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ORIGINAL ARTICLE

Trio-WES reveals a novel *de novo* missense mutation of *KMT2A* in a Chinese patient with Wiedemann-Steiner syndrome: A case report

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Abstract

Background: Wiedemann-Steiner Syndrome (WSS) is an autosomal dominant genetic condition caused by mutations in the *KMT2A* gene. Lysine methyltransferase, encoded by *KMT2A*, plays critical roles in the regulation of gene expression during early development.

Methods: Trio-based whole exome sequencing (Trio-WES) was performed on a 15 months old Chinese girl and her two parents by MyGenostics (Beijing, China) using the Illumina HiSeq X ten system. Variants were confirmed with Sanger sequencing. She exhibited mild/moderate intellectual disability (ID), hypotonia, hypertrichosis cubiti, hypertrichosis on the back, dysmorphic facies, psychomotor retardation, growth delay, small and puffy hands, fat pads anterior to calcanei, and palmar/plantar grooves.

Results: Trio-WES revealed a novel *de novo* mutation of *KMT2A* gene (NM_001197104.1: c.3566G>T, p.Cys1189Phe). WSS was diagnosed based on WES and clinical features.

Conclusion: Our findings expand the phenotypic and mutation spectra of WSS.

KEYWORDS

de novo mutation, KMT2A, whole exome sequencing, Wiedemann-Steiner syndrome

1 | INTRODUCTION

Wiedemann-Steiner Syndrome (WSS) [OMIM: #605130] is an autosomal dominant disease first described by Wiedemann in 1989, and defined as a syndrome by Steiner in 2000 (Steiner, 2000). WSS is characterized by hypertrichosis cubiti, hypertrichosis on the back, short stature, psychomotor retardation, growth delay, small and puffy hands, and dysmorphic facies including thick and arching eyebrows and downslanting palpebral fissures. WSS is considered as a major cause of intellectual disability (ID) (Baer et al., 2018).

The *KMT2A* (lysine methyltransferase 2A, also known as MLL) gene [OMIM: *159555], located on chr11q23.3, encodes a histone methyltransferase enzyme which regulates the gene expression profile during the early embryonic development and hematopoiesis (Ansari & Mishra, 2009). The initial association between WSS and mutations of the *KMT2A* gene was found in 2012 by Jones et al. (Jones et al., 2012). To date, 89 individuals with public variants of the *KMT2A*

