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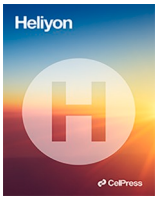

Case report

A novel nonsense variant in *POGZ* expanding the spectrum of White-Sutton syndrome: A case report

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ABSTRACT

White-Sutton Syndrome (WHSUS) is a rare neurodevelopmental genetic disorder with an autosomal dominant mode of inheritance. Truncating mutations in pogo transposable element with zinc finger domain (*POGZ*) gene have been reported in cases of WHSUS. In this article, we present the first diagnosed case of WHSUS in Lebanon. The 10-month-old infant presented with failure to thrive, chronic diarrhea, vomiting and recurrent upper respiratory tract infections. Molecular testing was performed showing a novel nonsense variant in the *POGZ* gene: c.1135C > T p.(Arg379*). With a relatively mild form of the disease, our findings suggest that WHSUS patients may present heterogenous clinical features.

1. Introduction

White-Sutton Syndrome (WHSUS) (OMIM: 616364) is a rare neurodevelopmental genetic disorder with an autosomal dominant mode of inheritance [1,2]. Various symptoms are reported in patients with WHSUS, such as intellectual disability (ID), developmental disability (DD), autism, hypotonia, and other dysmorphic features including microcephaly, brachycephaly, hypertelorism, flat nasal bridge, triangular mouth, in addition to sensorial hearing loss and increased risk of obesity [2–5]. The prevalence of WHSUS remains unknown, and this is mainly due to undiagnosed cases and to the clinical overlap with other related disorders [6,7].

Generally, WHSUS cases are isolated and not familial. They are caused by *de novo* pathogenic variants occurring during germ cells formation or during embryonic development. Truncating mutations in pogo transposable element with zinc finger domain (*POGZ*) gene have been identified in patients with WHSUS [8]. *POGZ,* located on chromosome 1q21.3, is reported to play a role in the setting of ID and neurodevelopmental diseases [9]. Several genes are reported to interact with *POGZ* in an interconnected network, such as *PSIP1*, *MAD212*, *CBX5*, *CHAMP1* and *CBX1* [7,8]. Consequently, molecular confirmation mainly by Whole Exome Sequencing (WES) or gene panels is essential to confirm the clinical diagnosis of WHSUS. Life expectancy and quality of life in patients with WHSUS remain not well defined, and rely mainly on the severity of the symptoms [10].

In 2023, it was reported that only around 140 cases of WHSUS have been documented in the medical literature [7,11,12]. Herein, we present the first diagnosed case of WHSUS in Lebanon, featuring a novel nonsense variant in the *POGZ* gene. Our findings aim to expand both the molecular and clinical spectrum of the disease, shedding light on its genetic basis and contributing to a better understanding of its clinical presentation in diverse populations.

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2. Clinical presentation

A Lebanese 10-month-old boy from the Bekaa region in Lebanon presented to the clinic with failure to thrive, chronic diarrhea, vomiting and recurrent upper respiratory tract infections. Clinical examination showed a height of 72.5cm (<10th percentile), a weight of 10.18kg (25th percentile) and a head circumference of 44.5cm (<5th percentile). He was referred for genetic testing at the Centre Jacques Loiselet for Medical Genetics and Genomics (CGGM) at the faculty of Medicine at Saint Joseph University of Beirut (USJ), Lebanon.

The parents are not consanguineous and there was no family history of any particular genetic disease (pedigree, Fig. 1A). Genetic counseling was performed. Both parents signed informed consent to perform all analyses and to publish the study.

A WES was performed. The following HPO terms were used as input: Abnormal sweat homeostasis, Chronic diarrhea, Colitis, Diarrhea, Episodic vomiting, Failure to thrive, Increased fecal calprotectin level, Recurrent upper respiratory tract infections, Villous atrophy and Vomiting. An in-house bioinformatics pipeline was applied, including read alignment to GRCh37/hg19 genome assembly and revised Cambridge Reference Sequence (rCRS) of the Human Mitochondrial DNA (NC_012920), variant calling, annotation, and comprehensive variant filtering.

