Autism with dysphasia accompanied by mental retardation caused by FOXP1 exon deletion: A case report

Shuangzhu Lin,[1] Xinyu Zhou,[2] Wanqi Wang,[3] Kai Jiang[4]

Corresponding Author: Kai Jiang, 2835221172@qq.com

[1] Diagnosis and Treatment Center for Children, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, Jilin | 61858@163.com

[2] Diagnosis and Treatment Center for Children, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, Jilin | 114187810@qq.com

[3] Diagnosis and Treatment Center for Children, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, Jilin | 508293387@qq.com

[4] Diagnosis and Treatment Center for Children, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, Jilin | 2835221172@qq.com

Abstract

BACKGROUND

FOXP1 (OMIM: 605515) at the chromosomal region 3p14.1 plays an important regulatory role in cell development and functions by regulating genetic expression. Earlier studies have suggested that *Foxp1*, an oncogene, is capable of initiating tumorigenicity depending on the cell type. Researchers have found that *Foxp1* also plays an important role in regulating the cell development and functions of the immune system, e.g., regulating B-cell maturation and mononuclear phagocyte differentiation, and in the occurrence and development of various immune diseases. The mRNA of this gene is widely expressed in humans, and its differential expression is related to numerous diseases.

CASE SUMMARY

A 5-year-old boy presented mainly with attention deficit and hyperactivity disorder and developmental retardation accompanied by gait instability and abnormal facial features (low-set ears). DNA samples were extracted from the child's and his parents' peripheral blood to detect whole-exome sequences and whole-genome copy number variations. Results revealed heterozygous deletions of exon 6-21 of *FOXP1* gene in the child. Physical examination upon admission showed that the child was generally in good condition, had a moderate nutritional status, a slightly slow response to external stimuli, equally large and equally round bilateral pupils, was sensitive to light reflection, and had poor eye contact and joint attention. He had no meaningful utterance and could not pronounce words properly. He was able to use gestures to simply express his thoughts, to perform simple actions and to listen to instructions. He had no rash, cafe-au-lait macules, or depigmentation spots. He had thick black hair and low-set ears. He had highly sensitive skin, especially on his face and palms. He had no abnormal palm

fingerprint. Cardiopulmonary and abdominal examinations revealed no abnormalities. He had normal limb muscle strength and tension. He showed normal tendon reflexes of both knees. His bilateral Babinski and meningeal irritation signs were negative. He had a normal male vulva.

CONCLUSION

We report the characteristic features of autism with dysphasia accompanied by mental retardation caused by *FOXP1* exon deletion. This study provides a molecular basis for etiological diagnosis and treatment of the child, as well as for genetic counselling for the pedigree.

Keywords: Mental retardation ，Developmental retardation, Foxp1, Genetic expression, Case report

Introduction

Mental retardation accompanied by dysphasia in the absence or presence of autism (OMIM: 613670) is a developmental disease that manifests as mild to moderate mental retardation, dysphasia, and autism. This disease is clinically manifested by systemic developmental retardation, delay in walking and language, and behavior disorders, including irritability, attention deficit and hyperactivity disorder (ADHD), aggression and stiff behavior. The occurrence of this disease is mainly affected by various factors, such as heredity, immunity, and history of medications during pregnancy. Clinically, there are no specific drugs to treat this disease, and the normal physiological functions of a child can be primarily improved with combined training.

FOXP1 (OMIM: 605515) at the chromosomal region 3p14.1 plays an important regulatory role in cell development and functions by regulating genetic expression. Earlier studies have suggested that *Foxp1*, an oncogene, is capable of initiating tumorigenicity depending on the cell type[1-3]. Researchers have found that *Foxp1* also plays an important role in regulating the cell development and functions of the immune system, e.g., regulating B-cell maturation and mononuclear phagocyte differentiation, and in the occurrence and development of various immune diseases[4, 5]. The mRNA of this gene is widely expressed in humans, and its differential expression is related to numerous diseases. Therefore, diseases related to mutations at the genetic locus must be diagnosed in the early phase to be able to treat them in a timely manner.

Narrative

A 5-year-old boy presented mainly with attention deficit and hyperactivity disorder and developmental retardation accompanied by gait instability and abnormal facial features (low-set ears). DNA samples were extracted from the child's and his parents' peripheral blood to detect whole-exome sequences and whole-genome copy number variations. Results revealed heterozygous deletions of exon 6-21 of *FOXP1* gene in the child.

