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Report of one case with de novo mutation in TLK2 and literature review

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Abstract
TLK2 variants were identified as the cause for several neurodevelopmental disorders by impacting brain development. The incidence of mutation in TLK2 is low, which has common clinical features with other rare diseases. Herein, we reported a 5-year-old boy with TLK2 heterozygous mutation who presented distinctive facial features, gastrointestinal diseases, short stature, language delay, autism spectrum disorder, heart diseases, abnormal genitourinary system and skeletal abnormality. Moreover, we reviewed previous reported patients and our case in order to investigate more information on genotype-phenotype correlation and identify significant clinical characteristics for better diagnosis.

Keywords Autism spectrum disorder, Language delay, TLK2 mutation

Introduction

Tousled-like kinases (TLKs) are expressed in most tissues of animals and plants [1]. TLK1 and TLK2 genes mainly are encoded in human cells, play an important part in chromosome segregation and cell cycle progression, which are also associated with human cancers [1]. However, TLK2 has recently been suggested to be involved in nervous system development. TLK2 gene variants cause common clinical features including intellectual disability, language delay, behavioral problems, autism spectrum disorder (ASD), distinctive facial features, gastrointestinal disorders, short stature with the morbidity of 1/566 (17/9, 625) according to the DDD study [1–4]. A number of 40 patients cohort from 26 centers suggested de novo and heterozygous *TLK2* variants resulted in distinct neurodevelopmental disorders (NDDs) and other sporadic phenotypes of eye abnormalities, musculoskeletal abnormalities, hypertrichosis, microcephaly and emotional problems et al. [2]. Besides it was identified haploinsufficiency of *TLK2* may lead to neurodevelopmental problems [2]. The disorder caused by heterozygous mutations in TLK2 gene is called intellectual developmental disorder, autosomal dominant 57 (MRD57, MIM#618050). MRD57 can cause damage to children's nervous, digestive and skeletal system, affecting children's normal growth and development, language, cognitive, sensory and motor function [1–4]. Several rare genetic disorders such as Angelman syndrome (AS) and Prader-Willi syndrome (PWS) also show speech impairment, intellectual disability and behavioral problems, leading to difficulty in diagnosis [5, 6]. Clinical consensus was suggested for AS and PWS, but lack comprehensive information in MRD57.

Herein, we reported a 5-year-old boy with de novo mutation in *TLK2* to compared our case with previous patients and made a literature. The poor specificity and low incidence of *TLK2* variants may cause missed diagnosis, misdiagnosis and delayed treatment. The aim of

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this study is to conclude noteworthy clinical characteristics to raise the awareness of pediatricians.

Clinical presentation

A boy was admitted to our unit because of language delay and social problems at the age of 5 years and 10 months. He was the first child of consanguineous parents, born with the neonatal jaundice and normal family history. By the age of 2 years, the child only spoke several single words and was not able to develop sentences. In addition to abnormal language development, he had a tendency to acquire typical features of ASD. He was silent in response to instructions and calls. The eye contact and common attention were poor. He was presented abnormal behaviors including repeatedly opening the door, turning around, and running around. He underwent cardiac surgery due to patent ductus arteriosus (PDA). He also had gastrointestinal diseases including gastro-esophageal reflux and sensitivity of milk. Other concern about motor milestone presented mild delay with walking alone at 24 months.

On physical examination at the age of 5 years and 10 months, his height was 105.5 cm (about- 2SD) with a weight of 15 kg (about- 2SD). Dysmorphic facial features including short philtrum and upturned upper lip were presented. No microcephaly, plagiocephaly, vesico-ureteric reflux, hypotonia, scoliosis, hearing loss, hypertrichosis and strabismus were discovered. Left undescended testis, micropenis, oblique inguinal hernia on the right and overlapping with longer fourth toe and middle toe of left foot were noted (Fig. 1a). The child presented growth delay (Fig. 1b and c) with a height of 111 cm (about- 2SD) and a weight of 20 kg (about- 1.5SD).

Determination of trace elements and thyroid hormones (containing TSH, T4, FT4, T3 and FT3) showed normal level. TORCH antibody was negative. Brain MRI and clinical electroencephalography were normal. X-ray of left carpal bone discovered 5/10 small ossification centers (Fig. 1d).

