case report

A case of congenital Rett variant in a Chinese patient caused by a *FOXG1* mutation

Yan Niu,[a] Lirong Cao,[b] Peng Zhao,[a] Chunquan Cai[c]

From the [a]Department of Rehabilitation, Tianjin Children's Hospital, Tianjin, China; [b]Affiliated Hospital of Hebei University, Hebei, China; [c]Department of Neurosurgery, Tianjin Children's Hospital, Tianjin, China

Correspondence: Mr. Chunquan Cai · Tianjin Children's Hospital, No.238 Longyan Road, Beichen District, Tianjin 300134, China · Cqcns6@126.com · ORCID: https://orcid.org/0000-0002-7265-9387

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Rett syndrome (RTT) is a severe progressive neurodevelopmental disease characterized by psychomotor regression. The *FOXG1* gene is one of the pathogenic genes associated with the congenital Rett variant, which is less studied. Only a few Chinese patients with *FOXG1* mutation have been reported. In this study, we describe a Chinese female patient with congenital Rett variant who presented with psychomotor retardation, developmental regression, microcephaly, seizure, stereotypic hand movement and hypotonia. Targeted high-throughput sequencing was conducted, and a heterozygous *FOXG1* mutation [NM_005249.4: c.506dupG (P.G169Gfs* 286)] was identified. It was a frameshift mutation resulting in alteration of the reading frames downstream of the mutation.

SIMILAR CASES PUBLISHED: 10.

CONFLICT OF INTEREST: None.

Rett syndrome (RTT) is a serious neurodevelopmental disorder predominantly in females with an incidence about 1 in 10000 live births.[1] The *MECP2* gene is the major pathogenic gene of RTT, which accounts for 95-97% of typical RTT cases and 50-70% of atypical RTT cases.[2] Mutations in the *CDKL5* gene are correlated with the early-onset seizure variant of RTT. Additionally, the *FOXG1* gene is associated with the congenital Rett variant, which is less studied. In 2008, Ariani et al[3] first recognized that the *FOXG1* gene was correlated with the congenital Rett variant. The incidence is reported to account for 1.5-15% depending on different inclusion criteria.[2] There are more than 50 mutations reported in the literature.[4] The mutation types include missense mutation, deletion and duplication mutation as well as copy number variation involving the *FOXG1 gene*.Mutations of the *FOXG1* gene associated with RTT are rarely found in Asians.[2] The mutation rate in China is also lower, as (0.7% in Chinese patients).[5] To our knowledge, only two reports with ten patients appear in the literature.[5,6] In this study, we present a Chinese patient with a congenital Rett variant caused by a mutation of *FOXG1*. Informed consent was obtained from all participants.

CASE

An 11-month-old female patient was admitted to our hospital due to psychomotor retardation after birth. She was a full-term spontaneous delivery after an uneventful pregnancy. Birthweight was 2900 g. The patient was the first child of healthy no-consanguineous parents. There was no family history of psychomotor retardation or relevant genetic diseases. She was unable to roll over, crawl and sit. Her head control was unsteady. She dis-

played repetitive thrusting of the tongue, stereotypical movement of the hands and sucking fingers. She did not respond to others. She ate little, and only slowly gained weight. Sleep disturbance was also observed with shortened sleep duration and she was easily woken. There was no history of seizure. On physical examination, her head circumference was 40.5 cm with closed anterior fontanel. Facial signs consisted of synophridia, slightly round nose, high palatomaxillary arch and micromandible. Additionally, she also had hypomyotonia of the upper limb, dystonia of the lower limb and hyperreflexia of the knee. Ocular investigation showed horizontal nystagmus, and the eye could not gaze. Gesell development scale evaluation showed the developmental quotient was seriously delayed with a score of 27 in adaptability, 19 in gross motor, 24 in fine motor, 22 in language, 10 in person-society. International scoring system score was 23.

Routine chromosome analysis showed 46, XX karyotype. On nerve electrophysiological examination, somatosensory evoked potential revealed abnormality of cortical segment in extremity. Visual evoked potential displayed an almost normal right latent period with decreased amplitude. Electroencephalogram (EEG) revealed middle amplitude sharp waves in the bilateral occipital region (**Figure 1**). Cerebral magnetic resonance imaging (MRI) displayed dysplasia of the corpus callosum, and the frontal and parietal lobes (**Figure 2**).