A heterozygous likely pathogenic variant was identified in the *POGZ* gene in the patient (II.2). This result is consistent with a genetic diagnosis of autosomal dominant WHSUS. No further clinically relevant variants related to the described phenotype were detected. The identified *POGZ* variant, c.1135C>T p.(Arg379*), (or, p.(Arg379Ter)) introduces a premature stop codon in exon 8 (of 19). To the best of our knowledge this is a novel variant, not previously reported in the literature. The gnomAD database does not list this variant, highlighting its potential rarity. ClinVar lists this variant as likely pathogenic (Variation ID: 1343243). It is classified as likely pathogenic based on the ACMG/AMP/ClinGen SVI guidelines (PVS1, PM2 and PP5). Additionally, most bioinformatics prediction tools are in favor of the pathogenicity of this novel variant, such as BayesDel addAF and BayesDel noAF showing Very Strong Pathogenic (0.625) and Strong Pathogenic (0.66) scores, respectively.

A complementary familial analysis was conducted. Specific primers (Forward: acttctcagggagtgtttgac; Reverse: gccacttaagctggatcaca) were used to amplify the region containing the variant by PCR. Bidirectional Sanger sequencing was then performed, and samples were run on ABI 3500 sequencer (Applied Biosystems). The analysis confirmed the presence of the heterozygous variant in the patient (II.2) and demonstrated that both parents (I.1 and I.2) do not carry the variant, indicating that it is a *de novo* variant (Fig. 1B).

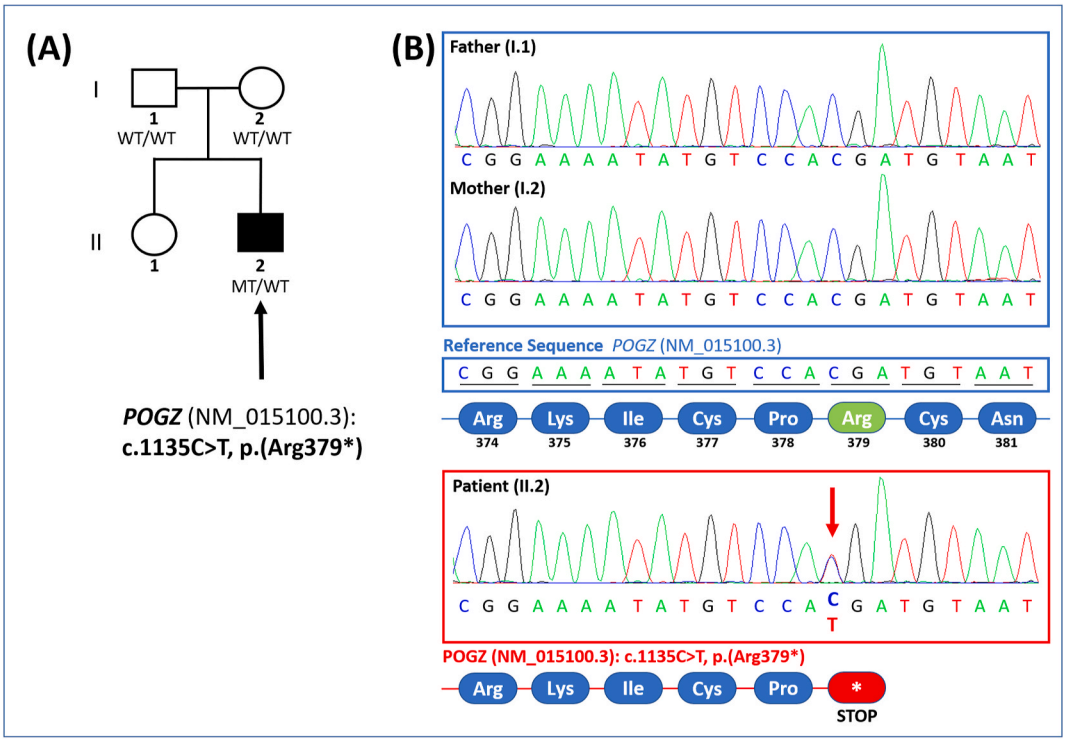

Fig. 1. (A) Pedigree of the family. The proband (II.2) is indicated by an arrow. (B) Sanger sequencing confirmation of the variant identified by WES in the *POGZ* gene. Electropherogram of the patient (II.2) showing the heterozygous variant c.1135C>T, p.(Arg379*); while both parents (I.1 and I.2) showed a normal result.
MT: Mutant allele. WT: Wild type allele.