Cytogenetics detected normal male karyotype (46, XY). Trio whole-exome sequencing (WES) was performed and presented heterozygous c.1015 C>T mutation in *TLK2* (NM_006852.6) at chromosome 17 (Fig. 1e) and a 2.2 Mb repetitive variation (Chr 3:24536058–26751971) (Fig. 1f) inherited from his mother including *THRB*, *RARB*, *TOP2B*, *NGLY1*, *OXSM* and *LRRC3B*. The c.1015 C>T mutation was missense mutation that affected the function of exon12 and disturbed the production of amino acid species, causing p.R339W. The variant (c.1015 C>T) was not detected in his parents, which was identified to be a de novo mutation. According to ACMG, this mutation was likely pathogenic.

Discussion

NDDs were comprised of broad disorders, involved in mental, behavior, communication and motor [7]. NDDs were associated with genes variants by abnormal brain development such as *SLC13A5* and *SLC6A1* [8]. As part of NDDs, intellectual disability and ASD were linked with *TLK2*, identified by a statistical meta-analysis [9]. TLK2 as a Tousled-like kinases family member was involved in DNA replication, repair and transcription, existed in human numerous organisms, expresses high level inhibiting DNA damage [1]. *TLK2* mutation contained different variants, causing NDDs and other clinical phenotypes.

Language delay, motor delay, distinctive facial features, intellectual disability, gastrointestinal problems, short stature, behavioral disorders and skeletal abnormalities were common clinical manifestations in MRD57 (Table 1). Congenital heart disease, undescended testis, micropenis, inguinal hernia and sensitive hearing of our case were not described in previous cases, medullary nephrocalcinosis and hydronephrosis were discovered in one case (Table 1). Language delay was domain feature in our patient, the most common clinical manifestations in MRD57 [2]. Blepharophimosis, telecanthus, prominent nasal bridge, broad nasal tip and thin vermilion of the upper lip were main facial dysmorphisms (Table 1). Short philtrum and upturned upper lip were presented in our case. Previous cases presented musculoskeletal abnormalities including joint hypermobility, pes planus, toe walking, scoliosis and contractures of the hands (Table 1). However skeletal abnormality in our patient was overlapping toe which enriches the phenotypes of MRD57.

TLK2 mutation contained various variants, the different type affected underlying disease mechanism. The missense mutation (c.1015 C>T) destroyed exon12 function, causing p.R339W affected gene expression. It was not only *TLK2* mutation was found in this case but also a 2.2 Mb repetitive variation including *THRB*, *RARB*, *TOP2B*, *NGLY1*, *OXSM* and *LRRC3B*. However, no pathogenic significance was found in this repetitive variation [10–17]. More studies are needed on this gene fragment.

Different genes contributed to the NDDs with broad subtypes. Though rare genetic disorder has own specificity, clinical diagnosis is insufficient due to the variety of clinical manifestations. WES was a useful diagnostic method to identify *TLK2* variants [2]. Studies observed that WES demonstrate cost-effectiveness and higher diagnostic rate than conventional testing tools [18]. Accurate and efficient diagnosis is important to improve outcome of patients and quality of family life.

Long-term multidisciplinary management is necessary for treatment of patients with MRD57 including neurologist, rehabilitation physician and primary care physicians. Neurological and mental disorders were main