Perspective

History of present illness

In 2018, a 3-year-old boy presented to our hospital with a 3-year history of developmental retardation. Since birth, the child had lagged behind in development; he had progressive improvements, could not pronounce words properly, could not utter any meaningful sentences, had symptoms of ADHD, and could perform only simple actions. The child learned to sit when he was aged ~9 mo. He could crawl when he was 1 year old and only learned to walk independently when he was 2 years old. He was admitted to our hospital for etiological diagnosis and treatment. Now, the child has ADHD, developmental retardation, gait instability, and low-set ears.

History of past illness

The child was his parents' first. He was delivered by cesarean section at term, with a birth weight of 3.35 kg and a body length of 50 cm. He had no birth trauma or puerperal tetany, but he had a history of amniotic infection and jaundice for 1 mo. No obvious reason could be proposed for his developmental retardation with progressive improvements. The child had a normal diet without preferences. Hydrocephalus and atrial septal defect were revealed during prenatal examination at 32 wk. The parents were in good health, and they denied consanguineous marriage and a history of familial inherited diseases.

Physical examination

Physical examination upon admission showed that the child was generally in good condition, had a moderate nutritional status, a slightly slow response to external stimuli, equally large and equally round bilateral pupils, was sensitive to light reflection, and had poor eye contact and joint attention. He had no meaningful utterance and could not pronounce words properly. He was able to use gestures to simply express his thoughts, to perform simple actions and to listen to instructions. He had no rash, cafe-au-lait macules, or depigmentation spots. He had thick black hair and low-set ears. He had highly sensitive skin, especially on his face and palms. He had no abnormal palm fingerprint. Cardiopulmonary and abdominal examinations revealed no abnormalities. He had normal limb muscle strength and tension. He showed normal tendon reflexes of both knees. His bilateral Babinski and meningeal irritation signs were negative. He had a normal male vulva.

He exhibited restricted interest in common things and even had imaginary play with toys as a substitute for real things. He was capable of sitting and walking independently. He could pinch small pills with his thumb and forefinger and unscrew bottle caps. He could doodle with a pen in hand and build three layers of blocks. He showed uncoordinated walking movements. He was observed to easily fall. He was incapable of running, jumping.

Laboratory examinations and Imaging examinations

Auxiliary examinations were conducted. Head magnetic resonance imaging on September 3, 2018 revealed slight dilatation of the right ventricle, with inborn anomalies considered. Vacuole turcica electrocardiography showed trace tricuspid regurgitation (with physiological considerations). Cardiac function and electroencephalography (EEG) found no abnormalities.

Further diagnostic work-up

Before treatment, the patient was rated according to the Autism Behavior Checklist (ABC), Gesell Developmental Schedules, and S-S Language Delay Assessment. He had an ABC score of 67 points on August 16, 2018. According to S-S Language Delay Assessment, the patient was categorized as Class I, with language delay, and the development level was about 2.0–2.5 years old. According to Gesell Developmental Schedules, the patients had an adaptive development quotient of 44.13, with his language and personal–social skills severely lagging behind, and his other skills were moderately lagging behind.

The patient was preliminarily diagnosed with autism with dysphasia accompanied by mental retardation on the basis of his clinical manifestations and laboratory results. After regular rehabilitation treatment and functional exercises, his abilities in various fields developed: he could maintain eye contact; he could flexibly communicate every day using different sentence patterns; he could clearly articulate every note, although his speech was a little slow; he could perform two-step actions; and he could play simple drama games with adults familiar to him to reproduce life scenes, as well as perform parallel plays with peers without understanding the rules of the games. He was now capable of running, jumping, alternating his feet while going up and down the stairs, ride a scooter, build nine layers of blocks, and imitate circles, squares and crosses.

Microbiological identification of the causative agent

In 2020, whole-exome sequencing (WES) and whole-genome sequencing analysis of copy number variations (CNVs) were performed at our hospital to seek genetic counseling and clarify the etiology of the child's condition.