During a follow-up period of 18 months, she suffered tonic clonic seizures at the age of 16 months. The EEG result was the same as before. At the age of 29 months, she could only take a small amount of liquid diet with severe salivation. The development was delayed with the height of 90 cm (-2SD) and weight of 1250 g (-1SD). She was able to crawl a short distance, but she did not sit alone. The bilateral ankle joint became contracted with limitation of dorsiflexion. Eye contact, attention and purposeful hand use were improved but at the age of 40 months, she presented with regression in the cognitive ability, language, motor and sociality. She could recognize a family member before, but at 40 months she could not distinguish a family member from a stranger. She could say mother and father before, but could not speak any words. With respect to sociality, she could express emotion and play simple games with others as before, but could not respond to external stimuli. In motor skills, she even lost the ability to grasp things to her mouth.

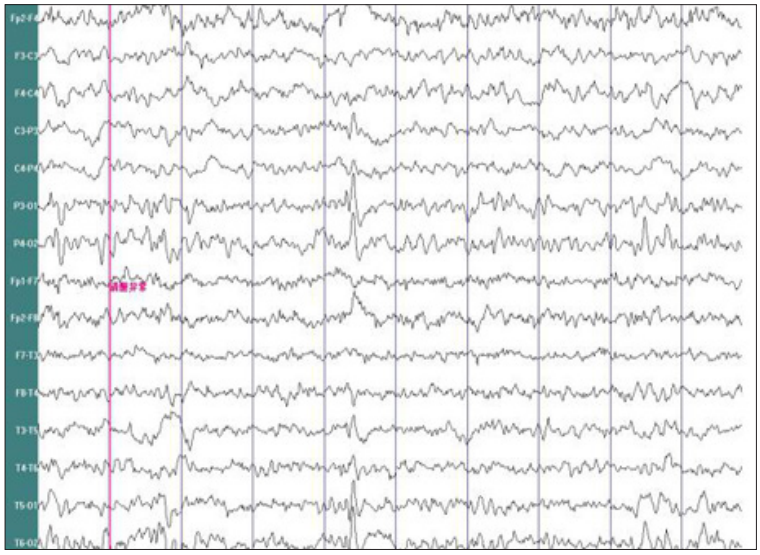

Figure 1. EEG showing middle amplitude sharp waves in the bilateral occipital region. The 5~7 Hz theta rhythm was dominant, and bilateral cerebral hemispheres were roughly symmetrical.

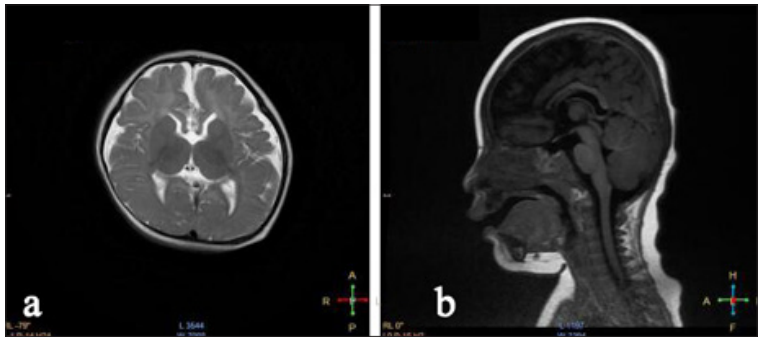

Figure 2. Cerebral MRI a) Sagittal MRI of the brain revealed wide extracerebral space and enlarged frontal gyrus; b) Cerebral coronal MRI displayed hypoplasia of the corpus callosum.

Gene mutation analysis

Genomic DNA extraction

This study was approved by the medical ethics committee. Informed consent was obtained from the guardians of the patient. Blood samples were collected from the peripheral venous blood of the patient and her parents. Subsequently, genomic DNA was extracted from blood samples using DNA Extraction Kit (Tiangen Biotech Co., Ltd., Beijing, China) according to the manufacturer's instructions. The quality and quantity of DNA were quantified by Thermo Fisher Multiskan FC (Thermo Labsystems, Multiskan FC, USA). The purity and concentration were measured by calculating the absorbance at 260 nm and 280 nm. Pure DNA has an A260/A280 ratio of 1.7-1.9.

