A child with Myhre syndrome presenting with moyamoya disease: a case report and literature review

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Case report

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Abstract

Background: Myhre syndrome (MS) is a very rare connective tissue disorder characterized by facial dysmorphism, thickened skin, muscular pseudohypertrophy and joint limitation. Developmental delay is common. But there are no reports of MS combined with moyamoya disease (MMD). Here, we present the first Chinese case of MS complicated with MMD. Case presentation: A 7-old-year girl presented with developmental disorder, short stature, brachydactyly, short stature, and intellectual deficiency with behavioral problems. We sequenced SMAD4 using exome sequencing and identified a denovo mutation (p.Ile500Thr) in the patient. In addition, The patient also had recurrent hemiplegia and seizures was diagnosed with definitive MMD by digital subtraction angiography (DSA) according to the diagnostic criteria. Conclusions: MMD has never been described in the individual with the clinical presentation of MS. we present an unusual association of MS with a typical moyamoya syndrome in a young girl who developed recurrent hemiplegia and seizure in an effort to explore whether MS may contribute to the MMD.

Background

Myhre syndrome (MS, OMIM 139210) is a rare autosomal dominant inherited disease, initiated by a missense mutation in the SMAD4 gene on chromosome 18q21.2[1,2] and is characterized by low birth weight ,intellectual disability, short stature, brachydactyly, facial dysmorphism (including short palpebral fissures, prognathism and short philtrum), thick skin, generalized muscle hypertrophy, restricted flexibility of joints and deafness. X-ray findings of MS include mandibular protrusion thick calvarium, hypoplastic iliac wings , mild rib broadening, shortening of the tubular bones, and flattened vertebral bodies with large[3]. Le Goff and colleagues performed whole exome sequencing to a group of subjects clinically suspected as MS, and identified SMAD4 as a candidate gene that contributes to this syndrome on the basis of its the pivotal role of in bone morphogenetic pathway (BMP) and transforming growth factor (TGF-β) signaling. In this study, three distinct heterozygous missense SMAD4 mutations were identified affecting the codon for Ile500 in 11 individuals with Myhre syndrome [4]. To our knowledge, 58 affected individuals with a molecularly confirmed diagnosis of Myhre syndrome have been reported[1,4-16]. The four pathogenic variants reported to date are missense variants p.Ile500Thr, p.Ile500Val, p.Ile500Met and p.A496Cys [1,2,4,11]. In current report, we revealed a recurrent mutation of SMAD4 gene (p.Ile500Thr). Moreover, the clinical symptomatic spectrum of the patient is featured by sudden onset of right hemiplegia and seizure which are characteristics indicating existence of MMD, which led to prescription of DSA (Gold standard for MMD diagnosis) and an ultimate MMD diagnosis. MS complicated with MMD have been never reported before. Because of the extremely rare nature of this condition and its relatively recent discovery, there is still much to be understood the relationship between MS and MMD.

Case Presentation

A 7-year-old girl, was born to non-consanguineous parents with no relevant family history, is the only child of the Chinese parent . The father was aged 38 years and mother 35 years at her birth. The parent is

healthy and clinically normal. The patient was born at term after an uneventful pregnancy with a toe deformity. At birth, she was proportionally small for gestational age with a birth weight of 2100g (<3rd centile) and and a birth length of 45cm (<3rd centile). At the age of 8 months, during a routine developmental assessment, she was found to have a atrial septal defect and ligated, post-operatively she remained well and continued to make developmental. However, early developmental milestones, especially speech, were delayed. Psychomotor delay was apparent at an early age, but this did not come to the attentions of their parents until she was 7 years old. Currently the patient was admitted to our hospital because of suffered sudden right hemiplegia and seizure.

Physical examination at 7 years showed: weight 20Kg (<3rd centile), height 115cm□50 centile). The patient had dysmorphic facial features, such as brachycephaly, frontal bossing, hypertelorism, a broad and prominent nasal bridge, deep-set eyes with short palpebral fissures, low set ears, a short philtrum,a thin upper lip, brachydactyly of the hands and feet, and normal skin and joint movements **(Fig 1)**. The muscle strength examination showed decreased muscle strength of the both bilateral lower limbs and upper limbs. Grade II changes in muscles strength of calves and grade III changes in muscles strength of thighs and upper limbs. Blood pressures, recorded in series were normal.

