A case of White–Sutton syndrome arising from a maternally-inherited mutation in POGZ

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POGZ is located on chromosome 1q21.3, encoding a pogo transposable element-derived protein with a zinc finger cluster. White–Sutton syndrome (WHSUS, OMIM:616364) is a genetic disorder resulting from de novo heterozygous pathogenic variants in POGZ, which manifests as intellectual disability, autism spectrum disorder, specific facial features and other phenotypic spectra. To date, a total of twenty-one de novo POGZ mutations in WHSUS have been reported. Here we report the identification of a novel missense variant in the coding region of the POGZ gene (c.4042G>C), which occurred in a 15-year-old male and his mother with WHSUS. We describe their clinical features and compare them with clinical data of patients with WHSUS from the literature. Our finding broadens the spectrum of POGZ mutations and provides a good example of precision medicine through the combination of exome sequencing and clinical testing. *Psychiatr Genet* 31: 135–139 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Background

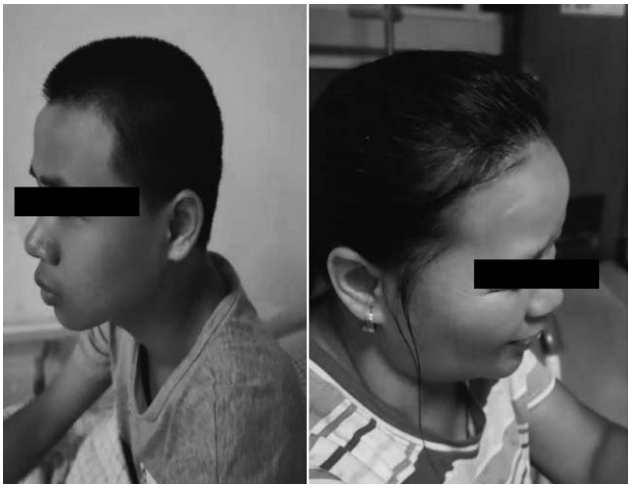
White–Sutton syndrome (WHSUS, OMIM:616364) is a genetic disorder resulting from de novo heterozygous pathogenic variants in POGZ on chromosome 1q21.3(Assia *et al.*, 2020). WHSUS manifests as intellectual disability, autism spectrum disorder (ASD), CNS malformations, developmental delay, special facial features, epilepsy and other phenotypic spectra (Fukai *et al.*, 2015; Ye *et al.*, 2015; Tan *et al.*, 2016; Dentici *et al.*, 2017; Ferretti *et al.*, 2019). It is estimated that de novo gene mutations associated with WHSUS might describe up to 0.14% of individuals with undefined ASD or intellectual disability (Stessman *et al.*, 2016).

POGZ (pogo transposable element with zinc finger domain gene) is a transcriptional regulator gene in neuronal networks located on human chromosome 1q21.3 (Bartholomeeusen *et al.*, 2009). It encodes a heterochromatin protein 1α-binding protein containing a cluster of multiple C2H2-type zinc fingers that may regulate gene expression, a centromere protein (CENP) B-like DNA-binding domain, a DDE domain that originated from a transposase encoded by a *pogo*-like DNA transposon (Nozawa *et al.*, 2010). The dysfunction of POGZ can lead to the majority of cells being unable to form metaphase plates and exiting mitosis prematurely, disrupting brain development and function (Ye *et al.*, 2015). Here we report a case of maternally-inherited mutation in POGZ of ethnic Chinese patients with WHSUS.

Case presentation

The patient, a 15-years-old boy, was born after an uneventful pregnancy at 38th gestational week from related parents. His mother presented with intellectual disability, autistic spectrum disorder, special facial features. His mother graduated from elementary school and had no job. Dysmorphic facial features of the patient and his mother were noted including palpebral ptosis, epicanthus, short palpebral fissures, pear-shaped nose, thin everted upper lip and prognathism (Fig. 1). The patient's physical development was normal, but his intelligence was extremely low. At the age of 7 years, he can only count the number up to 20. He also had limited social interactions and communication difficulties, so he dropped out of school. At the age of 11 years, he started presenting with paroxysmal episodes, mainly when awake, characterized by sudden weakness of legs and psychomotor arrest with eyes deviation, lasting a few minutes.EEG and neck/chest/waist MRI (Siemens 3.0T Magnetom Verio, Erlangen, Germany) were normal, but brain MRI (Siemens 3.0T Magnetom Verio) revealed abnormal signal changes in the bilateral subcortical cerebral and right occipital lobe, with local atrophy (Fig. 2). Those episodes were considered as epileptic seizures which were well controlled with valproate. At the age of 14 years, he presented with

