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BRIEF COMMUNICATION

De novo nonsense mutation in *WHSC1* (*NSD2*) in patient with intellectual disability and dysmorphic features

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Abstract

Intellectual disability is the most common developmental disorder caused by chromosomal aberrations as well as single-nucleotide variants (SNVs) and small insertions/deletions (indels). Here we report identification of a novel, probably pathogenic mutation in the *WHSC1* gene in a patient case with phenotype overlapping the features of Wolf–Hirschhorn syndrome. Deletions involving *WHSC1* (*Wolf–Hirschhorn syndrome candidate 1* gene) were described earlier in patients with Wolf–Hirschhorn syndrome. However, to our knowledge, single-point mutations in *WHSC1* associated with any intellectual deficiency syndromes have not been reported. Using whole exome sequencing, we found a de novo nonsense mutation in *WHSC1* (c.3412C>T, p.Arg1138Ter, NM_001042424.2) in patient with syndromic intellectual disability. This finding is challenging regarding a possible causative role of *WHSC1* in intellectual disability syndromes, specifically Wolf–Hirschhorn syndrome. From the clinical standpoint, our finding suggests that next-generation sequencing along with chromosome microarray analysis (CMA) might be useful in genetic testing for patients with intellectual disability and dysmorphic features.

Introduction

For many microdeletion syndromes, the role of specific genes involved in the pathogenesis of a disease remains questionable [1]. In regard to the *WHSC1* (*NSD2)* gene, its role in Wolf–Hirschhorn syndrome (WHS) is recognized, but there is no clear evidence of disruption of the gene being critical in the development of the full clinical presentation of WHS [2, 3].

WHS is characterized by distinct craniofacial features observed in infancy, consisting of 'Greek warrior helmet' appearance of the nose (wide nasal bridge continuing to forehead), hypertelorism, distinct mouth with downturned corners and thin upper lip, short philtrum, and micrognathia. Most affected individuals have prenatal-onset growth deficiency followed by postnatal growth retardation and hypotonia with muscle underdevelopment. Patients with WHS suffer from variable intellectual disability. Over 80% of patients have microcephaly, and the ears are usually poorly differentiated. Seizures occur in over 90% of patients, with onset within the first 3 years of life and peak incidence around 6–12 months of age [4].

The cause of WHS is well established; it is monosomy of at least the distal part of the chromosome 4 short arm within 4p16.3. The Wolf-Hirschhorn syndrome critical region (WHSCR), causing the recognizable syndrome, has been narrowed to a 200 kb region about 1.9 Mb from the telomere of 4p [5].

In our case, the observed de novo mutation in *WHSC1* (*Wolf–Hirschhorn syndrome candidate 1* gene) suggests the gene's role in pathogenesis of syndromic intellectual deficiency. However, the evidence is not sufficient to determine whether loss-of-function *WHSC1* mutations could be considered the cause of WHS or rather a distinct WHSC1-associated clinical entity.

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Case report

The proband is a 16-month-old boy (G5P3, two previous pregnancies ended with spontaneous abortions at early stages) referred to the clinics because of psychomotor retardation from around 3 months of age. The child's birth weight was 3050 g, birth length 50 cm, head circumference 33 cm, and Apgar score 8/10 (parameters at different ages shown in Table 1, Supplementary materials). The child was born in a radiation pollution zone (Chernobyl area), from both parents living there at the time of the accident. The proband has low physical development and moderate muscular hypotonia; his head circumference could be considered as microcephaly but it is concordant with height. A clear set of minor developmental abnormalities was noticed: high forehead, epicanthus, ocular hypertelorism, wide nasal bridge, protruding ears with attached earlobes (Fig. 1), tooth enamel dystrophy, clinodactyly of fifth fingers (more on the left hand), and widely spaced nipples (features not shown). Hepatomegaly and rotation of the right kidney were noticed during ultrasound evaluation. From the patient's phenotype and the available clinical data, a genetic cause was suspected.

Fig. 1 Photo of the proband showing some craniofacial features overlapping with Wolf–Hirschhorn syndrome: high forehead, epicanthus, ocular hypertelorism, wide nasal bridge, and protruding ears with attached earlobes. Permission to publish was obtained from the patient's parents

Methods

Whole-exome sequencing was performed on an Illumina NextSeq 500 instrument with average on-target coverage 165.7× using Nextera Rapid Capture Exome v1.2 reagents (Illumina) for library preparation. Bioinformatics analysis was performed using an in-house software pipeline designed to detect both single-nucleotide variants (SNVs) and copy number variations (CNVs) (see Supplementary materials for details). The absence of significantly large chromosomal abnormalities was subsequently confirmed by chromosome microarray analysis (CMA; Affymetrix CytoScan HD array). The de novo status of the mutation observed in the proband was confirmed using Sanger sequencing of the family trio (parentage verified) (Fig. 2a).

Results and discussion

A de novo nonsense mutation in *WHSC1* gene (c.3412C>T, p.Arg1138Ter, NM_001042424.2) was discovered in patient with syndromic intellectual disability. According to the UniProt and PDBsum databases, the observed mutation affects the SET domain, leading, in particular, to deletion of highly conserved ligand-binding residues (Fig. 2b, c) [6, 7]. The patient demonstrated minor craniofacial anomalies observed in WHS such as ocular hypertelorism and wide nasal bridge, along with low physical development, hypotonia, and some degree of intellectual disability. The proband did not demonstrate some features that are regarded as WHS core phenotype, like seizures and intrauterine growth retardation, although it should be noted that 20% of WHS patients have normal intrauterine size and some do not suffer from seizures at all or until older age [4].