The laboratory examination including routine blood and urine tests, lipid and thyroid profiles, screening tests for metabolic defects gave negative results. Blood lactic acid(2.1mmol/L) was slightly raised. Screening for organic acid and amino acid metabolism of blood and Urine was normal.The electrocardiogram, echocardiographic studies, MRV and spine MRI were normal. Magnetic resonance imaging (MRI) of the brain demonstrated a well-defined abnormality on T1 images**(Fig 2a)**, with a low signal intensity lesion in the right parietal-frontal and left frontal, parietal and temporal lobes regions, but a high signal intensity lesion in T2 and T2-weighted images **(Fig2b, 2c).** Magnetic Resonance Angiography (MRA) findings: the marked stenosis of lef supraclinoid internal carotid vasculature with a proliferation of collateral vessels (Puffs of smoke appearance) suggestive MMD were noted **(Fig 2d)**. The neurons are significantly damaged and lactate acid peak was increased on magnetic resonance spectroscopy(MRS) **(Fig 2g)**. Finally the patients diagnosed with moyamoya disease by DSA **(Fig 2e, 2f)**. The children have mental retardation and typical facial dysmorphism□we considered the girl may have other inherited metabolic diseases□so, with the consent of her parents, we further performed the genetic examination by using whole DNA exome sequencing. The mutation of c.1499T>C in exon 11 of *SMAD4* (OMIM 600993) was found in the patient with Sanger sequencing, leading to the substitution of an amino acid from Ile to Thr position 500, but this mutation was not found in her parents **(Fig 3)**. The proband heterozygous denovo mutation conforms to the pathogenesis of autosomal dominant inheritance (AD) disease. Since this disease is a congenital disease, there is no effective treatment and the prognosis is poor. The child did not return to the hospital for a follow-up visit.

Discussion And Conclusions

MS is a multi-system disorder with typical phenotype spectrum of short stature, facial dysmorphism, scleroderma-like skin, joint contracture, and sensorineural deafness. Other relatively rare clinical features

include skeletal anomalies (e.g. macrocephaly, brachydactyly, platyspondyly), congenital heart defect (e.g. aortic valve stenosis, aortic coarctation), ocular disease, cleft palate, pubertal delay and cryptorchidism, and autistic behavior. Radiological imaging findings reported are distinctive mandibular protrusion, thick calvarium, shortening of the tubular bones, hypoplastic iliac wings, and large pedicles and thick neural arches [17,18]. Genetic diseases that possess similar phenotypes and need to be clinically differentiated could be, but not limited to, geleophysic dysplasia, acromicric dysplasia, Weil–Marchesani syndrome and oligophrenia syndrome **[TABLE 1].** Although controversial data reported regarding the pathogenesis of these inherited diseases at molecular level, increasing evidences are immerging suggestive of pivotal role of TGF-β signaling dysregulation on disease development [19-22].