Fig. 1

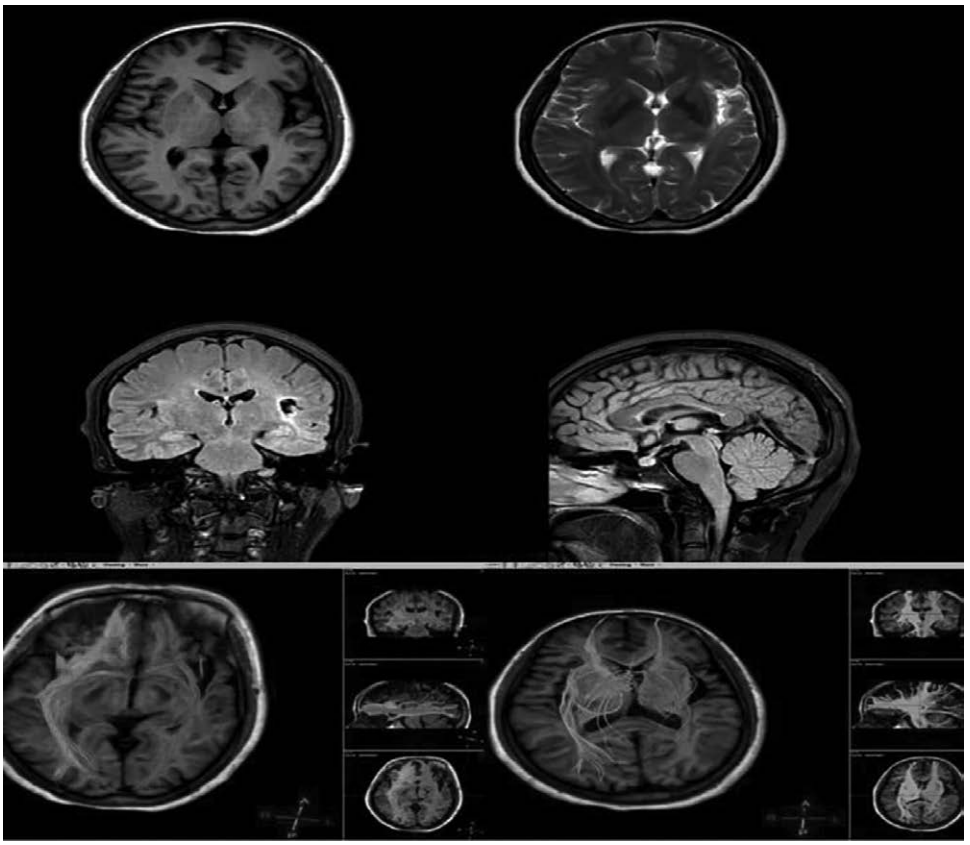


Special features of the patient and his mother demonstrating broad and low nasal bridge, anteverted nares and upturned corner of the mouth.

severe headache and unbearable pain in his back, lasting half an hour. This recurred once a month on average. He was given anti-inflammatory agents and calcium supplements, but his pain did not ease. His exome sequencing (as published) performed revealed a POGZ heterozygous missense variant, which was derived from his mother with abnormal phenotype (Fig. 3b,c).

