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Case Report

A *STAT3* mutation in hyper-immunoglobulin E syndrome: A case report

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Abstract. Hyper-immunoglobulin E syndrome (HIES) is a rare immunologic disorder. This syndrome is caused by mutations in signal transducer and activator of transcription 3 gene. The described case report showed clinical HIES features such as recurrent bacterial pneumonia, lung cysts, characteristic facial features and a newborn dermatitis. We found a clinical features score of 35 and a positive family history, which, together, made a HIES diagnosis very probable. During DNA analysis, a new, formerly unknown, 1067C→G (p.P356R) mutation, with reference sequence NM_139276.2, was found in the DNA binding site of the *STAT3* gene. Both the child and his mother were affected. Thus, this family is affected by the autosomal dominant, HIES. This case report reveals a formerly unknown mutation, 1067C→G (p.P356R) in this gene.

Keywords: MeSH, *STAT3* transcription factor, hyper-Ig E syndrome, autosomal dominant, allergy, immunology, child

1. Introduction

Hyper-immunoglobulin E syndrome (HIES) is an immunologic disorder initially described as Job's syndrome by Davis et al. [1] in 1966. This syndrome involves recurrent Staphylococcal abscesses, sinopulmonary infections, and severe eczema. Since an associated increase in serum levels of Immunoglobulin E was described in 1972 by Buckley et al. [2], the syndrome was renamed HIES. It is a rare syndrome with an assumed incidence of 1/106 [3]. Worldwide, approximately 250 cases have been reported [4]. The syndrome appears to be distributed equally among races and sexes [5].

The HIES syndrome is classified in two types based on clinical and etiological criteria. The autosomal dominant type of HIES includes both sporadic (>90% of the cases) and familial autosomal dominant inheritance. The clinical findings associated with this type are dental and skeletal abnormalities and pulmonary cysts [6]. This HIES, the autosomal dominant and sporadic form, is caused by mutations in the signal transducer and

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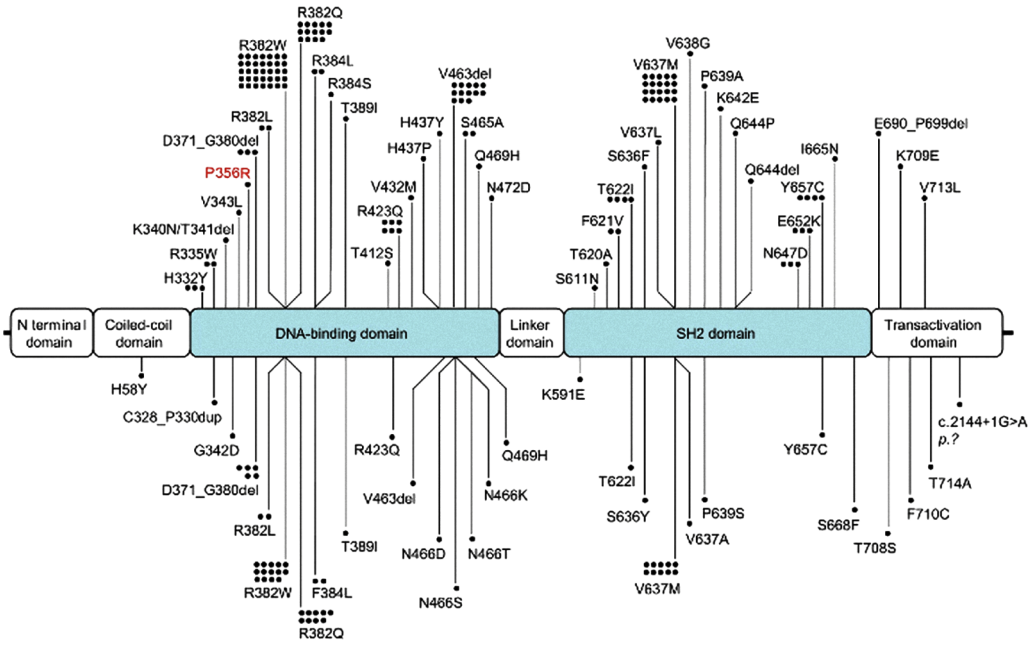