After the initial hypothesis that a single gene could be responsible for the core WHS phenotype, the pathogenesis of WHS was later considered to be multigenic [8]. Two critical regions were defined earlier based on available clinical and genomic information: WHSCR1 and WHSCR2, overlapping at the *WHSC1* gene [9]. *WHSC1* (*NSD2*) is a gene that spans a 90 kb genomic region and contains four domains present in other developmental proteins: a PWWP domain, an HMG box, a SET domain, and a PHD-type zinc finger. The temporal and spatial expression of *WHSC1* in early development and protein domain identities suggest that WHSC1 may play a significant role in normal development.

Rauch et al. [10] reported the first known patient with a small de novo interstitial microdeletion encompassing 191.5 kb including *WHSC2* gene and a part of *WHSC1* gene. The patient presented partial WHS phenotype consisting only of low body weight for height, speech delay, and minor facial anomalies; shortness of stature,

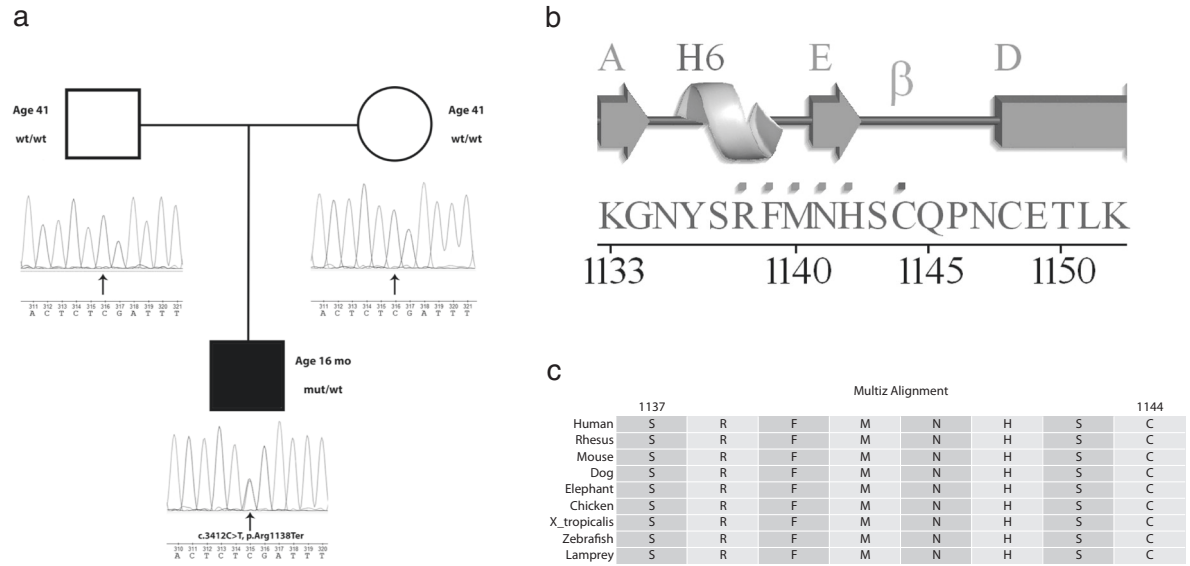

Fig. 2 **a** Pedigree of the trio and results of Sanger sequencing. The index patient is affected (black), the mutation is represented as mut, and the wild-type allele as wt. **b** Part of WHSC1 protein sequence including mutated Arg1138, adapted from PDBsum database. Functionally important residues are marked with colored dots: red, ligand-binding residue; blue, metal-binding residue. **c** Protein multiple sequence alignment of the affected region around Arg1138 in different species shows very high levels of conservation (multiz alignment)

microcephaly, seizures, and intellectual disability were absent. Authors hypothesized that seizures described in WHS might be associated with the deletions of *LETM1* gene.

Zollino et al. [11] agreed that typical WHS phenotype is a result of chromosome deletion event, however, they note that *WHSC1* is likely to be a developmental gene whose loss-of-function mutations could possibly result in clinical signs resembling WHS, although no such patients were known. Based on previous reports and their own results, Zollino et al. concluded that seizures in WHS are likely to be caused by hemizygosity of *LETM1* and other genes residing within the terminal 1.9 Mb region of chromosome 4p.

Hannes et al. [9] reported a deletion outside the known WHS critical regions, which does not include *WHSC1*, although in a patient with milder phenotype. They hypothesized that the discovered locus either harbors regulatory sequences that affect gene expression in WHSCR1-2 or is additive to deletions of WHSCR1-2, increasing the phenotypic expression.

In vivo functional studies showed *WHSC1* to have a crucial role in developing immunodeficiency observed in patients with WHS [2].

Our case suggests that the disruption of *WHSC1* causes syndromic intellectual disability that shares some clinical features with WHS. As noted by Zollino et al. [11], full-blown WHS phenotype should not be expected in patients with *WHSC1* mutations, and our observations correspond with their predictions. This case strongly suggests that the gene is clinically relevant regarding a monogenic form of syndromic intellectual disability. However, further investigations on the role of loss-of-function SNVs in *WHSC1* are needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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