With the consent of the child's guardian, 2 mL peripheral blood was extracted for genomic DNA analysis. WES and whole-genome sequencing analysis of CNVs were done by MGExome. The distribution frequency of mutation sites of the genetic variations detected were referred to 1000 Genomes, ESP6500 (NHLBI Exome Sequencing Project), EXAC (The Exome Aggregation Consortium) and EXAC-EAS (EXAC data on about 4000 East Asians). The reported pathogenic loci were confirmed by referring to the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk) and the Online Mendelian Inheritance in Man (http://omim.org). The pathogenicity of the variants was evaluated in accordance with the Guideline for Interpretation of Sequence Variants[6] published by the American College of Medical Genetics and Genomics (ACMG).

WES revealed a heterozygous deletion mutation in *Foxp1* of the child, and this mutation was located at exons 6–21 and indicated a heterozygous deletion (Figure 1). This mutation was a zero effect (exon deletion) that may have resulted in a loss of function of the gene. Moreover, the frequency of the mutation was negative relative to normal. Hence, it was a low-frequency mutation. However, as revealed by the pedigree, no mutation at the locus of the child's father or mother was found (Figure 2). Thus, this mutation was spontaneous. According to the ACMG Guidelines, it was a pathogenic variant. No obvious genetic abnormalities were found in the CNV results.

FINAL DIAGNOSIS

The final diagnosis of the presented case is autism with dysphasia accompanied by mental retardation due to the heterozygous deletions of exon 6-21 of Foxp1 gene.

TREATMENT

The patient, Since his diagnosis, has been undergoing related speech and motor rehabilitation training in the hospital.

OUTCOME AND FOLLOW-UP

After treatment, the patient remained in Class I of S-S Language Delay Assessment on March 5, 2019: language delay was still observed, and his developmental level was about 2.0–2.5 years old. According to Gesell Developmental Schedules, his adaptive development quotient increased to 49.46 on March 6, 2019. His adaptability and personal–social skills were moderately lagging behind, and his other skills remained slightly lagging behind.

Discussion

FOXP1 mutations may cause mental retardation accompanied by dysphasia in the absence or the presence of autism. *FOXP1* mutations are manifested by dysphasia, motor retardation, mental retardation, stereotyped behaviors, hyperactivity, facial changes, heterotropia, nystagmus and obesity, with clinical symptoms progressing slowly but not affecting life expectancy. The child was diagnosed with autism with dysphasia accompanied by mental retardation because of *FOXP1* mutations and the corresponding clinical manifestations with a better prognosis.

The Fox genome is a large and highly conservative family of transcription factors. Foxp, a subfamily of the Fox family, has four members, namely, Foxp1–Foxp4, which not only maintain a high degree of conservatism in structure but also participate in different developmental processes, such as neural development related to language and cognition, the formation and development of organs, such as the heart and lungs, and the development of the immune system[7-10].

As a member of the Foxp family, Foxp1 has been confirmed to be widely and abundantly expressed in normal tissues early in the embryo. Banham *et al*[2, 4] obtained a full-length cDNA encoding Foxp1, which is characterized by a DNA domain with a length of 100 amino acids and an evolutionarily conserved DNA domain called the forkhead or the forkhead/winged helix domain. Members of the Foxp subfamily have several atypical features in the Fox protein: the forkhead domain is located near the carboxyl terminal region, and it contains leucine zipper motifs that promote the homodimerization and heterodimerization of Foxp, and it has a highly selective tissue-/cell-type-specific activity.

In this case, the *FOXP1* gene of the child had a heterozygous deletion variation, and the mutation site was heterozygous deletion in exon 6-21. Since the detection method was second generation WES, the regional deletion fracture could only be determined according to the region of exon captured by the gene. Therefore, we could only ascertain that the approximate location of the gene deletion in children was about 345 kb, the maximum deleted region is chr3: 71003864 - 71349076.

A total of 15 cases with *FOXP1* mutations have been reported thus far[11-20]. Eight cases had partial gene deletions, six had abnormal amino acid synthesis caused by base mutations, and one had

abnormal amino acid synthesis and expression with a base (T) added (Table 1). Noticeable facial changes were observed in 10 of the reported cases and conduct disorders in seven cases. No study has reported that *FOXP1* mutations affect the lifespan of the patients, however, according to previous reports, this gene may have a tendency.