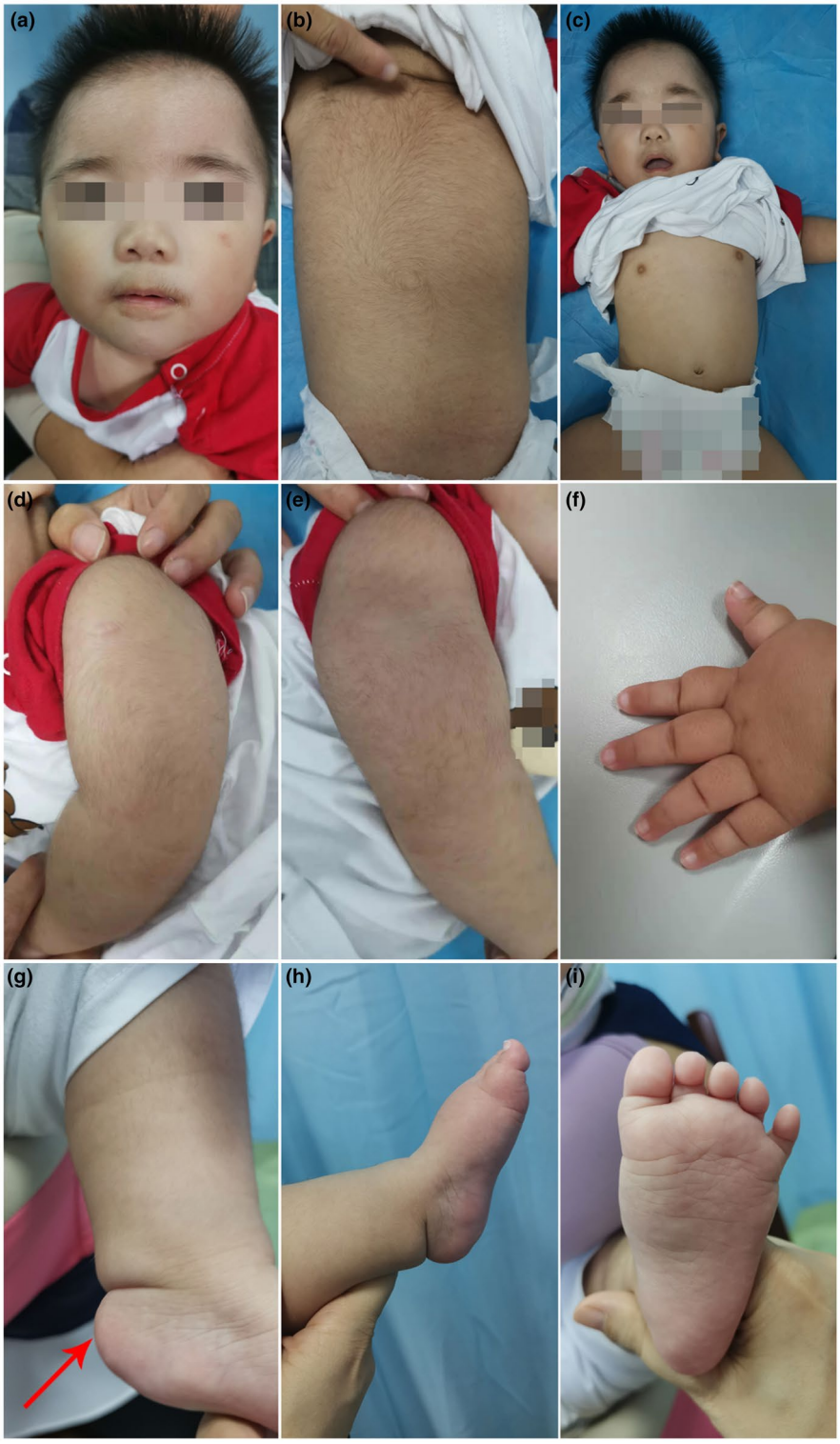

FIGURE 1 Physical appearance of 15-month-old girl with WSS. (a) Dysmorphic facies and thick hair Characteristic facial features include: thick and arched eyebrows, downslanting palpebral fissures, thick hair, and a broad nasal tip. (b) Hypertrichosis on the back. (c) Normal appearance of the abdomen. (D AND E) Hypertrichosis was observed on both arms. (f) brachydactyly. (g and h) Fat pads anterior to calcanei. I, fetal pads. Fat pads anterior to calcanei was labeled by arrow. Written informed consent for publication of these images was obtained from the patient's parents

gene has been reported in Leiden Open Variation Database (LOVD, https://databases.lovd.nl/shared/genes/KMT2A) (Arora et al., 2020; Baer et al., 2018; Chan et al., 2019; Chen et al., 2019; Feldman et al., 2019; Grangeia & Leao, 2020; Jinxiu et al., 2020; Li, Wang, et al., 2018; Ramirez-Montano, 2019; Stoyle et al., 2018). A total of 149 variants have been

