Genetic analysis of a child with 18q Deletion Syndrome and Developmental Dysplasia of Hip

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Research Article

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Abstract

Objective To analyze genotypes and phenotypes of a child with Developmental Dysplasia of Hip (DDH), developmental delays, recurrent fever, hypothyroidism and cleft palate.

Methods G-banding karyotypeing analysis and Next-generation Sequencing(NGS) were performed on the child. The parents of the child were verified by copy number variations (CNV) and Sanger sequencing to determine the source of variations.

Results The karyotype of the child was 46, XX. A 10.44Mb deletion(chr18:67562936-78005270del) at 18q22.2q23 was found by NGS, as well as *HSPG2* variation (chr1: 22206699, c.2244c > A, exon 17, p.h748q; chr1: 22157321–22157321, c.11671 + 154insA, Intron) originated from father and mother, respectively.

Conclusion This is the first 18q deletion syndrome case which accompanied by DDH. Most phenotypes of the child ,such as developmental delays, cleft palate, may be related to 18q22 2q23 deletion, while no variant genes related to DDH were found in this deletion region. DDH may be related to mutation of *HSPG2.*

1. Background

18q deletion syndrome is one of the common types of chromosome 18 aberrations [1]. The locations and breaking points of chromosome deletion in this disease are often difference. Whats more, penetrance of gene in each key region is different, so the clinical phenotypes of this disease are various[2]. The fracture points of the syndrome are generally distributed between 18q11 and 18q23 [3], most of them are terminal deletion. Some common clinical phenotypes have been identified to be related to the missing coding genes in this region, such as short stature, developmental delays, congenital heart disease, cleft palate, IgA deficiency, hearing loss, etc. [4]. There are also some phenotypes that may be related to missing genes, but the related regions have not been accurately located, such as autoimmune diseases, cryptorchidism, hypospadias. What's more, causes of some phenotypes, such as fever and hypothyroidism, are unknown so far.

Developmental dysplasia of the hip(DDH), formerly known as congenital dislocation of the hip. Its incidence rate is about 1‰, which of girls is about 6 times of boys[5]. The manifestations of the disease include hip dislocation, subluxation and acetabular dysplasia [6, 7], and bilateral dysplasia accounts for about 35%. Its pathogenesis is currently considered to be related to genetic and acquired factors [8]. The acquired factors are mainly breech production, oligohydramnios and primipara [9]. At present, there is no report of DDH in children with 18q syndrome, this case is the first case. In order to further explore the relationship between phenotypes and genotypes of this case, we performed G-banding karyotypeing analysis and NGS on the child. At the same time, the parents of the child were verified and analyzed by CNV analysis and Sanger sequencing.

2. Materials And Methods

2.1 Clinical Report

This case was female, 89 days, G1P1, born by cesarean section due to breech position on 38 weeks, birth weight 2470g. She was hospitalized in our hospital because of "body weight increased slowly for 73 days and recurrent fever for 11 days". On the 16th day after birth, the child was found that the body weight increased slowly, thyroid function inferred hypothyroidism, FT3 3.81pmol/l (normal level: 3.3-8.95pmol/l), FT4 11.57pmol/l (normal level : 11.9-25.6pmol/l), TSH 82.35uIU/ml (normal level: 0.73-8.35uIU/ml). Thyroid ultrasound showed increased thyroid blood flow. Left thyroxine (Euthyrox, 4ug/kg, Qd) was given orally. On the 56th day after birth, the child was diagnosed with bilateral dislocation of hip(DDH), and fixed with DDII sling. On the 78th day after birth (11 days before admission), she began to have recurrent fever, no cough, no vomiting, no diarrhea. Her parents were not consanguineous marriage, her mother was in good health, suffered from cleft lip, her father was in good health. Physical examination: T 38.3℃, P 145 times/min, R 60 times/min, Wt 3kg, body length 54cm, head circumference 38cm. Poor spirit. The skin was scattered with patterns, subcutaneous fat was thin and with poor elasticity. Cleft palate, strabismus, hypotonia. Lower limb fixed by DDII sling. Joint ultrasound showed bilateral hip dislocation; Cardiac ultrasound showed patent foramen ovale and tricuspid regurgitation; Brain MRI showed encephalomalacia in the right basal ganglia; Internal auditory canal MRI showed bilateral large vestibular aqueduct dilation, brainstem auditory evoked potential examination showed that both ears failed; Chest CT showed a small amount of inflammatory changes in the lungs. Serum IgA: 0.09g/l (normal range: 0.03-0.78g/l), IgG: 4.95g/l (normal range: 1.8-8.0g/l), IgM: 0.4g/l (normal range: 0.4-2.3g / L), IgE < 15 IU / ml (normal range: 0–15 IU / ml). Blood routine examination indicated moderate anemia (Hb 84g/L). Thyroid function, CRP, PCT, ESR, urine routine, stool routine, liver and kidney function, blood gas analysis, etc. were generally normal. There were no bacterial growth in multiple blood bacterial cultures, no abnormality in peripheral blood smears, no abnormality was found in 3-hour video EEG, and no abnormality in G-banding karyotypeing analysis (Fig. 1).