Fig. 1. STAT3 base: schematic of mutations causing hyper-immunoglobulin E syndrome (9). The mutation described in this case report, p.P356R, was added in red.

activator of transcription 3 (*STAT3)* gene on chromosome 17q21 [5,7,8]. Mutations are most often found in the deoxyribonucleic acid (DNA) binding site and the Src homology 2 region, although a few mutations are reported in the trans-activation domain. Missense mutations, in-frame deletions and exon skipping have all been described (Fig. 1) [5]. *STAT3* plays a key role in the regulation of Th17 cells. Th17 cells are IL-17 producers, which are involved in the defense against *Staphylococcus aureus* and candida infections [9].

In the autosomal recessive type of HIES, pulmonary cysts or skeletal manifestations are rare, but, viral infections (herpes simplex, molluscum contagiosum) with neurological complications are often found. It is still unknown whether the neurological problems are due to the autosomal recessive type of HIES, or secondary to latent infections in central nervous system [6]. One report discussing a genetic defect causing this type of HIES, describes a homozygous null mutation in tyrosine kinase 2 [4]. But, in general, the autosomal recessive form of HIES, is most often caused by homozygous or compound heterozygous loss-of-function mutations in dedicator of cytokinesis 8 [10].

The management of the patient with HIES is difficult, principally because the pathophysiology of the immunodeficiency leading to infection has not been completely elucidated. Since there is no specific treatment for HIES, therapy is supportive. First, there is a need for antimicrobial prophylaxis to avoid recurrent Staphylococcal infections. Drug of choice is trimethoprim-sulfamethoxasole. Immunomodulators are used with limited and variable success and need further research [5,11].

Secondly, deep-seated infections should be treated aggressively with systemic antibiotics and/or surgical drainage to prevent complications. Pulmonary complications include pulmonary insufficiency and pneumatoceles. Systemic symptoms are often lacking, so there is a need for active suspicion of invasive infection. Finally, extended skin management is equally important to control the pruritus and eczematoid dermatitis. Diluted bleach baths are most successful in preventing Staphylococcal infection [5,11].

In this article, we described a case who showed clinical HIES features such as recurrent bacterial pneumonia, lung cysts, characteristic facial features and a newborn dermatitis and revealed a formerly unknown mutation, 1067C→G (p.P356R) in the *STAT3* gene.

2. Case report

A 4-year-old Caucasian boy and his parents consulted at our hospital because of the child's recurrent

respiratory infections. The child was born at 40 weeks gestational age, without neonatal complications. At the age of 6 months, he suffered from pneumonia and since then on from recurrent respiratory infections. He had already been started on various unknown antibiotics prior to the consultation at our hospital without any signs of improvement. In addition, the patient has a medical history of eczema since birth, episodes of coughing, occasionally with fever or wheezing and rhinitis. No failure to thrive was documented.

Family history revealed that the infant's mother suffers from a hearing disorder of unknown origin and that she also has a medical history of recurrent, possibly bacterial, respiratory infections and episodes of facial dermatitis. In addition, the child's father suffers from a hearing disorder, most likely caused by ototoxic antibiotics administered after birth. No serious dental problems have been reported in the family. A younger sibling shows none of the above-described symptoms.

Clinical examination showed a 4-year-old boy with weight and height on the 95th and 90th percentile, respectively. On the child's face, remnants of prurigo scarring, along with a broad nasal bridge were noticed. Heart and lung auscultation and inspection of ear, nose, and throat were normal. No other clinical abnormalities were found. A standard blood test was unremarkable except for an eosinophil count of 125/mm^3.

