Heliyon 11 (2025) e42408

Contents lists available at ScienceDirect

Heliyon

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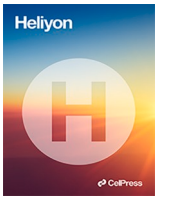

Case report

Whole-exome sequencing assists in the diagnosis of hyperimmunoglobulin E syndrome: Insights into dual genetic abnormalities

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A B S T R A C T

Hyperimmunoglobulin E syndrome (HIES) is a rare primary immunodeficiency disorder characterized by recurrent infections, severe eczema, and elevated serum immunoglobulin E (IgE) levels. Genetic testing traditionally focuses on known genes such as *STAT3* and *DOCK8*, responsible for the majority of autosomal-dominant (AD-HIES) and autosomal-recessive (AR-HIES) cases, respectively. However, a significant subset of patients with HIES-like symptoms remain genetically unexplained. Whole-exome sequencing (WES) has emerged as a transformative diagnostic tool, enabling the identification of both novel and incidental genetic mutations. This report highlights the role of WES in diagnosis of AD-HIES, showcasing its utility in detecting a *STAT3* mutation while revealing a concurrent *BRCA2* pathogenic variant. While the *STAT3* mutation confirmed the diagnosis of AD-HIES, the incidental *BRCA2* finding underscores the importance of genetic counseling and long-term surveillance.

1. Introduction

Hyperimmunoglobulin E syndrome (HIES) is a rare immunodeficiency characterized by recurrent infections, eczema, and elevated serum IgE levels. Initially described as "Job syndrome" in 1966 [1]. The classic autosomal-dominant form (AD-HIES) is often associated with mutations in the *STAT3* gene, which disrupts the Janus activated kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway and results in multisystem involvement [2]. Autosomal-recessive (AR-HIES) variants, frequently linked to *DOCK8* mutations, present with similar clinical features but lack skeletal and dental abnormalities [3]. The complexity and heterogeneity of HIES underscore the importance of genetic investigations in its diagnosis. While traditional testing has focused on known genes, a subset of patients remains unexplained, necessitating a broader diagnostic approach. Whole-exome sequencing (WES) enables genome-wide identification of genetic variants, allowing for the discovery of both novel causative mutations and incidental findings that may influence patient management.

This case involves a 39-year-old female, who presented with long-term and recurrent cutaneous abscesses and elevated IgE levels, diagnosed with AD-HIES through WES, which identified a pathogenic *STAT3* mutation. Additionally, WES uncovered an incidental *BRCA2* mutation, raising important considerations for secondary findings and their implications for long-term care.

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https://doi.org/10.1016/j.heliyon.2025.e42408
Received 10 June 2024; Received in revised form 6 January 2025; Accepted 30 January 2025
Available online 4 February 2025

1.1. Case report

A 39-year-old woman was admitted to our hospital in January 2024 with a history of recurrent cutaneous abscesses, which had been occurring since she was 7 months old. The abscesses typically presented as 2cm subcutaneous nodules that gradually enlarged, softened, and discharged pus. These episodes recurred 1–2 times per year. In 2012, she developed an abscess in her left hip joint, which was initially suspected to be tuberculous in origin. She was treated with a two-year course of combined anti-tuberculosis therapy with limited success. A subsequent ultrasound in 2015 revealed a persistent abscess around her left femoral neck, measuring 8.5cm by 2.6 cm. Surgical debridement was performed, and pathology revealed inflammatory granulation tissue with abscess formation. Since 2019, she has been experiencing recurrent abscesses on her chest and back, with microbiological cultures consistently positive for methicillin-sensitive *Staphylococcus aureus* (MSSA). Biopsy pathology findings were indicative of subacute giant cell granulomatous inflammation. Despite repeated courses of cephalosporins and low-dose corticosteroids, treatment attempts with cephalosporins and low-dose corticosteroids, the patient exhibited suboptimal response and poor tolerance. She also complained frequent infection in upper respiratory tract annually, along with multiple episodes of pneumonias, which had led to bronchiectasis as evidenced by chest CT scans. She denied any family history of similar symptoms.,

Physical examination was notable for her widened nasal alae, retrognathia, and macroglossia. Additionally, a 3- to 4-cm abscess was observed on the lateral aspect of the right thigh, along with multiple non-tender subcutaneous nodules in the axillae, groin, and neck. Her fingers appeared short and stubby, with notable clubbing and bilateral hallux valgus (Fig. 1). Auscultation of the lungs revealed bibasilar coarse crackles.

