⁺ cells; value in healthy control individuals, >0.2% CD4⁺ cells), whereas subject I.2, with the wild-type *STAT3* sequence in peripheral blood, had normal values (1.40% CD4⁺ cells).

As with other autosomal dominant diseases, STAT3-HIES in children with unaffected parents is suggested to be a result of spontaneous *in utero* mutations. Thus the risk of subsequent offspring being affected with the same condition is thought to be negligible. However, the fact that individual I.2 has healthy parents and 3 children with the complete clinical spectrum of STAT3-HIES caused by the identical heterozygous *STAT3* mutation (R382Q) involving subjects I.1 and I.3 suggests a paternal germline mosaicism.

Mosaicism is present if 1 individual has 2 or more cell lines with a different genotype that developed from a single fertilized homogeneous zygote.⁷ Because only the germ cells of the semen and not the somatic cells (oral mucosa and PBMCs) are mutated, subject I.2 is healthy but can pass down the mutation to his offspring (individuals II.1, II.2, and II.3) with variable penetration. The cause is usually a mutation that occurred in an early stem cell that gave rise to the gonadal tissue. The maximum amount of affected germ cells is 50% and is dependent on the developmental stage at which the mutation occurred.⁷

This family illustrates the complexity of genetic counseling in cases of autosomal dominant inherited diseases. Sequencing the gDNA of the parents' peripheral blood might not be sufficient in patients with STAT3-HIES to rule out an

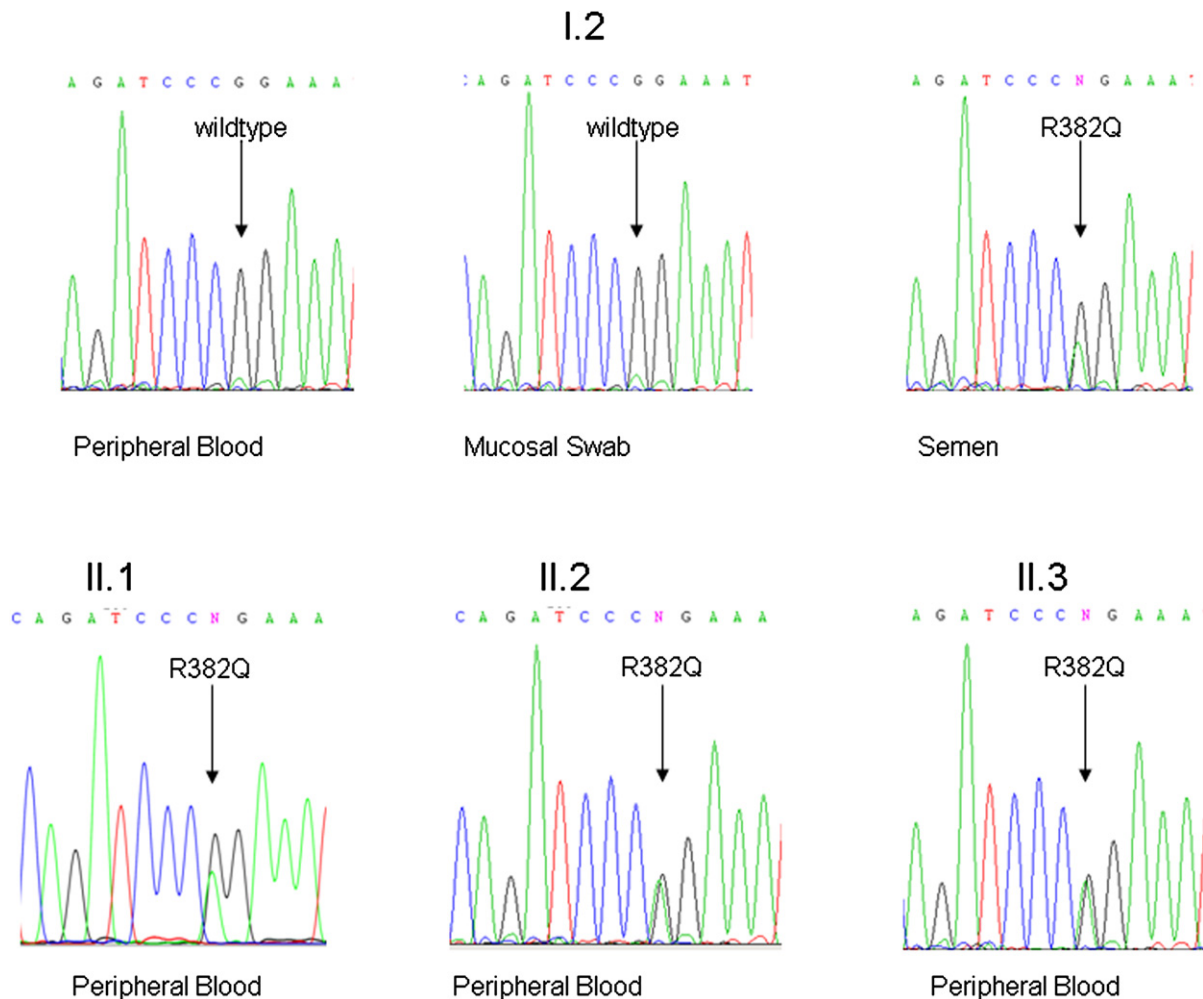


FIG 2. Mutation analysis of affected family members. Mutation analysis of subject II.2 shows the wild-type sequence of gDNA isolated from peripheral blood and mucosal cells. The gDNA of individual II.2 isolated from semen carries the heterozygous *STAT3* mutation c.1145G>A, R382Q, which has been identified in all his clinically affected offspring (individuals II.1-II.3).

increased risk for additional affected children. An increased risk of penetrance caused by an unknown mosaicism in germ cells has to be considered. Zlotogora et al⁷ stated in 1998 that there are too few data on carriers of germline mosaicism and its recognition in genetic diseases. Only a few germline mosaicisms have been observed in patients with primary immunodeficiencies, such as Wiskott-Aldrich syndrome, X-linked severe combined immunodeficiency, DiGeorge syndrome, and severe congenital neutropenia.⁸⁻¹¹ This report of a germline mosaicism in an additional autosomal dominant primary immunodeficiency should further raise awareness of this condition.

Overall, we recommend informing family members of patients with STAT3-HIES about the possibility of mosaicism. Furthermore, genetic testing of every newborn in families with known members carrying *STAT3* mutations is suggested to ensure the diagnosis of STAT3-HIES early in life. Only an early diagnosis of STAT3-HIES allows initiation of the right treatment necessary for limiting complications caused by infections and to benefit the quality of life of the individual patient.

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