The closest patient to this case was a girl with a 390-kb deletion of exon 4-14 of her *FOXP1* gene. As in this case, no abnormality was found in either parent[14]. The patient was not able to say words until she was 3 years old, and since then she has been able to respond to language, but this response is mostly repeated language content, rather than language to answer questions. Despite the behavioral characteristics of autism, the patient had stereotyped behavior, compulsive behavior, hyperactivity, and was not diagnosed with autism.

Previous reports have shown that FOXP1 and FOXP2 (OMIM :605317) are closely related.[13, 19] Both of them are homeostructures sharing similar amino terminal domains, and active in the foregut and brain in human development. The lack of FOXP1 and FOXP2 can be seen in the delay of language development (such as vocal retardation, dysarthria, grammatical monotony, etc.),[11] but FOXP2-related cases tend to describe the facial muscle fine motor dysfunction (such as lip, tongue muscle, etc.), whose variants are often accompanied by language expression and receptivity abnormalities, while FOXP1 tend to affect the nerves of children and lead to language retardation.

Analysis of the condition of the present case and those previously reported suggested that a certain correlation may exist between the *FOXP1* mutation site and clinical phenotypes. Fifteen cases had dysgnosia, bradykinesia and cognitive modifiability that affected motor development. However, compared with the abnormal expression caused by base mutation, patients with gene interruption are more likely to show more severe language and motor retardation, accompanied by limb deformities and organic lesions.

In children with facial changes, they often have the same type of performance: giant malformation, wide eye distance, excessive strabismus, and wide nose tip.[13, 19] In this case, the ear position of the child was slightly lower and there was a typical facial change. In some of the patients who had provided the relevant examination, some of the results showed abnormal structural development such as periventricular white matter, but there was no nervous system examination and EEG was abnormal. In this case, there was hydrocephalus during pregnancy. Postnatal examination showed that the right ventricle was dilated, and vacuolar sella and EEG were not abnormal. This may be related to the abnormal expression of *FOXP1* gene deletion.

In addition to the motor retardation, some patients reported decreased muscle tension and referred to gait abnormalities in phenotypic description[20]. In this case, the children also had abnormal gait (such as walking instability, easy to fall), and achieved more obvious improvement after rehabilitation, which suggests that our timely and early intervention can improve the living standards of patients.

According to previous reports, children with clinical manifestations, such as dyskinesia, developmental retardation, dysphasia, cognitive modifiability and facial changes (low-set ears),

meet the diagnostic criteria for phenotypic changes of mental retardation accompanied by dysphasia in the absence or the presence of autism. Notably, the illness episodes of Asian populations have never been defined or described in previously reported cases. Hence, the present case may provide new insights into the illness episodes and manifestations of a different race. Our clinical assessment of patients helps to describe the core phenotype of *FOXP1*-related disorders, which may contribute to disease identification.

Conclusion

In the present study, WES was conducted to resolve three aspects. First, the etiology was established to clarify the genetic causes of the disease; this information is useful in genetic counseling. Second, genotype analysis is helpful to guide clinical treatment and prognosis evaluation, and modern rehabilitation training, such as educational intervention, behavior modification, speech therapy and sensory integration training, are conducive to early intervention and improvement in the quality of life of patients. Finally, the discovery of a new *FOXP1* mutation with heterozygous deletions at exons 6–21 enriches our understanding of the *FOXP1* mutation spectrum. The results of the present study suggested that investigation of intelligence development cannot be neglected for children with clinical manifestations of dysphasia and motor retardation. In such a case, the possibility of *FOXP1* mutation should be raised.

Acknowledgements

We would like to thank the child and his family members for agreeing to participate in this study.

References

[1] Wang B, Lin D, Li C, Tucker P. Multiple domains define the expression and regulatory properties of Foxp1 forkhead transcriptional repressors. J Biol Chem. 2003. 278(27): 24259-68. [PMID: 12692134 DOI: 10.1074/jbc.M207174200]

[2] Banham AH, Beasley N, Campo E, et al. The FOXP1 winged helix transcription factor is a novel candidate tumor suppressor gene on chromosome 3p. Cancer Res. 2001. 61(24): 8820-9.[PMID: 11751404]

[3] Streubel B, Vinatzer U, Lamprecht A, Raderer M, Chott A. T(3;14)(p14.1;q32) involving IGH and FOXP1 is a novel recurrent chromosomal aberration in MALT lymphoma. Leukemia. 2005. 19(4): 652-8.[PMID: 15703784 DOI: 10.1038/sj.leu.2403644]