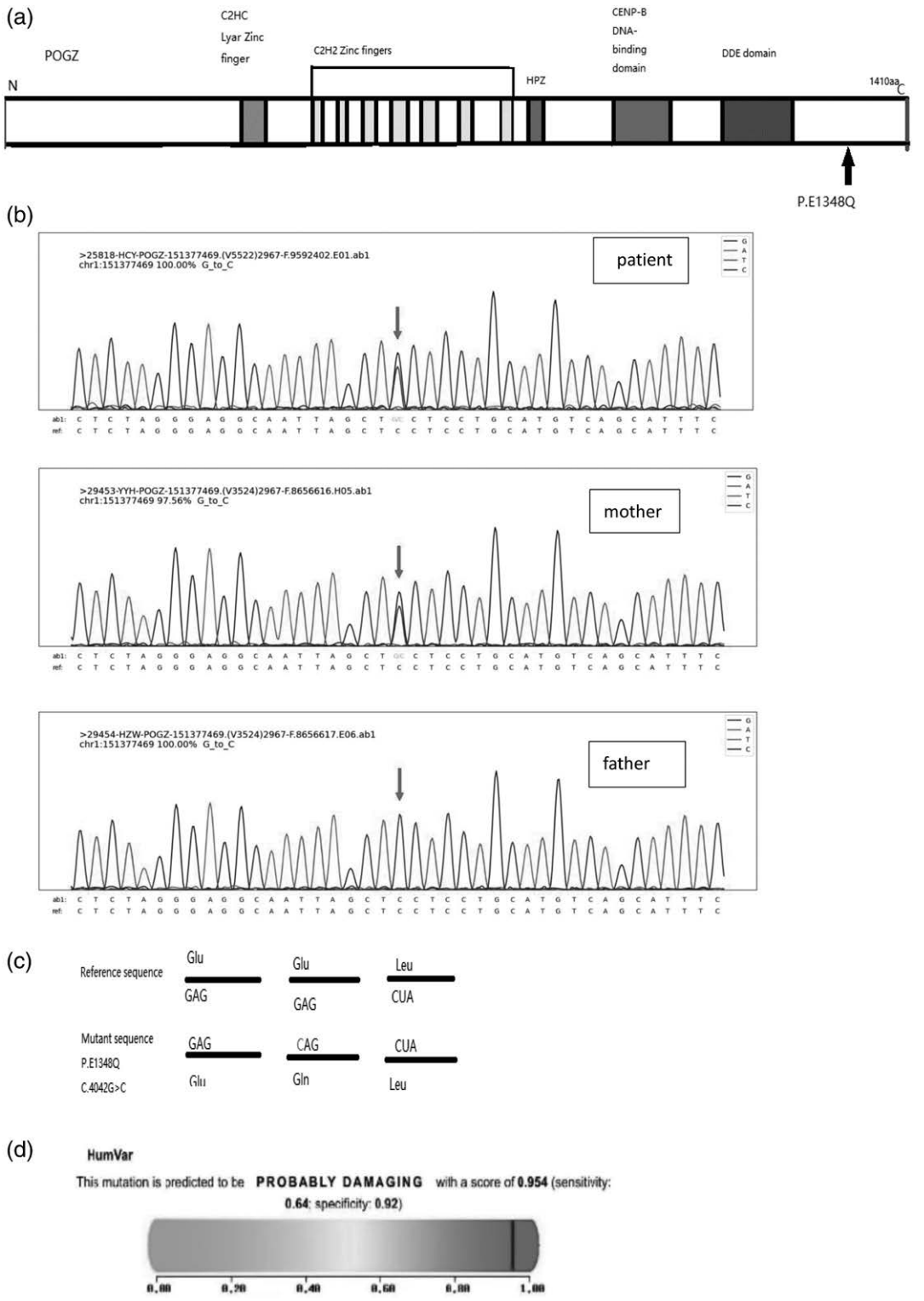
Genomic DNA was extracted from peripheral blood using the Solapur Blood DNA kit. The genomic DNA of the patient was then fragmented by a Q800R Sonicator to generate 300–500 bp insert fragments. The paired-end libraries were prepared following the Illumina library preparation protocol. Custom-designed NimbleGen SeqCap probes were used for in-solution hybridization to enrich target sequences. Enriched DNA samples were indexed and sequenced on a NextSeq500 sequencer (Illumina, San Diego, California, USA) with 100–150 cycles of single-end reads, according to the manufacturer's protocols. Primary data came in FASTQ format after image analysis, and base calling was conducted using the Illumina Pipeline. The data were filtered to generate

Fig. 2



Brain MRI of the patient revealed abnormal signal changes in the bilateral subinsular cortex and right occipital lobe, with local atrophy.