Targeted high-throughput sequencing

The high-throughput sequencing was conducted by the

Illumina HiSeq 2500 platform (Illumina, United States). Briefly, the library was first constructed after sheared, end-repaired, adaptors ligated, size selected, PCR amplified and normalized with special kits or devices. The library was prepared using the NimbleGen SeqCap EZ Choice Kit (Roche, Switzerland). Referred to the relevant literature and the OMIM database (*https://www.omim.org*), approximately 4000 genes related to RTT and psychomotor retardation were involved, such as *CDKL5, FOXG1, CNTNAP2, FOLR1, FOXG1* and so on.

Candidate mutation confirmation by Sanger sequencing

The candidate variant was confirmed by Sanger sequencing among the patient and her parents. The specific primers were designed using Primer3 (*http://primer3.ut.ee/*). The primers were as follows: F: TACATGACTTGCCAGCGCCCGAGCC; R: CCCACATTGC ACCTCGCTGA CACTCC. The reaction condition was as below: pre-denaturation at 95′ for 5 minutes and 30 cycles of denaturation at 95′ for 30 s, annealing at 65′ for 30s and extension at 72′ for 10s. The amplification products were sequenced by ABI 3730 DNA Sequencer (Applied Biosystems, CA, USA). The Sanger sequencing data were analyzed by DNASTAR software.

Chromosomal microarray analysis

The DNA sample was detected by Affymetrix CytoScan HD Array (Affymetrix, USA). Data analysis was performed using the software of Affymetrix® Chromosome Analysis Suite 2.0.

RESULTS

A heterozygous mutation of *FOXG1* gene [NM_005249.4: c.506dupG (P.G169Gfs*286)] was detected in the patient, which has been reported previously.[4] It was a de novo mutation, which was not inherited from her parents (**Figure 3**). It resulted in the frameshift at 169 position of the protein, and caused an alteration of the reading frames downstream of the mutation. The detection of other genes was negative. The chromosomal microarray analysis showed no copy number variants with clinical significance.

A literature search was performed on the Pubmed (*https://www.ncbi.nlm.nih. gov/pubmed*) from the time when the library was built to February 2018. The search terms were RTT, Rett syndrome and *FOXG1* mutation. Studies were considered eligible if complete clinical data were contained including age of onset, clinical features and imaging data. Twenty relevant reports were retrieved from the databases, but only 10 were selected due to incomplete or obscure clinical data (**Table 1**). Among these, there are 18 patients with congenital Rett variant caused by *FOXG1* mutation. There are 18 variants of *FOXG1* including 8 frameshift, 5 nonsense and 5 missense mutations. Except for two cases,[5,7] no family history was reported.

DISCUSSION

RTT is a serious neurodevelopmental disorder involving defects in motor, cognitive and social ability.The *FOXG1* gene is one of the pathogenic genes of congenital Rett variant. In 2008, Ariani et al[3] first recognized that the *FOXG1* gene was correlated with the congenital Rett variant. The mutation rate of *FOXG1* is lower. The report-