At admission, the white blood cell count was 4.86×10^9/L ($3.5–9.5 \times 10^9$/L), with a slightly elevated eosinophil count of 0.61×10^9/L ($0.2–0.5 \times 10^9$/L).During hospitalization, the eosinophil count ranged from 0.54×10^9/L to a peak of 1.08×10^9/L. Liver and renal function was within normal limits. However, the inflammatory markers were elevated, with an erythrocyte sedimentation rate of 81 mm/h (reference range, 0–20mm/h) and a C-reactive protein level of 37 mg/L (reference range, 0–10mg/L). Immunoglobulin levels showed normal IgM and IgA, but an increased IgG (21.94g/L, reference range 7–17g/L). Notably, serum immunoglobulin E (IgE) was markedly elevated, exceeding 5000 KU/L (reference range, 0–60 KU/L). Analysis of lymphocyte subsets revealed an elevated B cell count (560/μL, reference range 180–324/μL), a normal NK cell count (213/μL, reference range 175–567/μL), and a decrease T cell count (1164/μl, reference range 1185–1901/μl), predominantly due to a reduction in $CD8^+$ T cells (240/μL, reference range 404–754/μL). Furthermore, activated $CD8^+$ T cells (CD8+DR+/CD8+%) were increased at 48.2 % (reference range, 6.3–23.8 %), while the proportion of memory $CD4^+$ T cells ($CD4^+$CD45RA-/CD4+) was reduced to 37.4 % (reference range,45.6–68.4 %). Cytokine analysis showed an IL-17a level of less than 10pg/ml, with other cytokine level in normal range. Thyroid function, serologic tests for syphilis, human immunodeficiency virus, and hepatitis, as well as complement levels were unremarkable. Antinuclear antibody was positive at a titer of 1:80 and speckled with negative double-stranded DNA and extractable nuclear antigens. The neutrophil oxidative burst test and anti-gamma interferon antibody assays were negative. Microbiological cultures from the right back abscess grew MSSA while the sputum culture yielded *Pseudomonas aeruginosa*. Subcutaneous mass incision drainage and biopsy were performed, revealing fibrofatty tissue composition in the cyst wall with marked infiltration of lymphocytes and neutrophils accompanied by granulation tissue formation. The complexity of the patient's clinical presentation, including recurrent infections and the absence of family history, necessitated the use of WES for a comprehensive genetic investigation. This approach not only confirmed the diagnosis of AD-HIES through the identification of a *STAT3* mutation (NM_139276.2: c.1915C > T, p.Pro639Ser) but also revealed an incidental *BRCA2*