MS is induced by heterozygous mutations in SMAD4, which lies in its Mad homology 2 (MH2) domain that mediates SMAD oligomerization, allowing initiation of TGF-β/BMP signal transduction. Although the exact downstream mechanism of TGF-β and BMP are not yet fully understood, it is thought that altered ubiquitination of SMAD4 leads to increased expression of TGF-β [23]. Data from several studies were in support of the role of SMAD4 in MS. Knocking out SMAD4 in chondrocytes causes dwarfism in mice and severe growth disorders[24]. Mice with conditional knockout of SMAD4 in chondrocytes showed phenotypes of bone malformation, smaller cochlear volume, and basilar membrane have been reported to lead to severe hearing loss in mice [25]. These observations suggest that SMAD4 loss of function might be a key starting factor of MS.
MMD is a cerebrovascular disease characterized by progressive stenosis of the intracranial internal carotid arteries and their proximal branches [26]. MMD is most prevalent in East Asia and is among the major causes of cerebral stroke in adults and children. Generally, most children that suffered from MMD developed cerebral infarction or transient ischemic attack (TIA) . Previous stydies showed Treg cells and TGF-β are involved in pathophysiology of MMD by upregulating the expression of vascular endothelial growth factor (VEGF) which may promote MMD angiogenesis. Moreover Treg-produced TGF-β can also induce the production of VEGF and stimulate subsequent angiogenesis. The increased of VEGF was positively correlated with TGF-β, suggesting that a functional promotion of TGF-β to the proliferation of vascular endothelial cell that leads to vessels hyperplasia in MMD [27,28,29]. Interestingly, as mentioned previously, the SMAD4 mutations in the individual with MS can also result in increased TGF-β signaling and TGF-β may induce production of VEGF which may lead to abnormal vessels hyperplasia in MMD. We thus hypothesize that vessel abnormality found by our DSA detection could theoretically be a result of molecular abnormality shared by MS pathogenesis, or MMD and MS are just two unrelated diseases.

In conclusion, we present an rare comorbidity of MS and MMD in a young female who developed recurrent hemiplegia and seizure aside of classic MS phenotypes. There is the limitation in this study due to a single case report, MS might be associated with angiographic findings of moyamoya vessels. However, precise evidences for a common pathogenesis at molecular level of the two diseases was missing. In our future study more similar cases should be collected for further study, and animal models should be created to prove whether the two diseases have the same pathway or mechanism.

Abbreviations

MS: Myhre syndrome; BMP: bone morphogenetic pathway; TGF-β: transforming growth factor; MRI: Magnetic resonance imaging; MRS: magnetic resonance spectroscopy; DSA: digital subtraction angiography; MMD: Moyamoya disease; ECM: extracellular matrix; TIA: transient ischemic attack; VEGF: vascular endothelial growth factor; MMPs: matrix metalloproteases;

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the patient's parents and this study was approved by the ethics committee of the Second Xiangya Hospital of Central South University.

Consent for publication

Consent to publish was obtained in written form from the patient's parents. Additionally, the patient consented to the publication of all personal and medical details included in the case report as well as the accompanying images.

Availability of data and materials

The datasets used during this study are provided from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest.

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Authors' contributions

All authors were involved in the study and agree with the contents of the manuscript. ZJ and LLQ provided concepts. LLJ, ZJ and MDA conducted the nerve conduction study and analyzed the data.ZJ, XJ, XYY and LLQ acquired the data. ZJ,WAP and LLQ did the literature review. ZJ drafted the initial manuscript. All authors checked and revised the manuscript carefully. All authors read and approved the final manuscript.

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Tables

Table 1 Disorders to Consider in the Differential Diagnosis of Myhre Syndrome

Disorders	Gene(s)	Mode of inheritance	Clinical Features of the Disorder	
			Overlapping with Myhre Syndrome	Distinguishing from Myhre Syndrome
Geleophysic dysplasia	*ADAMTSL2*	AR	IUGR Short stature Short hands and feet Progressive joint limitation and contractures Progressive cardiac valvar thickening Thickened skin	Hepatomegaly Characteristic facies
	FBN1	AD		
Acromicric dysplasia (OMIM 102370)	*FBN1*	AD	IUGR Short stature Brachydactyly Joint stiffness Thickened skin	Characteristic external notch of the fifth metacarpal and internal notch of the femoral head Absence of hearing loss Less frequent cardiac anomalies Absence of calvarial thickening
Weill-Marchesani syndrome	*ADAMTS10* *LTPBP2*	AR	IUGR Short stature Brachydactyly Joint stiffness	Distinctive lens abnormalities Lack of hearing loss

AD autosomal dominant AR : autosomal recessive IUGR intrauterine growth restriction