After the child admission, we gave her Left thyroxine (Euthyrox, 4ug/kg/d, Qd, 7d) by oral, piperacillin sodium and tazobactam sodium (100mg/kg/d, Tid, 7d) by intravenous. The child's spirit improved slightly, the thyroid function was normal, but she still had fever. The temperature fluctuated at 37.8℃-39℃, dry skin, no sweat, and the effect of physical cooling and antipyretics was poor. Combined with the child's clinical manifestations, we highly suspected that the child had hereditary diseases. In order to clarify the diagnosis, we obtained the child's blood samples for NGS after obtaining the consent of the child's parents.

2.2 Next-generation Sequencing(NGS)

Genomic DNA was extracted and the whole genome library was prepared from peripheral blood of the child and her parents by Beijing MyGenostics company, The gene exon region and its upstream and downstream 50bp region of the child and her parents, and then the captured region was sequenced by Illumina HiSeq X ten high-throughput sequencing platform, with a reading length of 150bp.

2.3 Whole Genome Sequencing and CNV Analysis

The data were filtered and compared by cutadapt (1.16), BWA(0.7.12), GATK(4.0.8.1) MarkDuplicates softwares by Beijing MyGenostics company after sequencing. The CNV was calculated mainly according to the read depth method. All obtained suspiciously deleted, repeat regions were compared with OMIM, genereviews, decipher, clinvar, DGV and other databases to obtain phenotypic information related to chromosome regions.

3. Results

3.1 NGS Results

NGS showed that the long arm of chromosome 18 had about 10.44Mb copy number loss, 18q22.2q23 (67562936-78005270del) (Fig. 2). This region involved TSHZ1,CTDP1,RBFA,ZNF516, *PARD6G*,MBP,TIMM21,CNDP1,FBXO15,NETO1,KCNG2,ZNF407, NFATC1,ZADH2,TXNL4A,CYB5A,ATP9B,SMIM21,ZNF236,CBLN2,C18orf63,GALR1,SALL3, SLC66A2,CNDP2,DIPK1C,HSBP1L1,ADNP2,RTTN,CD226,SOCS6. At the same time, we found *HSPG2* mutation,(chr1:22206699, c.2244C > A, exon 17, p.H748Q;chr1:22157321–22157321, c.11671 + 154insA, Intron), which may be related to DDH.

3.2 CNV Verification Results of Parents

No 18q22.2q23 deletion was found in CNV verification of the parents (Fig. 3, Fig. 4). It showed that the 18q deletion in this child was a new variation.

3.3 Sanger Sequencing of HSPG2 in Child and Her Parents

Sanger sequencing showed that the variation of exon site came from the father (Fig. 5), the variation of intron site came from the mother (Fig. 6).

3.4 Summary of Deletion Regions and Phenotypes in Some Reported Cases of 18q Deletion Syndrome(Table 1).

Table 1
Summary of deletion regions and phenotypes in some reported cases of 18q deletion syndrome