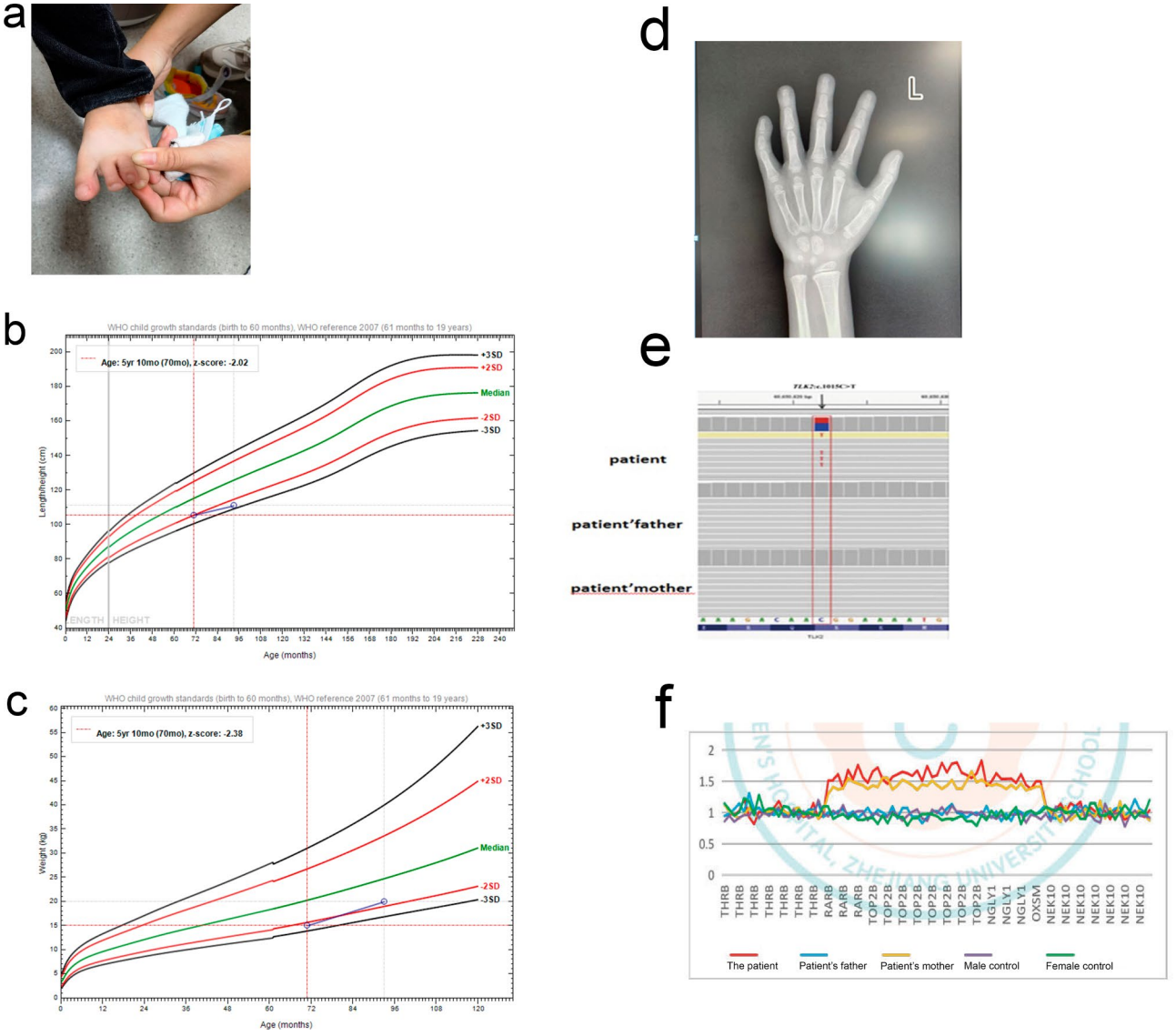

Fig. 1 Clinical data of our case. **a** Overlapping with longer fourth toe and middle toe of left foot. **b** The height chart of our patient (made by WHO AnthroPlus). **c** The weight chart of our patient (made by WHO AnthroPlus). **d** The bone age of our patient including 5/10 of the left carpal ossification centers appear, small shape, metacarpophalangeal epiphysis ossification, epiphysis plate patent. **e** The result of whole-exome sequencing (WES). **f** Capture sequencing signal strength of chr3:24536058–26,751,971.

features of *TLK2* mutations. Early intervention is critical for improvement of language delay including providing positive language environment and professional language therapy [19]. In addition to language delay, ASD was also prominent in our patient. Patients with ASD need early interventions including parent-mediated treatments and naturalistic developmental behavioral [20, 21]. Other symptoms also need corresponding treatment.

It is worth noting that due to small number of cases and limited data, some clinical manifestations are accidental. More cases and further studies are needed for clinical characteristics to discover more information on genotype-phenotype of MRD57.