Figures

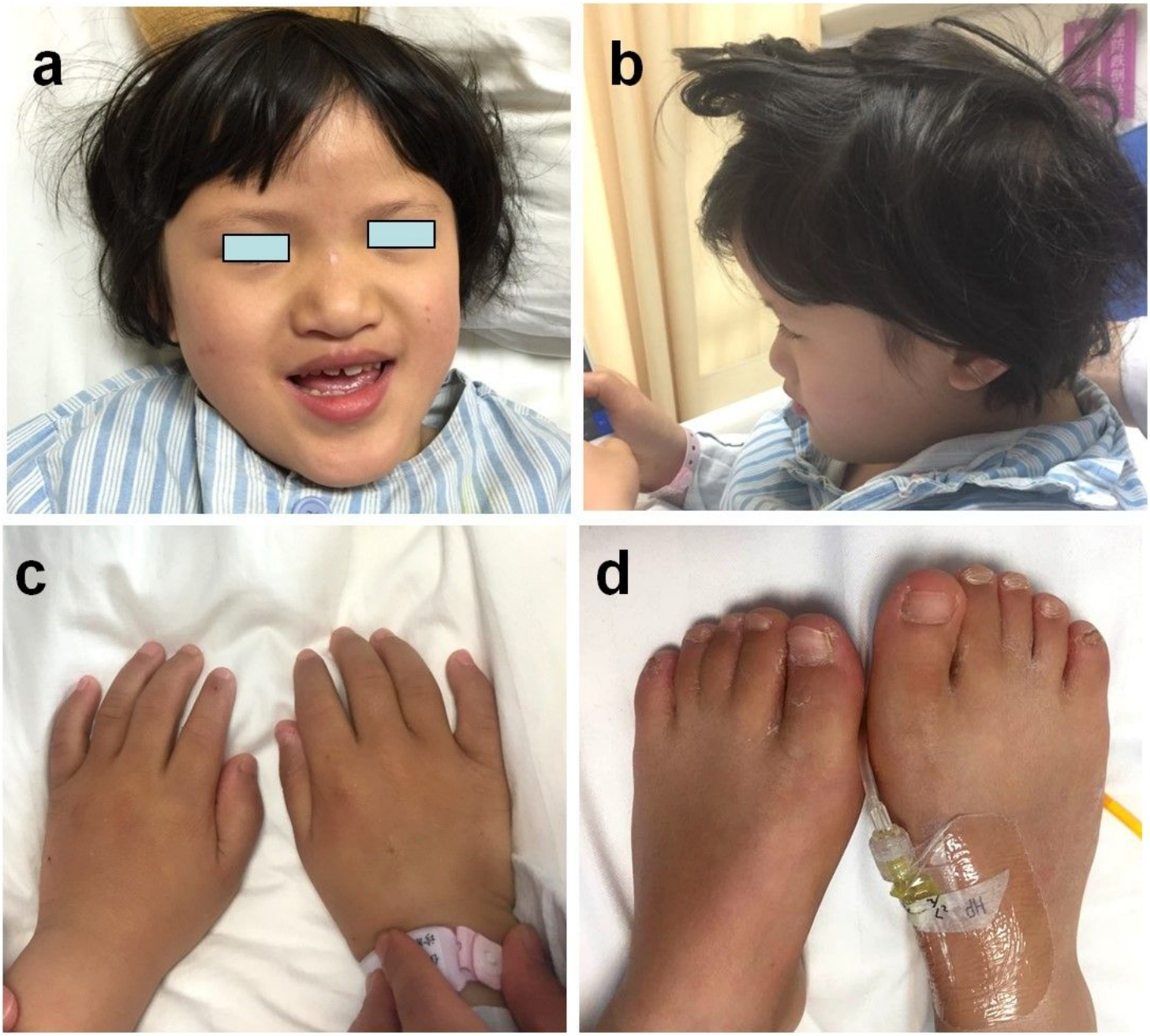

Figure 1

Typical facial features in the patient (a) Frontal view: ocular hypertelorism, broad and prominent nasal bridge, deep set eyes, short palpebral fissures and short philtrum. (b) Lateral view: Typical frontal bossing, middle part of face moved backward, short neck and low hairline. . (c)Brachydactyly at hands, (d) Brachydactyly at feet and syndactyly of the toes.