	Chromosome banding	Critical region borders	Size of region(Mb)	Clinical findings
Cody JD,et al. 2007 (5 cases)[3]	18q11.2-q21.1	-	19.5	Cryptorchidism, Hypotonia, Seizures, Vision, Hearing loss, Recurrent otitis, Recurrent URI, GU abnormalities, Other MRI fifindings, Developmental delays, Hypothyroidism
	18q12.3-q21.1	-	7.5	Hutch diverticuli, Hypotonia, Hearing loss, Recurrent otitis, GU abnormalities, Delayed myelination, Other MRI fifindings, Developmental delays
	18q12.3-q21.1	-	5	Hypotonia, Seizures, Developmental delays
	18q12.3-q21.1	-	5	Hypotonia, Vision, Developmental delays
	18q12.3-q21.1	-	5	Hypotonia, Developmental delays
Ester Margarit, et al. 2012 (2 cases)[1]	18q23	71236891–76093303	4.8	GH insuffificiency, dysmyelination, Small adenohypophysis, Renal hypoplasia, Umbilical hernia, Reduced hearing, Smooth philtrum, Thin upper lip, Prognathism, Joint laxity, Neonatal hypoglycemia, Developmental delays
Cody JD,et al. 2014 (16 cases) [10]	18q22.1	59807588–61568468	17.6	GH insuffificiency, dysmyelination, Developmental delays, Hearing loss, Foot anomalies, Atretic, Stenotic ear canals, Hypospadias, Tapered fingers, Flat mid-face, Proximally placed thumbs, Congenital heart abnormalities, Autoimmune disorders (Myalgia, Arthritis, Hypothyroidism), Palatal abnormalities, Neonatal complications (Jaundice, Apnea, Respiratory difficulties, Meconium Aspiration), Gastroesophageal reflux

	Chromosome banding	Critical region borders	Size of region(Mb)	Clinical findings
Feng JB,et al. 2016 (8 cases) [11]	18q21.31-q23	55040745–78014123	22.973	Cleft palate
	18q21.32-q23	56288429–78013728	21.725	Developmental delays, Hearing loss, Atrial septal defect, Cryptorchidism
	18q21.32-q23	56817426–78014123	21.196	Developmental delays, Cleft palate, Atrial septal defect, Strephenopodia
	18q21.33-q23	59581097–78013728	18.432	Flatfoot
	18q21.33-q23	60090078–780013728	17.923	Developmental delays, Cleft palate, Ventricular septal defect, Pulmonary valve stenosis
	18q21.33-q23	61221941–78013728	16.791	Developmental delays
	18q22.1-q23	61985155–78013728	16.028	Developmental delays
	18q22.3-q23	71400740–78013728	6.612	Hearing loss, Pulmonary valve stenosis
Shi SS, et al.2017[4]	18q22.2-q23	68158880–78014123	9.855	Developmental delays, Hypotonia, Hypothyroidism, Recurrent fever, Seizures,Other MRI fifindings(abnormal cerebral white matter development, Dysplasia of corpus callosum),Polydipsia, Polyuria
Yu SF,et al.2022	18q22.2-q23	67562936–78005270	10.44	Developmental delays, Hypotonia, Hearing loss, cleft palate, Other MRI fifindings(abnormal cerebral white matter development), Vestibular dysplasia, Strabismus, Hypothyroidism, DDH, Recurrent fever

4. Discussion

Since the first case of 18q deletion syndrome was reported in 1964[12], many scholars have tried to study the relationship between phenotype and deletion region or genotype. After years of research, it has been found that some common clinical phenotypes are identified to be related to the missing coding genes in those region. For example, the regions related to short stature and growth hormone deficiency are 18q12.1q12. 3, 18q21. 1q21. 33, 18q22.3q23, the possible main pathogenic gene is *GALR1*[1, 13–15]. The region related to developmental delays and abnormal cerebral white matter development is 18q22.3q23, the possible related pathogenic genes are *ZNF236*, *ZNF516*, *MBP*, *GALR1* and *IOC284276*[2,

16, 17]. The region related to congenital heart disease is 18q22.3q23, the possible main pathogenic gene is *NFATC1*[18]. The region related to cleft lip and cleft palate is 18q22.3q23, the possible related pathogenic genes are *SALL3* and *TSHZ1*[19]. The region related to IgA deficiency and renal dysplasia is 18q22.3q23, the gene related to hearing impairment and abnormal ear development is *ZNF407* [1, 4].

The case in this report had many phenotypes, including developmental delays, cleft palate, hypotonia, abnormal cerebral white matter development, hearing loss, vestibular dysplasia, strabismus, hypothyroidism, DDH and recurrent fever. The NGS results revealed that there was a 10.44Mb deletion at 18q22.2q23. The deletion region contained genotypes related to developmental delays, short stature, cleft palate, hypotonia, abnormal cerebral white matter development, hearing impairment. There was a case report with the same missing region as this case in the past, whose phenotypes included developmental delays, hypotonia, hypothyroidism, recurrent fever, seizures, abnormal cerebral white matter development, dysplasia of corpus callosum, polydipsia, polyuria[4]. What they had in common was the deletion region was 18q22 2q23, both appeared developmental delays, hypotonia, hypothyroidism, recurrent fever, abnormal cerebral white matter development. The differences were that the starting point of the deletion region in our case was 67562936, the end point was 78005270. Our case appeared cleft palate, hearing loss, vestibular dysplasia, strabismus and DDH. Combined with the analysis of previously reported cases, we highly suspect that most of the phenotypes in this child were caused by 18q22 2q23 deletion.