A possible diagnosis of cystic fibrosis, because of an inconclusive, borderline sweat test, was excluded after DNA analysis. This analysis revealed the child was not a carrier of one of the thirty-five most frequent cystic fibrosis trans membrane conductance regulator mutations in the Belgian population. Because of the infant's atopic constitution, additional immunoglobulin E tests were conducted. The total immunoglobulin E measured 3414 IU/mL whereas the total amount for our reference laboratory should be below 114 IU/mL. Because of the mother's medical history with recurrent respiratory infections, we also tested the mother's IgE levels. These were elevated as well and measured 2206 IU/mL. At first, conventional chest X-ray was performed. This showed signs of bronchitis, peribronchitis and a linear density in the superior lobe of the right lung. Follow-up computed tomography (Fig. 2) showed a thickening of the right superior lobar bronchus. In the superior lobe of the right lung bronchiectasis were seen with focal and nodular dilatation of the segmental bronchi up to 1.8 cm.

Due to persistent productive cough and persistent chronic inflammation, not responding to antibiotic treatment,

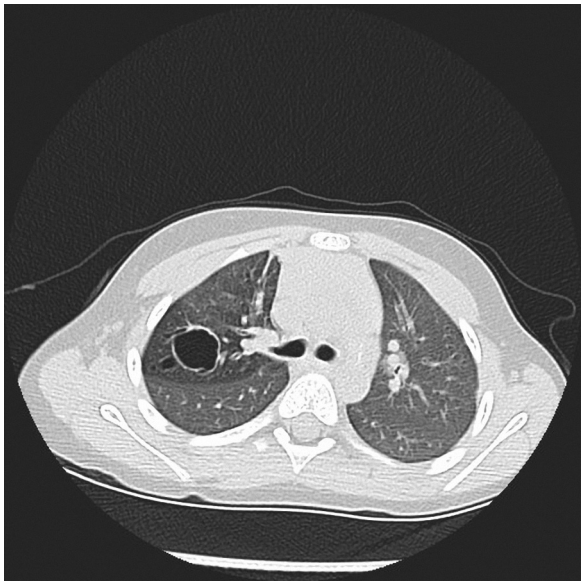

Fig. 2. Computed tomography of the child's thorax.

a decision to resect the right upper lobe was made. However, an intercurrent episode of pneumonia with pleural empyema of the inferior lobe of the left lung forced us to postpone surgery. Microbiology of the empyema showed *Streptococcus pyogenes*, susceptible for intravenous penicillin. After 4 weeks of intravenous and oral antibiotical treatment the resection was performed. The postoperative course was uneventful. Pathological analysis of the resected superior lobe of the right lung showed signs of chronic bronchitis, atelectasis and reactive changes in the tissue. Consistent with imaging, a cyst with a diameter of 1.2 cm was discovered. No atypical cell populations were seen on examination. The resected lymph nodes were found to be reactive lymph nodes. No other clinical signs, such as dental or musculoskeletal abnormalities were discovered, probably because the child was too young. The tentative diagnosis of HIES remained because of elevated IgE levels (>1000 IU/mL), eosinophilia, pustular and eczematous rash which affected the face and scalp, the history of pyogenic pneumonias and the positive family history for HIES [12].

Genetic blood analysis was performed in both the child and the mother to discover mutations in the *STAT3* gene. In both samples, a missense mutation of the *STAT3* gene was discovered. We found both patients to be heterozygote for the 1067C→G (p.P356R) mutation in the *STAT3* gene, with reference sequence NM_139276.2.

3. Discussion

3.1. Clinical diagnosis

The diagnosis of HIES is based on the criteria established by Grimbacher et al. [3]. These criteria combine clinical findings and laboratory findings. This scoring system was evaluated by Woellner et al. [9]. They found that a high total score was strongly associated with having a *STAT3* mutation. The optimal cut-off value was 49.5. This cut-off value had a sensitivity of 97% but a selectivity of only 58.8%.

Our patient showed clinical HIES features such as recurrent pneumonia, lung cysts, a characteristic face and a newborn rash. If we apply the criteria, established by Grimbacher et al. [3], on our patient, we find a score of 51 points, which is above the cut off value of 49.5.