TABLE 1 Clinical summaries of the patient with WSS

Sign	Result	Literature
Growth		
Prenatal growth retardation	+	1/1
Postnatal growth retardation	+	17/44
Developmental delay	+	24/30
Neurological abnormalities		
Intellectual disability	+	47/48
Seizures	−	4/31
Hypotonia	+	18/31
Craniofacial features		
Microcephaly	+	18/46
High forehead and hairline	+	−
Full cheeks	+	−
Narrow palpebral fissures	−	1/1
Downslanting palpebral fissures	−	30/47
Hypertelorism	+	34/48
Strabismus	+	10/46
Eversion of lateral third of lower eyelids	+	−
Long eyelashes	+	39/48
Ptosis	−	15/48
Broad and arching eyebrows	+	23/29
Synophrys	+	1/1
Wide nasal bridge	+	32/47
Broad nasal tip	+	1/1
Bulbous nose	+	−
Long philtrum	+	29/48
High palate	−	12/16
Cupid's bow, exaggerated	+	−
Downturned corners of the mouth	+	30/47
Internal organ problem		
Congenital heart defect	−	11/48
Feeding difficulties	+	25/47
Renal/uretero malformation	−	7/23
Musculoskeletal features		
Scoliosis	−	1/1
Small and puffy hands and feet	+	8/16
Brachydactyly	+	17/45
Fifth finger clinodactyly	−	10/44
Fetal pads	+	−
Fat pads anterior to calcanei	+	−
Palmar/plantar grooves	−	1/16
Absent palmar transverse crease	−	2/16
Tapering fingers	+	9/29
Sacral dimple	−	8/25
Integumentary features		

(Continues)

TABLE 1 (Continued)

Sign	Result	Literature
Hypertrichosis, cubiti	+	26/47
Hypertrichosis on the back	+	33/47
Hypertrichosis, generalized	+	17/40
Thick hair	+	14/16

documented in Human Gene Mutation Database (HGMD) database (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=KMT2A), and 216 entries have been reported in LOVD. With the application of whole exome sequencing (WES), more WSS patients have been molecularly diagnosed.

Currently, the complete phenotype of WSS is not understood fully. We report a 15 months old Chinese girl with clinical features of WSS. We have identified a novel *de novo* missense pathogenic variation of the *KMT2A* gene utilizing trio-based WES (trio-WES).

2 | CASE REPORT

This girl was born 2.3 kg (P3–P10) at 37 weeks of gestation in an uneventful spontaneous delivery. Her parents were non-consanguineous, and both were phenotypically normal. At 15 months old, she was able to hold her head up, but was unable to sit unaided. She showed feeding difficulties. Her head circumference, weight, and height were 42 cm (<−3SD), 7.5 kg (−3SD to −2SD), and 73.3 cm (−2SD to −1SD), respectively, at 15 months old. She exhibited mild/moderate ID, hypotonia, hypertrichosis cubiti, hypertrichosis on the back, psychomotor retardation, growth delay, small and puffy hands, fat pads anterior to calcanei, and palmar/plantar grooves. No epilepsy was observed. Physical examination revealed dysmorphic facies and thick hair (Figure 1a), hypertrichosis on the back (Figure 1b) but not on the abdomen (Figure 1c), hypertrichosis cubiti (Figure 1d,e), brachydactyly (Figure 1f), fat pads anterior to calcanei (Figure 1g,h), and fetal pads (Figure 1i). Her dysmorphic facies include microcephaly, high forehead and hairline, full cheeks, hypertelorism, strabismus, eversion of lateral third of lower eyelids, long eyelashes, broad and arching eyebrows, synophrys, wide nasal bridge, broad nasal tip, bulbous nose, long philtrum, exaggerated Cupid's bow, and downturned corners of the mouth. Detailed clinical summaries are listed in Table 1. She was referred for genetic assessment because of delayed psychomotor retardation and growth delay.