For the recurrent fever phenotype in this child, we did not find any related mutant genes. Some researchers believed that recurrent fever may be related to the lack of IgA [4], but this child had no infected symptoms, no growth of blood bacterias, normal contents of IgA and other immunoglobulins, and anti-infection treatment was ineffective. This inferred that the fever was not associated with IgA deficiency or immune deficiency combined with infection in this case. The child also had the symptom of less sweat secretion. Recurrent fever may be related to the diseases that could cause this symptom, such as abnormal development of cerebral cortex. As for hypothyroidism, no pathogenic genes were found that directly related to hypothyroidism in the deletion region of this child. But we found *CD226* coding gene in deletion region, which encodes a kind of glycoprotein expressed on the surface of NK cells, platelets, monocytes and T cell subsets. This kind of glycoprotein mediates the adhesion of platelets and megakaryocytes to vascular endothelial cells. It also plays a role in megakaryocyte maturation[20]. Diseases related to *CD226* mutation include a variety of autoimmune endocrine disorders, such as autoimmune thyroiditis (AITD)[21]. However, the child was too young to accurately assess autoimmune function. Whether this phenotype is related to this gene deletion needs further study in more cases. Some researchers consider that hypothyroidism is related to abnormal brain development or thyroid itself [4], in this case we can not exclude the possibility of temporary hypothyroidism as well.

The child also had a phenotype that had not been reported in patients with 18q deletion syndrome. The pathogenesis of DDH may be congenital or acquired. Acquired factors mainly include breech delivery. This case was breech delivered, but he was born by cesarean section smoothly without birth injury factors. Therefore, DDH in this case was unlikely to be related to breech delivered. The genetic mode and mechanism of DDH are not clear at present, the possible genetic mode may be autosomal dominant

inheritance with incomplete penetrance, which may be related to the variation of *CX3CR1*, *UFSP2*, *HSPG2* and *ATP2B4* [6, 22–24]. After NGS detection, there was heterozygous variation at exon site and intron site of *HSPG2* of this child. The variation at exon site, c.2244c > A (p.H748Q), was a new mutation comed from the father who had no clinical manifestation of DDH. Variation at intron site, c.11671 + 154insa, was located in the deep intron region, and was unlikely pathogenic. The diseases related to *HSPG2* mutation mainly include Dyssegmental dysplasia Silverman-Handmaker type (DDHS) and Schwartz Jampel syndrome type 1, both of which are autosomal recessive diseases.Clinical features of DDHS include a flat midface, narrow thorax, abnormal ears, short neck, severe short stature, short and bowed limbs, as well as decreased joint mobility, cleft palate and club feet[25]. Schwartz-Jampel syndrome type 1 characterized by permanent myotonic myopathy and skeletal dysplasia, which result in short stature, dystrophy of epiphyseal cartilages, joint contractures, blepharophimosis, unusual pinnae, myopia and pigeon breast, ect[26]. The clinical phenotypes of this case were quite different from these two diseases. Combined with the genetic mode, the possibility of these two diseases will not be considered for the time being. Previously, in a experiment on *HSPG2* mutant (C1532Yneo) mice[27], it confirmed that *HSPG2* mutant mice would have weight loss and DDH. Considering that the genetic mode of this disease may be autosomal dominant inheritance with incomplete penetrance, the possibility of DDH in this case caused by *HSPG2* variation was still not excluded. However, whether this phenotype was related to 18q deletion syndrome or other genes mutation need to be further studied.

5. Conclusion

18q deletion syndrome has many common phenotypes with great differences in clinical manifestations. Most abnormal phenotypes are caused by the deletion of coding genes in the deletion region, but the mechanisms of a few phenotypes are still unknown. With the study in this case, we speculated that recurrent fever was not necessarily related to IgA deficiency. DDH is a newly reported phenotype in patients with 18q deletion syndrome, which may be related to *HSPG2* mutation in this case. The relationship between phenotypes and genotypes of 18q deletion syndrome need to be further studied.