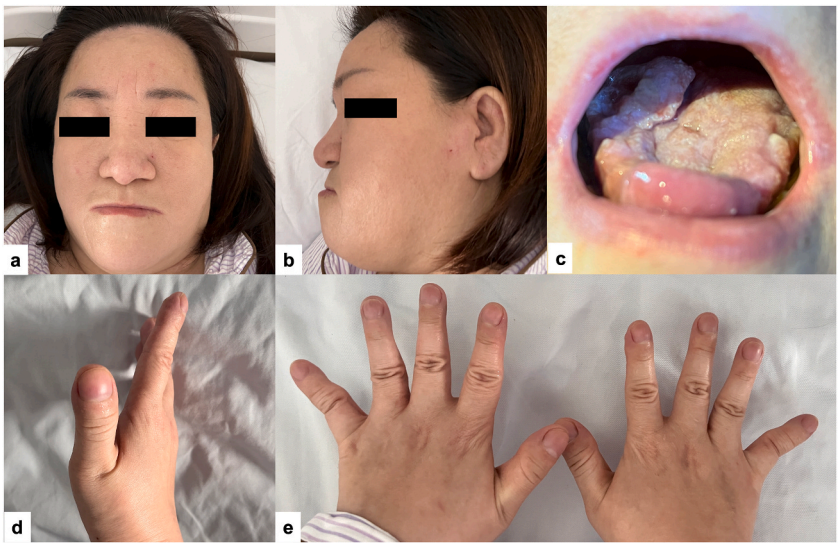

Fig. 1. Clinical findings on admission examination of the patient: a. widened nasal alae; b. retrognathia; c. macroglossia; d. hallux valgus; e. shortened fingers with clubbing.

pathogenic variant (NM_000059.4: c.1773_1776del, p.Ile591Metfs*22). The dual findings highlight the diagnostic power of WES and its ability to uncover clinically significant secondary findings.

After admission, the patient underwent incision and drainage of the abscess on her back, with an uneventful postoperative recovery. Additionally, a prophylactic antimicrobial regimen of sulfamethoxazole-trimethoprim was initiated. The patient was discharged and scheduled for monthly follow-up visits. To date, no signs of new infections have been observed.

2. Discussion

HIES features recurrent staphylococcal abscesses, sinopulmonary infections, and severe eczema and elevated serum IgE levels [4]. Skin and lung infections are common manifestations, frequently resulting in bronchiectasis due to recurrent infections. Patients may also have characteristic facial features such as a prominent forehead, lower lip, and broad nose. Most patients with classic AD-HIES, harbor a defect in *STAT3* gene, which disrupt the JAK-STAT signaling pathway affecting multiple families of cytokines, hormones, and growth factors [5]. The diagnosis of HIES is based upon clinical and laboratory findings, confirmed by molecular testing to identify a pathogenic *STAT3* variant [6]. In this patient, recurrent subcutaneous abscesses from early infancy, as well as recurrent respiratory tract infections leading to bronchiectasis were hallmark features. Laboratory tests revealed an increase in serum IgE level, peripheral eosinophilia count and an imbalance in lymphocyte subsets, suggesting chronic inflammation and impaired immune regulation. WES revealed a likely pathogenic de novo *STAT3* mutation, c.1915 C > T(p.Pro639Ser), which was not detected in her parents [5]. Variations at the same amino acid position including p.(Pro639Ala), p.(Pro639Gln), p.(Pro639Leu), and p.(Pro639Thr) have also been reported in other HIES cases [7,8]. According to the ACMG guidelines, this variant was classified as likely pathogenic because it fulfills multiple criteria, including PM2 (absent from population databases), PM1 (critical functional domain), PP3 (damaging in silico predictions), and PP4 (the patient's clinical presentation is highly specific for *STAT3*-related HIES) [9]. Therefore, genetic tests confirmed the diagnosis of AD-HIES, excluding other hereditary immunodeficiency and pathogenic variants in other genes that could mimic HIES-like disorders.

Traditional diagnostic approaches, such as the NIH scoring system (see Table 1) and targeted genetic testing, primarily rely on clinical features and immune profiles. However, these approaches lake sensitivity in identifying underlying genetic causes. In this patient, WES successfully detected a *STAT3* mutation despite the absence of a clear family history or phenotypic clues. Moreover, not all patients with HIES-like symptoms carry mutations in well-known genes such as *STAT3* and *DOCK8*. For example, a study in Taiwan revealed that only one out of eight patients exhibited a detectable *STAT3* mutation, highlighting the potential underdiagnosis of AR cases and the role of genetic diversity across population [10]. Additionally, research has demonstrated that WES can uncover novel genetic causes, such as *ZNF341* mutations in AR-HIES, further emphasizing its value in the diagnosis of rare disease [11].