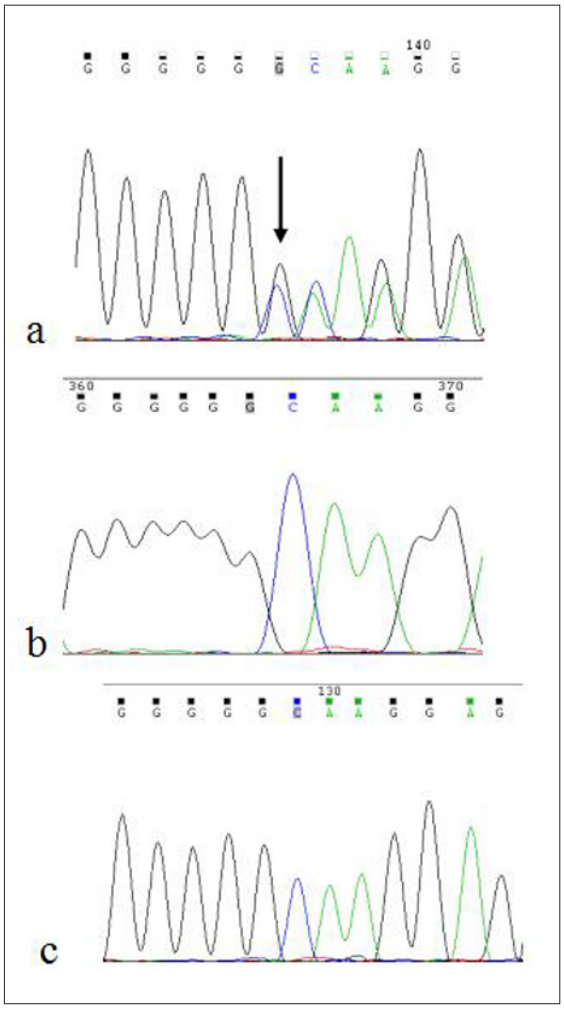

Figure 3. Sequencing diagram of the region verified by Sanger sequencing. a. A *FOXG1* mutation [NM_005249.4: c.506dupG (P.G169Gfs* 286)] was detected in the patient. b. Her mother did not show an unusual genotype at the locus; c. Her father had a normal genetic sequence at the locus.

Table 1. The clinical features of patients with congenital Rett variant caused by FOXG1 mutation.

Reference	Zhang et al[5]	Harada et al[8]	Byun et al[2]	Das et al[9]	Ellaway et al[10]	Takahashi et al[11]
Cases	3	1	1	1	1	2
Age of onset	0-3 months	C	C	C	-	C
Microcephaly	Y	Y	Y	Y	Y	Y
Height or weight abnormality	-	-	Y	Y	-	1
Hypotonia	Y	Y	-	Y	Y	Y
Scoliosis	-	-	-	-	N	1
Walking	N	N	Y	N	N	N
Limited hand function	Y	Y	Y	Y	Y	Y
Stereotypes of upper limb	Y	Y	Y	Y	Y	Y
Motor retardation	Y	Y	Y	Y	Y	Y
Dysgnosia	-	Y	-	-	Y	-
Speech	Y	Y	Y	Y	Y	Y
Attention disorder	Y	Y	Y	Y	Y	Y
Epilepsy	Y	Y	Y	Y	Y	Y
EEG abnormality	Y	-	Y	Y	-	Y
Hypoplastic corpus callosum, frontal and temporal	Y	Y	Y	Y	N	Y
Delayed myelination	Y	Y	Y	-	Y	-
Sleep disturbance	2	Y	Y	-	Y	Y
Mood abnormality	-	Y	Y	-	-	Y
Dysphagia, feeding difficulties	2	-	-	Y	Y	Y
Mutation of *FOXG1*	c.858duC; c.454dupG; c.972 dupT;	c.569T>A	c.209A>C	c.788_792delACGTG	c.256dupC	c.256dupC;c.689G>A
Geographical distribution	China	Japan	Koren	Indian	Australi-a	Japan

Table 1 (cont.). The clinical features of patients with congenital Rett variant caused by FOXG1 mutation.

Reference	Mencarelli et al[7]	Philippe et al[12]	Bahi-Buisso et al[13]	Le Guen T et a [14]	This case
Cases	4	2	2	1	1
Age of onset	C	4-6 months	2-3 months	C	C
Microcephaly	Y	Y	Y	Y	Y
Height or weight abnormality	2	1	Y	Y	Y
Hypotonia	Y	1	Y	Y	Y
Scoliosis	1	1	Y	-	N
Walking	N	1	N	N	N
Limited hand function	2	Y	Y	Y	Y
Stereotypes of upper limb	3	Y	Y	Y	Y
Motor retardation	Y	Y	Y	Y	Y
Dysgnosia	-	-	-	-	Y
Speech	Y	Y	Y	Y	Y
Attention disorder	Y	Y	Y	Y	Y
Epilepsy	2	1	1	-	Y
EEG abnormality	-	1	1	Y	Y
Hypoplastic corpus callosum, frontal and temporal	2	1	1	Y	Y
Delayed myelination	-	-	Y	Y	N
Sleep disturbance	2	1	Y	Y	Y
Mood abnormality	-	1	-	Y	N
Dysphagia, feeding difficulties	1	1	Y	Y	Y
Mutation of FOXG1	c.681C>G; c.643T>C;c.551_552insC; c.624C>G	c.924G>A; c.1200C>G	c.1248C>G; c.460_461dupG	c.256_257dupC	c.506dupG
Geographical distribution	Italy	France	France	France	China