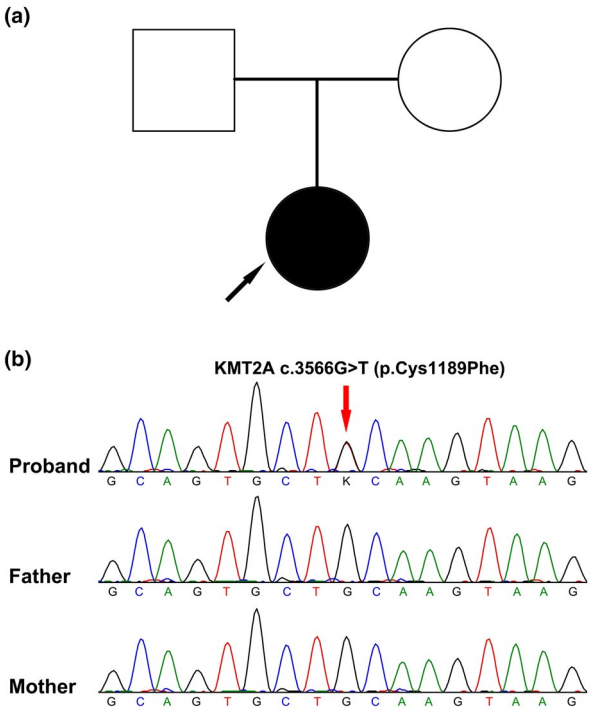

FIGURE 2 Validation of NM_001197104.1: c.3566G>T (p.Cys1189Phe) variation by Sanger Sequencing. (a) family tree of this patient. Blank square and circle represent unaffected male and female respectively. Filled circle indicates affected female, and the arrow indicates the proband. (b) Electrophogram showed heterozygous KMT2A c.3566G>T (red arrow). Both parents carried wild-type sequence at this nucleotide

3 | METHODS

Genomic DNA was isolated from peripheral blood of the patient and her parents. Trio-WES was performed by MyGenostics (Beijing, China) using the Illumina HiSeq X ten system. The trimmed reads were mapped to the reference human genome (hg19). Variants were filtered in the following databases, including dbSNP (https://www.ncbi.nlm.nih.gov/snp/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), The Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/), Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org/), 1000 Genomes Project (1000G, http://browser.1000genomes.org/), and HGMD (http://www.hgmd.cf.ac.uk/). Identified variants were confirmed with Sanger sequencing. The interpretation of sequence variants was performed according to the guidelines from American College of Medical Genetics and Genomics (ACMG) (Richards et al., 2015).

4 | RESULTS

A missense variant in the heterozygous state of the *KMT2A* gene was identified (NM_001197104.1: c.3566G>T). Neither of her parents harbored this variant, indicating a *de novo* variant. This variant has not been reported in these databases, including dbSNP, ClinVar, gnomAD, ExAC, 1000G, and HGMD, suggesting a novel variant. This variant results in a substitution of Cys with Phe at 1189 position (p.Cys1189Phe). This variant was confirmed by Sanger sequencing (Figure 2a,b).

5 | DISCUSSION

Wiedemann in 1989 and Steiner in 2000 described and defined WSS. In 2010, Koenig reported three further cases of WSS (Koenig et al., 2010). The clinical phenotypes varied between different ethnicities. Eating difficulties, hypertrichosis cubiti, and microcephaly were found in 65%, 61%, and 33% of all 33 cases in a French cohort, respectively (Baer et al., 2018). However, in a Chinese cohort of 16 cases, eating difficulties, hypertrichosis cubiti, and microcephaly were found in 31%, 44%, and 50% of all cases, respectively (Li, Wang, et al., 2018). Variations of the *KMT2A* gene are associated with neurodevelopmental disorders (NDDs) including WSS (Chan et al., 2019). Molecular diagnosis is helpful for patient care and genetic counseling, including targeted sequencing of the *KMT2A* gene, WES, or whole-genome sequencing (WGS). With the application of WES, especially the trio-WES, more and more cases of WSS have been reported (Baer et al., 2018; Li, Wang, et al., 2018; Strom et al., 2014), and the phenotypic and mutation spectra of WSS have accumulated. WES is an efficient approach in ID molecular diagnosis, but it also exposes to incidental discoveries.