[4] Banham AH, Connors JM, Brown PJ, et al. Expression of the FOXP1 transcription factor is strongly associated with inferior survival in patients with diffuse large B-cell lymphoma. Clin Cancer Res. 2005. 11(3): 1065-72. [PMID: 15709173]

[5] Hu H, Wang B, Borde M, et al. Foxp1 is an essential transcriptional regulator of B cell development. Nat Immunol. 2006. 7(8): 819-26.[PMID: 16819554 DOI: 10.1038/ni1358]

[6] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for

Molecular Pathology. Genet Med. 2015. 17(5): 405-24.[PMID: 25741868 PMCID: PMC4544753 DOI: 10.1038/gim.2015.30]

[7] Brunkow ME, Jeffery EW, Hjerrild KA, et al. Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet. 2001. 27(1): 68-73.[PMID: 11138001 DOI: 10.1038/83784]

[8] Enard W, Przeworski M, Fisher SE, et al. Molecular evolution of FOXP2, a gene involved in speech and language. Nature. 2002. 418(6900): 869-72.[PMID: 12192408 DOI: 10.1038/nature01025]

[9] Shu W, Lu MM, Zhang Y, Tucker PW, Zhou D, Morrisey EE. Foxp2 and Foxp1 cooperatively regulate lung and esophagus development. Development. 2007. 134(10): 1991-2000.[PMID: 17428829 DOI: 10.1242/dev.02846]

[10] Wang B, Weidenfeld J, Lu MM, et al. Foxp1 regulates cardiac outflow tract, endocardial cushion morphogenesis and myocyte proliferation and maturation. Development. 2004. 131(18): 4477-87.[PMID: 15342473 DOI: 10.1242/dev.01287]

[11] Mitchel J Pariani, Andrew Spencer, John Graham Jr, et al. A 785kb deletion of 3p14.1p13, including the FOXP1 gene, associated with speech delay, contractures, hypertonia and blepharophimosis .Eur J Med Genet. Mar-Jun 2009;52(2-3):123-7.[PMID: 19332160 PMCID: PMC2853231 DOI: 10.1016/j.ejmg.2009.03.012]

[12] Carr CW, Moreno-De-Luca D, Parker C, et al. Chiari I malformation, delayed gross motor skills, severe speech delay, and epileptiform discharges in a child with FOXP1 haploinsufficiency. Eur J Hum Genet. 2010. 18(11): 1216-20.[PMID: 20571508 PMCID: PMC2987472 DOI: 10.1038/ejhg.2010.96]

[13] Horn D, Kapeller J, Rivera-Brugués N, et al. Identification of FOXP1 deletions in three unrelated patients with mental retardation and significant speech and language deficits. Hum Mutat. 2010. 31(11): E1851-60.[PMID: 20848658 PMCID: PMC3049153 DOI: 10.1002/humu.21362]

[14] Hamdan FF, Daoud H, Rochefort D, et al. De novo mutations in FOXP1 in cases with intellectual disability, autism, and language impairment. Am J Hum Genet. 2010. 87(5): 671-8.[PMID: 20950788 PMCID: PMC2978954 DOI: 10.1016/j.ajhg.2010.09.017]

[15] O' Roak BJ, Deriziotis P, et al. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet. 2011. 43(6): 585-9.[PMID: 21572417 PMCID: PMC3115696 DOI: 10.1038/ng.835]

[16] Talkowski ME, Rosenfeld JA, Blumenthal I, et al. Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries. Cell. 2012. 149(3): 525-37.[PMID: 22521361 PMCID: PMC3340505 DOI: 10.1016/j.cell.2012.03.028]

[17] Le Fevre AK, Taylor S, Malek NH, et al. FOXP1 mutations cause intellectual disability and a recognizable phenotype. Am J Med Genet A. 2013. 161A(12): 3166-75.[PMID: 24214399 DOI: 10.1002/ajmg.a.36174]

[18] Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. Ann Neurol. 2014. 76(4): 473-83.[PMID: 25131622 DOI: 10.1002/ana.24251]

[19] Lozano R, Vino A, Lozano C, Fisher SE, Deriziotis P. A de novo FOXP1 variant in a patient with autism, intellectual disability and severe speech and language impairment. Eur J Hum Genet. 2015. 23(12): 1702-7.