Fig. 3



(a) Schematic of POGZ and its five functional domains. The novel mutation identified in our patient is indicated by the black arrow. (b,c) The original amino acid residue was altered by the de novo mutation. (d) Functional predictions of a de novo missense mutation in POGZ.

'clean reads' by removing adapters and low-quality reads. Sequencing reads were mapped to the reference human genome version hg19. Nucleotide changes observed in aligned reads were called and reviewed using NextGENe software. Sequence variants were annotated using population and literature databases, including 1000 Genomes, dbSNP, GnomAD, Clinvar, HGMD and OMIM. The gnomAD database gives the variant frequency of 0.0001504 in the East Asian population, and not present in other populations, and it may also be possible that the POGZ mutation in this family could be unrelated to disease. Some online software programs were used to analyze the structure of the protein, predict the conserved domains and functional domains and perform a multiple-sequence alignment. Variant interpretation was manipulated according to the American College of Medical Genetics guidelines.

Discussion and conclusion

To explore the genetic basis of WHSUS, we performed trio-based WES involving the patient and his parents. One missense mutation from the patient and his mother was detected and predicted to be pathogenic by SIFT (Ng, 2003) and PolyPhen2 (Adzhubei *et al.*, 2010): POGZ gene c.4042G>C (p.E1348Q). Sanger sequencing confirmed the mutation to be de novo.

White–Sutton syndrome (WHSUS, OMIM: 616364) is a genetic disorder, resulting from novel heterozygous pathogenic variants in POGZ. In several previous large studies, WHSUS manifested as intellectual disability, developmental delay and ASD (2015, Fromer *et al.*, 2014; Gilissen *et al.*, 2014; Iossifov *et al.*, 2014), POGZ was one of the recurrently mutated genes in intellectual disability and ASD (Matsumura *et al.*, 2016). Several reports have found that WHSUS also manifested as epilepsy, skeletal abnormalities, distinctive facial features, ocular abnormalities, hearing loss, gait abnormalities, obstructive sleep apnea and gastrointestinal phenotypes (Dentici *et al.*, 2017; Ferretti *et al.*, 2019; Assia *et al.*, 2020).WHSUS became recognized as a pleiotropic intellectual disability syndrome (Yavarna *et al.*, 2015). In our case, headache and back pain may be other symptoms of WHSUS. Our report may expand the phenotypic spectrum of WHSUS. Brain MR of WHSUS was reported to reveal cortical atrophy, progressive cerebellar atrophy, thin corpus callosum, delayed myelination with mild brainstem hypoplasia and mild Dandy–Walker malformation (Stessman *et al.*, 2016; Dentici *et al.*, 2017; Samanta *et al.*, 2020).

POGZ is involved in mitosis and neuronal proliferation, so mutations in this gene may disrupt brain development and function. To date, a total of twenty-one de novo POGZ mutations in WHSUS have been reported, including 20 sequence variants and one 32 kb deletion. Among them, Eighteen POGZ mutations occurred de novo and one was inherited from his mother who has mild intellectual disability and obesity (Assia *et al.*, 2020). A pathogenic mutation in exon 19 of the POGZ gene has been reported to be located between amino acids at sites 858 and 1404 (Assia *et al.*, 2020). The E1348Q mutation reported in this paper is located in exon 19 region and is highly conserved across different species. This mutation was predicted to be harmful using multiple software packages (SIFT:0.0, Damaging; Polyphen-2:0.996, Probably_damaging; Mutation Taster: 1.000, Disease_causing; CADD: 26.2, Damaging). Matsumura *et al.* (2020) also reported a pathogenic variant of D1404N.

In conclusion, we identified a novel POGZ mutation, c.4042G>C (p.E1348Q), which appears to be causative of White–Sutton syndrome. Our report also may expand the phenotypic spectrum of WHSUS: headache and back pain. Further studies are required to delineate the natural history of White–Sutton syndrome.

Acknowledgements

This case report was approved by the Ethics Board of Zhujiang Hospital, Southern Medical University.

The mother of the patient and the patient herself provided signed informed consent for publication of this case report and any accompanying images.

Conflicts of interest

There are no conflicts of interest.

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