Another important advantage of WES is its ability to uncover secondary findings—genetic variants unrelated to the primary condition but with potential clinical implications. For this patient, WES identified an incidental heterozygous variant NM_000059.4: c.1773_1776del, p.Ile591Metfs*22 in the *BRCA2* gene, which is associated with an increased risk of multiple malignancies including breast cancer, ovarian cancer, and prostate cancer [12]. The identification of incidental findings such as pathogenic *BRCA2* variants is not unexpected during WES [13]. As recommended by the ACMG, it should be encouraged to report incidental findings in 89 genes including *BRCA2*. Notably, to our knowledge, the concurrent presence of *STAT3* mutation with the incidental *BRCA2* mutation was a first-time finding because of the low probability of the co-occurrence of two mutations.

Beyond its primary diagnostic utility, WES offers clinicians a comprehensive view of a patient's genetic profile. This broader insight highlights the importance of developing a thorough follow-up strategy, including cancer surveillance and genetic counseling for at-risk family members. Although not yet universally adopted as the standard of care, WES is rapidly becoming an indispensable tool in the diagnosis of rare immunologic diseases. Its utility is particularly evident in cases where traditional genetic testing fails or when autosomal-recessive inheritance is suspected.

There are some limitations to our case. First, while the clinical relevance of the *BRCA2* mutation remains unclear, literature supports its pathogenicity and long-term monitoring is necessary. We initially aimed to report this case in order to provoke the significance of close follow-up due to pathogenicity of *BRCA2*. Second, due to technical limitations, certain immunological markers couldn't be assessed, though alternative data such as lymphocyte subsets and IL-17A levels were analyzed. Lastly, the mutation was not confirmed by Sanger sequencing, as the WES results met high-quality thresholds. Literature supports that Sanger sequencing is not always required for high-confidence variants [14].Therefore the diagnosis and genetic findings were considered robust.

3. Conclusion

This article reported a rare case of AD-HIES caused by *STAT3* mutation confirmed by WES. By identifying both primary pathogenic mutations and clinically significant secondary findings, WES improves diagnostic accuracy and facilitates comprehensive patient management. The findings highlight the importance of integrating WES into routine diagnostic workflows for HIES and other rare immunologic conditions, emphasizing its potential to uncover novel genetic causes and guide personalized care strategies.

CRediT authorship contribution statement

Si-yuan Li: Writing – original draft, Data curation, Conceptualization. **Wei Cao:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Ying Ge:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Wei Lvy:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Ya-ping Liu:** Writing – review &

Table 1
The NIH scoring system of this patient.

Clinical findings	Points										
	0	1	2	3	4	5	6	7	8	10	score
Highest serum-IgE level (U/mL)	<200	200 to 500			501 to 1000				1001 to 2000	>2000	10
Skin abscesses	None		1 to 2		3 to 4				>4		8
Pneumonia (episodes over lifetime)	None		1		2		3		>3		At least4
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele		6
Retained primary teeth	None	1	2		3				>3		0
Scoliosis, maximum curvature	<10°		10–14°		15–20°				>20°		0
Fractures with minor trauma	None				1 to 2				>2		0
Highest eosinophil count (cells/microL)	<700			700 to 800			>800				6
Characteristic face	Absent		Mildly present			Present					2
Midline anomaly	Absent					Present					0
Newborn rash	Absent				Present						0
Eczema (worst stage)	Absent	Mild	Moderate		Severe						0
Upper respiratory infections per year	1 to 2	3	4 to 6		>6						At least 1
Candidiasis	None	Oral	Fingernails		Systemic						0
Other serious infections	None				Severe						0
Fatal infection	Absent				Present						0
Hyperextensibility	Absent				Present						0
Lymphoma	Absent				Present						0
Increased nasal width	<1 SD	1 to 2 SD		>2 SD							0
High palate	Absent		Present								0
Young-age correction	>5 years			2–5 years		1–2 years		≤1 year			0

The scoring was mainly based on laboratory test, subjective deviations were strictly excluded. The total score was at least 37 points.

editing, Investigation, Formal analysis, Data curation. **Ling Qin:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

Funding statement

This work was supported by the National High-Level Hospital Clinical Research Funding (Grant 2022-PUMCH-B-117 to WC and 2023-PUMCH-E−012 to YP-L).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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