De novo null variants account for the majority of previously reported cases with WSS (Baer et al., 2018; Chen et al., 2019; Li, Wang, et al., 2018; Ramirez-Montano, 2019). Missense variants of the *KMT2A* gene represent a small but significant portion (Baer et al., 2018; Chan et al., 2019; Li, Wang, et al., 2018). One hundred eleven of the submitted 207 entries of *KMT2A* variants in LOVD database were classified as likely pathogenic or pathogenic. Fifty of the 111 entries were confirmed as *de novo* variants. Among the 111 entries, 49 variants (44.1%) were nonsense, 31 variants (27.9%) were frameshift, and 16 variants (14.4%) were missense. In a cohort of 33 French cases reported by Baer, frameshift (41%), nonsense (28%), and missense (28%) mutations ranked the top three mutations (Baer et al., 2018). In their literature of 31 patients, nonsense (53%) and missense (28%) mutations accounted for the majority (Baer et al., 2018). In a Chinese cohort of 16 patients reported by Li, the mutation spectrum was similar with French population, while missense (15%) mutation accounted for a smaller portion (Dunkerton et al., 2015). In this study, we reported a novel *de novo* missense variant of *KMT2A* (NM_001197104.1: c.3566G>T, p.Cys1189Phe) responsible for WSS in a 15 months old Chinese girl. The *de novo* mutation showed 1%-2% recurrence risk in future pregnancy (Rahbari et al., 2016; Wang et al., 2018), and her parents were informed about this risk. Annual renal and cardiac tests, as well as neurological follow-up were suggested for this family.

According to the guidelines from ACMG (Li, 2017; Richards et al., 2015), NM_001197104.1: c.3566G>T (p.Cys1189Phe) variant is classified as pathogenic with the following evidences (PS2, PM1, PM2, PM5, and PP3): PS2, *de novo* in a patient with WSS and no family history; PM1, located in a well-established functional domain (Zinc finger, CXXC-type) without benign variant; PM2, absent from controls in gnomAD, ExAC, or 1000G databases; PM5, novel missense variant at an amino acid residue where a different missense variant was pathogenic (c. 3566G>A, p.Cys1189Tyr) (Miyake et al., 2016); PP3: multiple functional prediction software tools support a deleterious effect, including MutationTaster (http://www.mutationtaster.org), SIFT (http://sift.jcvi.org), PROVEAN (http://provean.jcvi.org/index.php), and Polyphen2 (http://genetics.bwh.harvard.edu/pph2/) (Adzhubei et al., 2010; Choi, 2015; Li, Shi, et al., 2018; Schwarz et al., 2014).

This missense variant was located in the cysteine-rich CXXC zinc finger domain, which selectively bound to un-methylated CpG-containing islands of target genes (Lebrun et al., 2018). Previous studies showed that patients with missense variants in the CXXC presented more severe neurodevelopmental delay (Lebrun et al., 2018; Min Ko et al., 2017). In a French cohort of 33 cases, five patients, aged from 5 to 22 years old, carried missense variants in CXXC domain. All five patients showed ID (two moderate and three severe), four had hypotonia neonatal, and seizures occurred in three of the five patients (Baer et al., 2018). In a Chinese cohort reported by Li, Wang et al. (Li, Wang, et al., 2018), a 5 years old girl harbored KMT2A p.Gly1168Asp mutation, located in CXXC domain. This girl showed walking and language delay, ID, aggressive behavior, hyperactivity, and autism. Moreover, at the same position with our patient, *KMT2A* c.3566G>A (p.Cys1189Tyr) has been reported in a 4 years old Australian boy previously (Miyake et al., 2016). This boy showed similar phenotypes with our patient, including growth and neurological abnormalities. No seizure was observed in both our patient and the Australian boy. Taken together, Both ID and hypotonia were found in our patient and previously reported patients carrying variants in CXXC domain, while seizure was only found in three of seven French patients. The CXXC zinc finger domain of *KMT2A* gene has been suspected as a hotspot for missense variants in WSS patients with more severe neuro-phenotypes (Li, Wang, et al., 2018).

In conclusion, a 15 months old Chinese girl was diagnosed with WSS based on trio-WES and clinical features. Our findings expand the current knowledge about the phenotypic and variation spectra of WSS.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

WW and XL conceived the experiments and cared the patient. XW performed genetic test and wrote the manuscript. YL performed genetic counselling. GZ collected patient samples.

ETHICAL APPROVAL

This study was approved guidelines by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent were obtained from all family members.

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