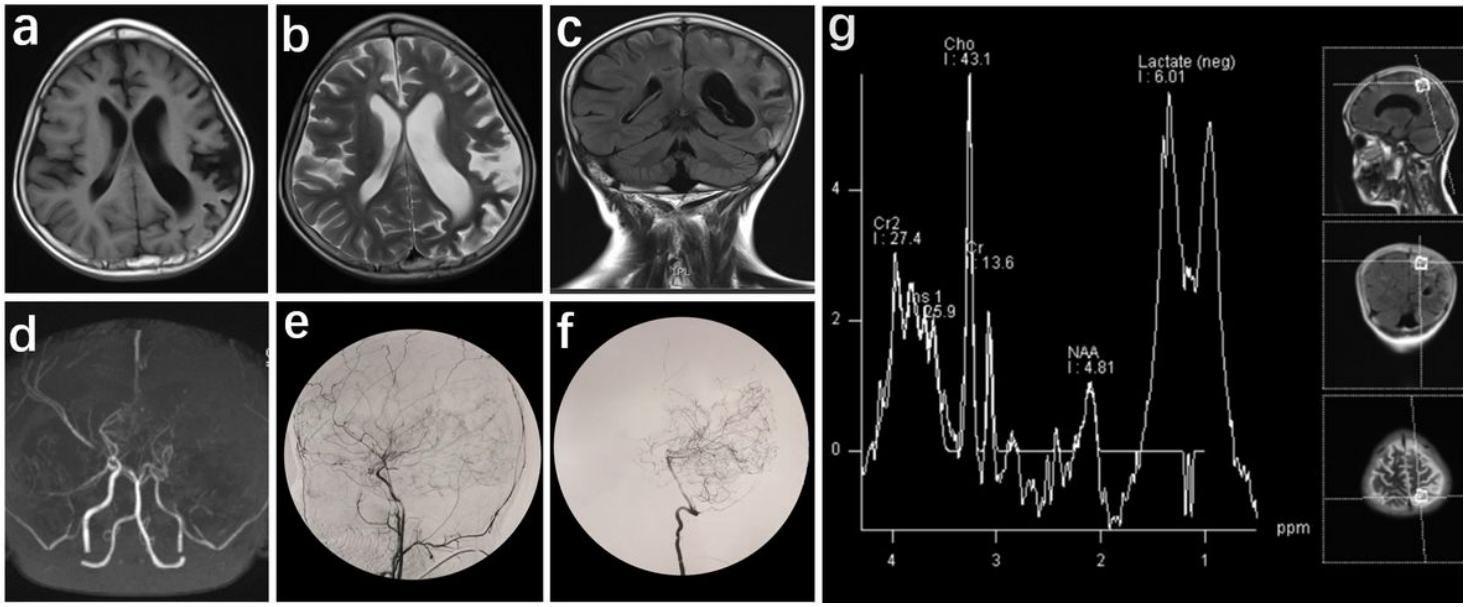

Figure 2

Imaging results of the patient Magnetic resonance imaging (MRI) of the brain demonstrated a well-defined abnormality with a low signal intensity lesion in the right parietal-frontal and left frontal, parietal and temporal lobes regions on T1 images(Fig 2a), but a high signal intensity lesion on T2 and T2-weighted images (Fig2b, 2c). Magnetic Resonance Angiography (MRA) findings showed the marked stenosis of lef supraclinoid internal carotid vasculature with a proliferation of collateral vessels (Puffs of smoke appearance) suggestive MMD were noted (Fig 2d). The neurons are significantly damaged and lactate acid peak was increased on magnetic resonance spectroscopy(MRS) (Fig 2g). Internal carotid artery angiograms and vertebral angiography showed Steno-occlusive changes in the bilateral internal carotid artery and the development of abnormal vascular networks. The left internal carotid artery was narrower than the right side. (Fig 2e, 2f).