[PMID: 25853299 PMCID: PMC4795189 DOI: 10.1038/ejhg.2015.66]

[20] Sollis E, Graham SA, Vino A, et al. Identification and functional characterization of de novo FOXP1 variants provides novel insights into the etiology of neurodevelopmental disorder. Hum Mol Genet. 2016. 25(3): 546-57. [PMID: 26647308 DOI: 10.1093/hmg/ddv495]

Attachments

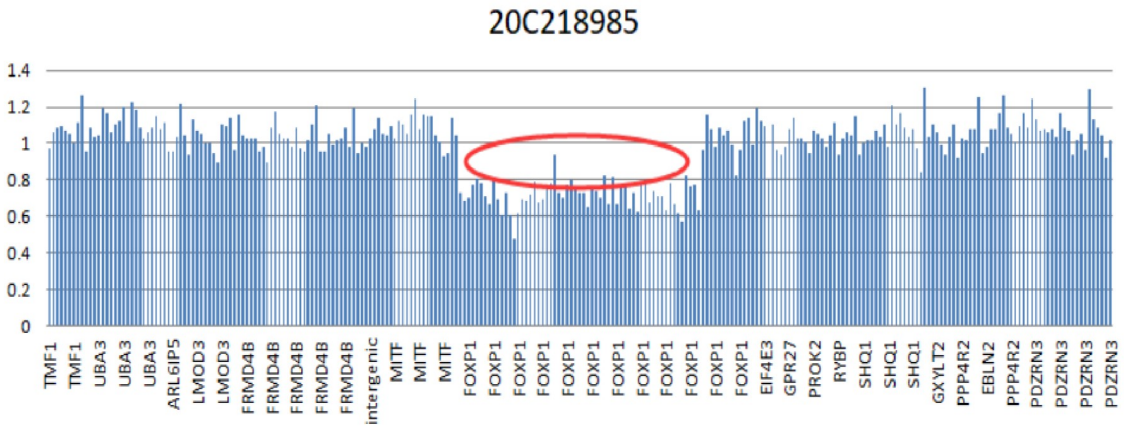

Figure 1. Heterozygous deletion mutations found at exons 6–21 in the child as revealed by whole-exome sequencing.

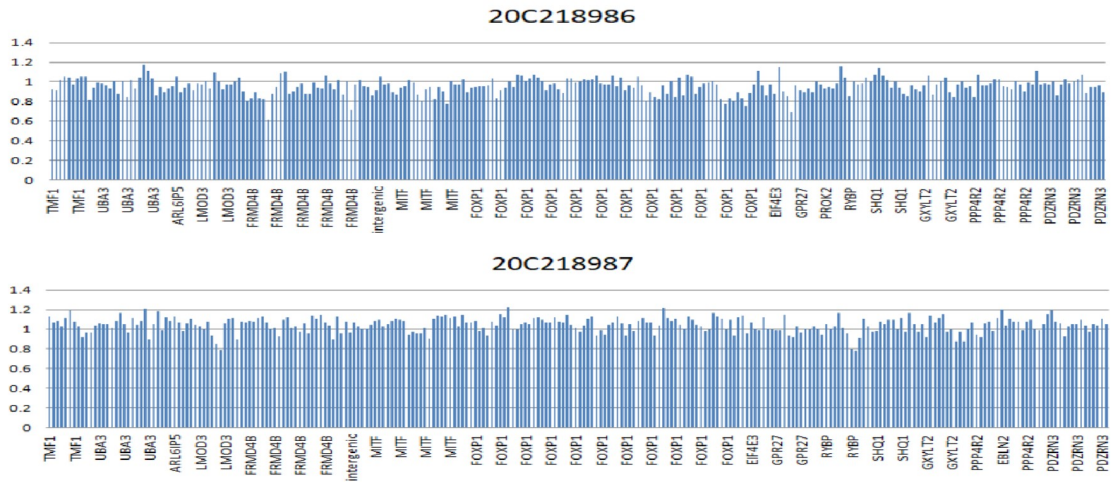

Figure 2. No anomalies were found at exons 6–21 in the child's parents as revealed by whole-exome sequencing.