In summary, MRD57 is a rare disease with different clinical features. Prominent manifestations of MRD57 are language delay, motor delay, distinctive facial features, intellectual disability, gastrointestinal diseases, short stature, behavioral disorders, and skeletal abnormalities. Other phenotypes including heart diseases, abnormal urinary and genital system should also be noted.

Table 1 The clinical features of our patient compared with the previous reported MRD57 patients

Feature	Our case	Case1 [4]	Case2 [3]	Case3 [3]	Cases [2] (%)
Language delay	+	+	+	+	92
Motor delay	+	+	-	+	92
Blepharophimosis	-	-	+	+	82
Telecanthus	-	+	+	+	74
Intellectual disability(ID)	Can not cooperate	+	+	Global delay. Likely ID	72
Prominent nasal bridge	-	+	+	+	68
Broad nasal tip	-	-	+	+	66
Thin vermilion of the upper lip	-	+	+	-	62
Constipation	-	+	-	-	55
Upslanting palpebral fissures	-	+	+	+	55
Neonatal feeding difficulties	-	+	-	+	42
Pointed and tall chin	-	-	+	+	42
Epicanthal folds	-	-	+	-	42
Hypotonia	-	+	-	-	37
Short stature	+	U (intrauterine growth retardation)	-	+	37
Narrow mouth	-	-	+	+	32
Tantrums	-	+	+	-	31
Autism spectrum disorder (ASD)	+	-	Features (not diagnosed)	Features (pending assessment)	31
High palate	-	-	-	-	30
Microtia	-	-	-	-	29
Refraction abnormality	-	-	-	-	29
Posteriorly rotated ears	-	-	+	+	29
Long face	-	-	-	-	27
Strabismus	-	-	-	+	26
Recurrent otitis media	-	-	-	-	24
Microcephaly	-	+	-	+	24
Ptosis	-	-	-	-	21
Joint hypermobility	-	-	-	-	21
Pes planus	-	-	-	-	21
Toe walking	-	-	-	+	18
Severe social-emotional problems	+	N.R.	+	-	17
Asymmetric face	-	-	-	-	16
Hypertrichosis	-	-	-	-	16
Attention-deficit disorder with or without hyperactivity	-	-	-	-	14
Epilepsy	-	+	-	-	13
Brain abnormalities	-	+	-	-	13
Low body weight	+	U intrauterine growth retardation	-	+	13
Scoliosis	-	-	-	-	8
Contractures of the hands	-	-	-	-	8
Overweight	-	U	-	-	8
Hoarse voice	-	-	-	-	8
Diarrhea	-	-	-	-	8
Big mouth	-	+	N.R.	N.R.	N.R.
Hemangioma	-	+	N.R.	N.R.	N.R.
Conductive hearing loss	-	+	-	-	U
Medullary nephrocalcinosis	-	+	N.R.	N.R.	N.R.
Hydronephrosis	-	+	N.R.	N.R.	N.R.

Table 1 (continued)

Feature	Our case	Case1 [4]	Case2 [3]	Case3 [3]	Cases [2] (%)
Heart diseases	+	N.R.	N.R.	N.R.	N.R.
Inguinal hernia	+	N.R.	N.R.	N.R.	N.R.
Undescended testis	+	female	N.R.	female	N.R.
Micropenis	+	female	N.R.	female	N.R.
Sensitive hearing	+	-	N.R.	N.R.	N.R.
Overlapping toe	+	N.R.	N.R.	N.R.	N.R.

N.R, not reported; U, unknown; +, feature present; -, feature absent

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Author contributions
Chao-Chun Zou supervised the study. Ruo-Yan Liu contributed to the data collection. Han-Yue Li wrote the original draft. Han-Yue Li, Chun-Ming Jiang, Ruo-Yan Liu contributed to the data organization and analysis. All authors have participated in revising the manuscript critically and gave their final approval of the version to be submitted.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by Ethical Committee of Children's Hospital of Zhejiang University School of Medicine. and National Clinical Research Center for Child Health (no. 2024-IRB-0085-P-01).

Consent for publication
The written consent form for publication was obtained from the parents of the patient.

Competing interests
The authors declare no competing interests.

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