C: congenital, hyphen no information.

ed incidence is as low as 1.5% or as high as 15% depending on the inclusion criteria.[2] In China, the main pathogenic gene of RTT is the *MECP2* gene. The mutation of *FOXG1* is rarely reported.[5,6] The mutation rate is 0.7% in Chinese patients.[5] In 2017, Zhang Q et al[5] described the first report of *FOXG1* mutations in Chinese patients, including c.858dupC (p.K287Qfs*168), c.454dupG (p.E154Gfs*301), c.972dupT (p.L325Ffs*130), c.694A>T (p.N232Y). Subsequently, Zhang Q et al[6] reported 471 patients associated with Rett and Rett-like syndrome. Only four patients carried the variants of *FOXG1* including c.858dupC (Lys287GInfs*168), c.893C>A (Thr298Asn), c.775C>T (Pro259Ser), c.694A>T (Asn232Tyr). In this study, another mutation of NM_005249.4: c.506dupG (p.G169Gfs*286) was identified in a Chinese patient, which was a novel variant in Chinese patients.

FOXG1 gene is located in 14q12, which encodes the *FOXG1* protein. The protein is a multidomain protein comprising three domains, including the forkhead DNA-binding domain (amino acids 181-275), the Gro-binding domain (amino acids 307-317), KDM5B binding domain (amino acids 383-406). In this study, the mutation [NM_005249.4: c.506dupG (P.G169Gfs*286)] is located at the 169 position of the protein. It may cause an abnormal truncated protein lacking the forkhead DNA-binding domain, which makes it non-functional.

In this study, the patient presented with psychomotor retardation, microcephaly, seizure, stereotypic hand movement, hypotonia and developmental regression, which was consistent with the diagnostic criteria of congenital Rett variant.[1] Compared with other types of RTT, the congenital Rett variant caused by the *FOXG1* mutation is characterized by congenital or early onset, acquired microcephaly, serious language defect, attention and social deficit, seizure, feeding difficulty, developmental delay, psychomotor regression and stereotypic hand movement.[15] Among the 19 cases (18 from the literature and one of our own), onset is after birth in most patients. The regression period is not identified in the majority probably due to the severe developmental delay in the early onset.[8] All patients present with shared characteristics of congenital or acquired microcephaly, movement retardation, language and attention disorder.[2,5,7-14] Several clinical features are also manifested in some patients: hypotonia, sleep disturbance, stereotypical upper limb, hand function disorder and mood abnormality. Microcephaly may be related to the role of *FOXG1* in the development of telencephalon.[14] The seizure types are unspecific and include generalized tonic-clonic seizures, drop attacks, myoclonic seizures, atonic seizures and generalized tonic seizures. The symptoms of seizure are relatively slight compared with CDKL-5 related seizure and are easily controlled with less than three antiepileptic drugs.[2]

Eleven patients including our case presented with dysphagia or feeding difficulty.[5,7,9-14] The muscles involved in swallowing mostly are voluntary motor muscles. They are prone to be complicated with dysmyotonia, which may be the cause of dysphagia or feeding difficulty. Malnutrition is common. Ten patients in this study had height and weight abnormalities. Several older cases were even treated by long-term nasal feeding or by a fistula in the digestive tract to improve nutrition.[11,13] It is suggested that dysphagia is the predominant cause of physical development disorder. Thus, therapy for dysphagia is the main part of clinical care. In addition, only a few reports described symptoms of scoliosis, strephenopodia and joint contracture in older patients, which may be correlated with the shorter long-term follow up.[7,11,13] Thus, we think it is necessary to prevent bone malformation in the early stage of the disease. On imaging, cerebral MRI usually reveals delayed myelination or hypomyelination, atrophy of frontal and temporal lobes with gyral simplification as well as a hypoplastic corpus callosum.[2,5,7-8,10-13] Hypoplastic hippocampus has also been reported.[8]

The management of congenital Rett variant caused by *FOXG1* is still challenging. There is no effective therapy method at present. Early comprehensive rehabilitation treatment is advised. The nervous system symptoms such as epilepsy and dystonia, can be treated with medicine. As for the treatment of patients with dysphagia or feeding difficulty, the proper feeding method should aim to improve the physical state of nutrition to prevent early skeletal deformity during the process of clinical treatment.

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