Following guidelines were proposed by Woellner et al. [9]: *Possible*: IgE ≥1000 IU/mL plus a weighted score of clinical features >30 based on recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic face, and high palate (Table 1); *Probable*: These characteristics plus lack of TH17 cells or a family history of definitive HIES; *Definitive*: These characteristics plus a dominant-negative heterozygous mutation in *STAT3*.

When we apply these revised criteria to our patient, we find a 'clinical features score' of 34.97. By Woellner et al. [9], we scored 2 proven pneumonias (10pt), a present newborn rash (8.32pt), and a characteristic face for Job's syndrome (16.65pt). Even without the proven mutation of the *STAT3* gene, the diagnosis of HIES remains very possible in this case. This was because of the elevated IgE ≥1000 IU/mL, a weighted score of clinical features >30, based on recurrent pneumonia, newborn rash, and characteristic face, together with a positive family history.

These criteria have a sensitivity of 93.9%, a specificity of 70.6% and an error rate of 14%. Some of the clinical features, however, accumulate over time, arguably under diagnosing young patients [9]. Because the patient is a young child, some clinical features may not have developed yet, which could, but not necessarily, increase the child's 'clinical features score'.

In the study of Holland et al. [8] all 30 patients defined as 'unaffected' (HIES score 0–15) did not show any *STAT3* mutation. In contrast, all 40 patients defined as 'definitely affected' (HIES score ≥ 60) all showed a *STAT3* mutation. In the study of Woellner et al. [9], none of the 100 healthy study persons carried a *STAT3* mutation. Of the 100 patients with a clinical suspicion of HIES, 80 had HIES scores ≥40, although some were lacking *STAT3* mutations. Because the infant's mother also showed clinical signs of HIES, recurrent, supposedly bacterial, infections, and facial dermatitis since birth, she also underwent computed tomography of the thorax after conventional radiography showed a less transparent zone in the superior lobe of the right lung (Fig. 3). This showed pneumatocoeles in the superior lobe of the left lung and pneumatocoeles, post-infectious remnants with calcifications and pleural thickening, in addition to bronchiectasis in the right lower lobe.

Table 1
Hyper-immunoglobulin E syndrome *STAT3*-Score (9)

STAT3-Score: Patient:_____ DOB:_____ Scoring date:_____ Gender:_____						
Clinical findings	Points					
	0	2	4	5	6	8
Pneumonias (X-ray proven, total #)	None	1	2	–	3	>3
Newborn rash	Absent	–	Present	–	–	–
Pathologic bone fractures	None	–	1–2	–	–	>2
Characteristic face for Job syndrome	Absent	Mild	–	Present	–	–
Cathedral palate	Absent	Present	–	–	–	–
Clinical findings	Points × Scale			Scaled points		
Pneumonias			2.5			
Newborn rash			2.08			
Pathologic bone fractures			3.33			
Characteristic face for Job syndrome			3.33			
Cathedral palate			2.5			
Total (sum 1–5) scaled points						

This score sheet is intended to help predict whether a patient is already known to have serum IgE above 1000 IU/mL is likely to have a mutation in *STAT3* ***STAT3*. A total number of scaled points greater than 30 predicts a *STAT3* mutation is likely.**

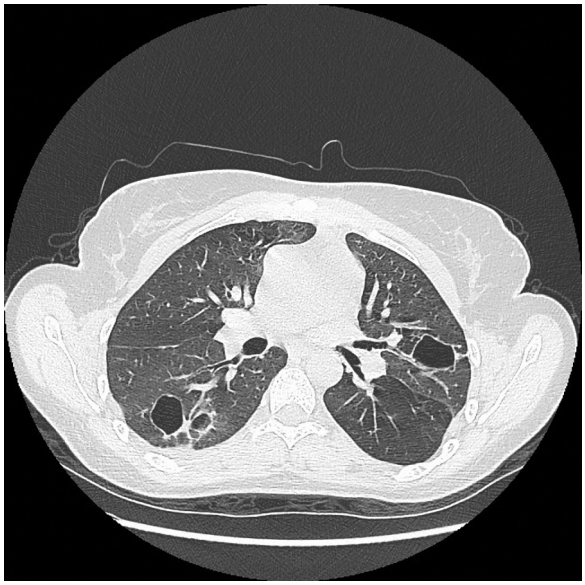

Fig. 3. Computed tomography of the mother's thorax.