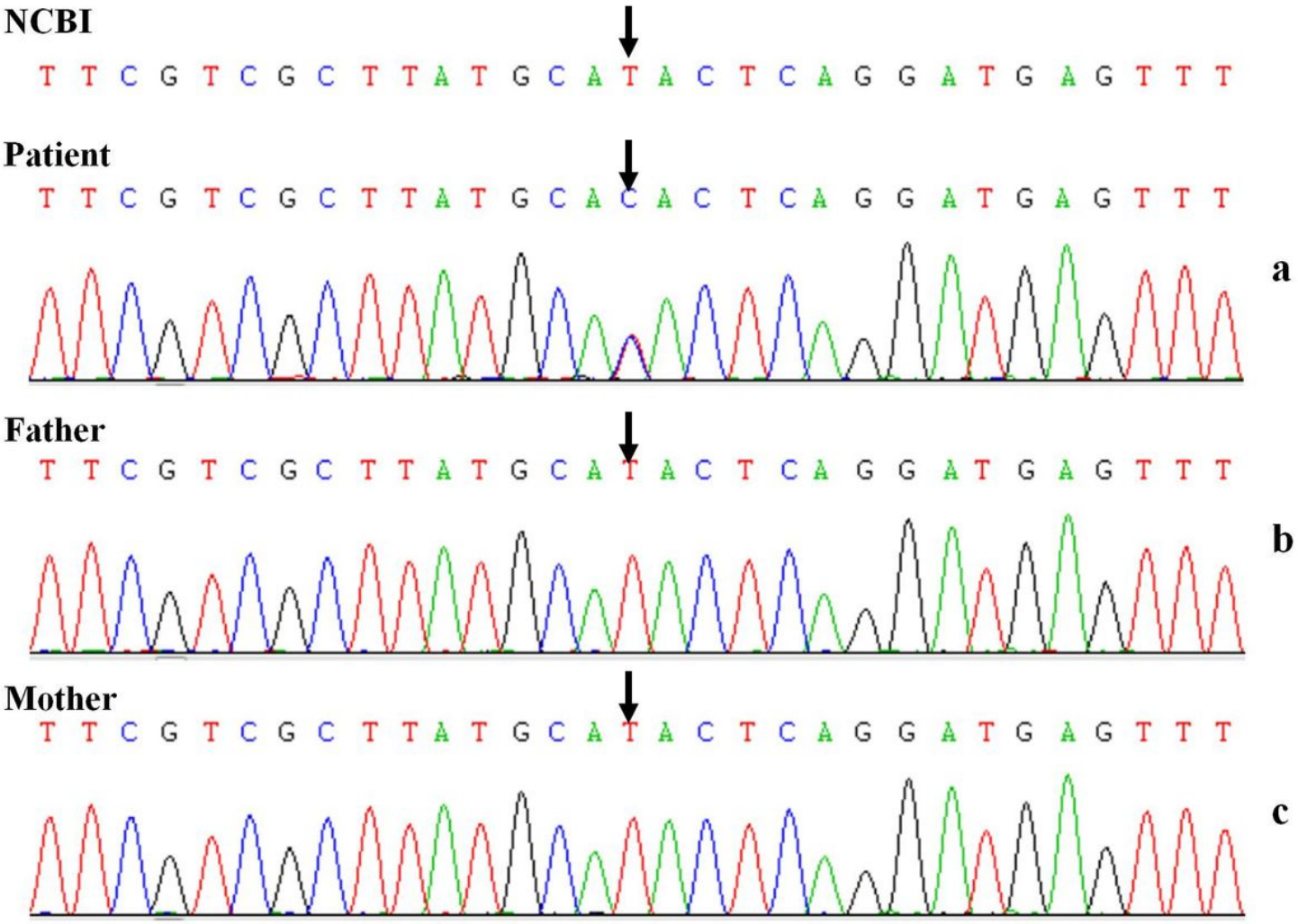

Figure 3

Genetic sequencing map of the child and her parents Sanger sequences of SMAD4 mutation (c.1499T>C) across the family. (a) A heterozygous mutation of SMAD4 in patient, (b) The father had no SMAD4 mutation, (c) The morther had no SMAD4 mutation. The red arrow indicated the mutation site.

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