3. Discussion

In this article, we present the first diagnosed case of WHSUS in Lebanon. WHSUS is a rare genetic disorder and to our knowledge, only one case has been documented in the broader middle east region, in Iran in 2023 [7]. Following clinical examination, a WES was requested for the patient revealing a likely pathogenic novel nonsense variant in the *POGZ* gene. This molecular diagnosis confirmed the clinical manifestations in the patient.

Following the identification of the novel variant by WES, molecular confirmation was done by Sanger sequencing and subsequent familial studies. The parents of the patient received genetic counseling, during which the "*de novo*" origin of the variant was explained, and the possibility of prenatal testing in case of future pregnancies. Similar to other rare genetic disorders, genetic counseling for WHSUS is crucial, as it ensures an accurate diagnosis, guides personalized management strategies, and empowers families with knowledge for informed decision-making.

In our study, WHSUS patient presented a novel nonsense mutation in the *POGZ* gene. It was reported that 34.8 % of *POGZ* mutations in WHSUS are nonsense mutations [12]. *POGZ* mutations are reported to disrupt the DNA-binding activity of the POGZ protein, mainly leading to a loss-of-function as the main mechanism of pathogenicity [12,13].

The identified *POGZ* variant in our patient, c.1135C>T p.(Arg379*), is a novel nonsense mutation, not previously described, leading to a premature stop at codon 379. Several nonsense mutations have been reported in *POGZ*, with a few located near the mutation detected in our patient. For instance, the p.(Ser278*) has been reported in a 3 years old patient with DD, seizures, behavioral abnormalities (autism) and ophthalmic anomalies [14]. And, the p.(Tyr404*) was detected in a 21 years old patient with ID/DD, speech delay and autism [15]. Compared to these two patients, our 1-year-old patient exhibits very mild ID/DD, almost within the normal range, with no seizures or signs of autism reported so far. To date, he is capable of saying only few words (~10 words). Additionally, our patient does not exhibit severe dysmorphic features and has not shown signs of visual abnormalities or hearing loss, which have been reported in other *POGZ* cases. This may be attributed to our patient's young age, or to the clinical heterogeneity observed in patients with *POGZ* mutations and WHSUS. Close clinical follow-up is necessary to monitor these symptoms and their potential future onset.

In WHSUS, Height and weight are reported to range from below the third percentile to above average. Indeed, short stature and failure to thrive have been reported in around 15 % of patients [2]. The patient we report herein exhibited a short stature (<10th percentile) and a failure to thrive. Also, microcephaly (<3^{rd} percentile) is a common clinical feature [2], and our patient showed a <5^{th} percentile microcephaly.

Gastrointestinal complications have been reported in patients with *POGZ* mutations, including feeding difficulties (65 %), gastroesophageal reflux (50 %) and swallowing difficulties (53 %) [11]. Our patient appears to exhibit these symptoms. Additionally, 47 % of *POGZ* patients experience constipation, whereas only 20 % are reported to have diarrhea [11]. Our patient is among the minority of patients suffering from diarrhea, presenting with an increased fecal calprotectin level. Interestingly, his chronic diarrhea improved with pancreatic enzyme supplementation and elemental formula.

Moreover, several "less common" features have been described in cases of WHSUS [2]. Among these, recurrent infections were observed. The case we report herein, suffered from recurrent respiratory tract infections.

In summary, we herein described a new case of the rare White-Sutton syndrome with a novel nonsense *de novo POGZ* variant c.1135C>T p.(Arg379*) and a relatively mild form of the disease. Our findings suggest that WHSUS patients may present heterogenous clinical presentations, including mild to severe cases. Additional WHSUS cases, along with further molecular and functional studies, would support these findings and enhance our understanding of WHSUS.

CRediT authorship contribution statement

Alain Chebly: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Nabiha Salem:** Software, Investigation, Formal analysis, Data curation. **Romy Moussallem:** Software, Methodology, Investigation, Formal analysis, Data curation. **Adib Moukarzel:** Writing – review & editing, Supervision, Data curation, Conceptualization.

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Ethics statement

Parents of the patient signed informed consents for participation and data publication.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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