When we scored the mother according to the guidelines proposed by Woellner et al. [9], we found a clinical feature score of 18.32. We are probably underscoring the infant's mother because we suspect her to have suffered from at least three bacterial pneumonias in her lifetime, but as we cannot document these pneumonias on conventional radiography, we scored only 2, documented on conventional radiography. She did not mention any problems related to retained primary teeth, pathological fractures or scoliosis. However, it is unclear how the mother came to adulthood without being diagnosed. Possibly, HIES was never considered in the differential diagnosis.

Clinically we already considered the child's symptoms to originate from HIES because of aforementioned reasons; nevertheless DNA testing was performed to gain a conclusive diagnosis.

3.2. Genetic diagnosis

Sequence analysis revealed the nucleotide change c.1067C→G, which results in the amino acid substitution p.P356R in the STAT3's DNA binding site, reference sequence NM_139276.2. No other pathogenic deviations were found. c.1067C→G (p.Pro356Arg), primer sequence exon 11: The sequence in italics is the attached M13 tail.

Forward: TGTAAAACGACGGCCAGTCTT CAAGAAAAGGTTATGGGAG;

Reversed: CAGGAAACAGCTATGACCTTC AAATGATGTCTGTCAAAGTTC

The software program Alamut® (Interactive Biosoftware, Rouen, France) was used to characterize the found variation [13]. This program integrates genetic information from different sources, among which three programs to predict pathogenicity of a mutation, Align-Grantham variation Grantham deviation (AGVGD) [14,15], Sorting Intolerant from Tolerant (SIFT) and Polymorphism Phenotyping 2 [16,17]. Both AGVGD and SIFT predict p.P356R to be benign. However, also other known pathogenic mutation in *STAT3*, such as p.R423Q, p.T389I and p.T622I are predicted to be tolerated by these programs. Apparently AGVGD and SIFT are not well suited to predict pathogenicity of *STAT3* mutations. Polyphen-2 evaluated the p.P356R substitution as possibly damaging. In addition, we would like to note that according to Holland et al. [8], indeed, Polyphen is more effective than SIFT in predicting pathogenicity for *STAT3*, but further research into this area is needed.

The most common reported mutations are missense mutations [18]. The described mutation changes proline, a conserved amino acid, to arginine. The chemical difference between proline and arginine is moderately radical (Grantham score: 103) [19]. Additionally, we sequenced 366 chromosomes from 183 individuals in our population. The mutation was not discovered in these 366 chromosomes. This could provide some confidence that this mutation could be causative to this syndrome in these patients as no polymorphism was found.

Because the child and the infant's mother shows clinical HIES features, in addition to a possibly damaging mutation, located in exon 11, in the DNA-binding site of STAT3 we believe that the family is a carrier of the type 1, autosomal dominant, HIES. Further analysis of this family revealed that the maternal grandmother is also a carrier of the c.1067C→G (p.P356R) mutation, with elevated IgE's. Among the other family members, no other carriers were found. Concerning the grandmother, further clinical investigations, including a computed tomography, are being planned in the near future.

After review of the literature, we can conclude that this is the first case of a formerly unknown, c.1067C→G (p.P356R), mutation in the *STAT3* gene [1,9]. In conclusion, HIES is a rare immunological disorder, caused by a mutation of the *STAT3* gene. This case report reveals a formerly unknown mutation: c.1067C→G (p.P356R) in this gene.

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