6. Declarations

6.1.Editorial Policies and Ethical Considerations

This study was performed according to the Helsinki Declaration. Written informed consent to participate in the study was obtained from the participant as well as thier parents/leagal guardians of the participant. The research was approved by Medical Ethics Committee of Affiliated Hospital of Qingdao University.

6.2.Conflict of Interest

The authors declare that they have no competing interests.

6.3.Authors' contributions

Shufeng Yu and Zhihong Chen wrote the main manuscript text. Xuefei Leng, Lijuan Zhang, Fei Tian prepared figure1-6, Caixia Wang, Ke Lei prepared table1. All authors reviewed the manuscript.

6.4.Consent for publication

Publication informed consent to participate in the study was obtained from the parents of the patient.

6.5.Availability of data and materials

The patient's data were provided by Affiliated Hospital of Qingdao University, and the data of NGS, CNV Verification, Sanger Sequencing were provided by Beijing MyGenostics company. All data were true and reliable.The dataset supporting the conclusions of this article is available from the first author Shufeng Yu (dryushufeng@126.com) or available in the Clinvar repository.

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Figures

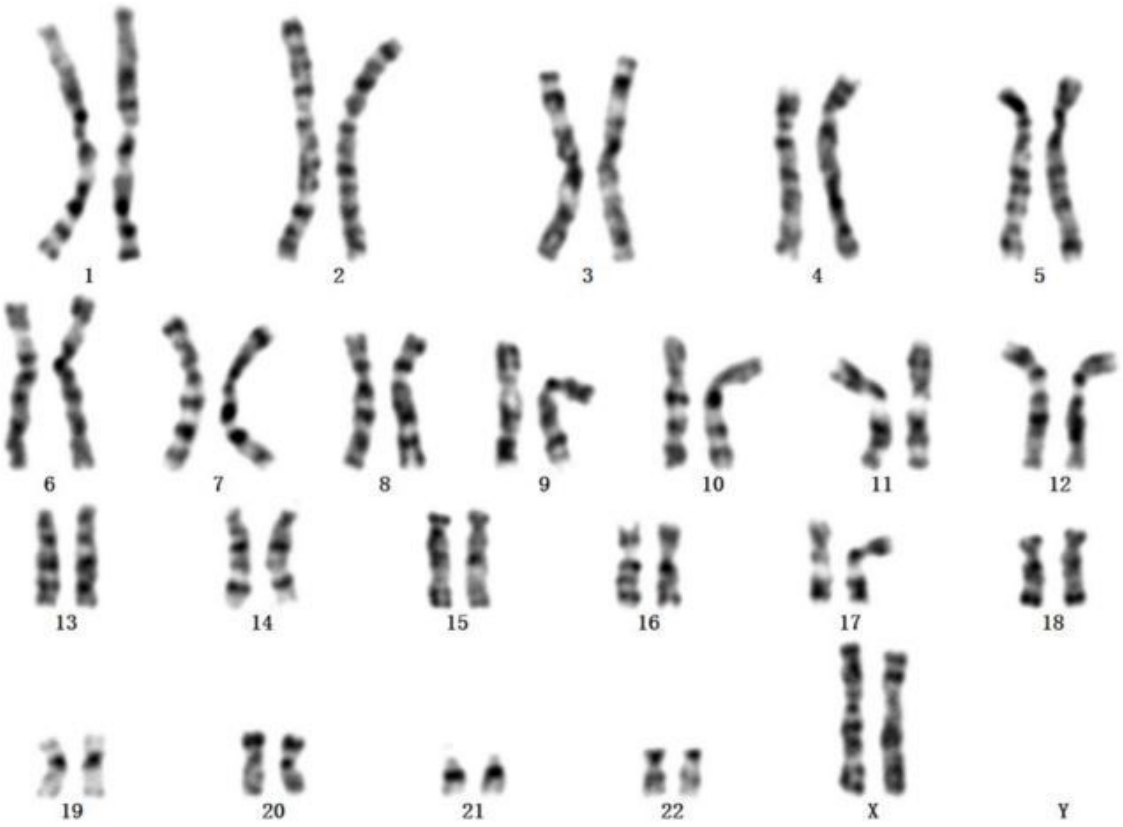

Figure 1

G-banding karyotypeing analysis of the chiid showed 46XX, no abnormality was found.

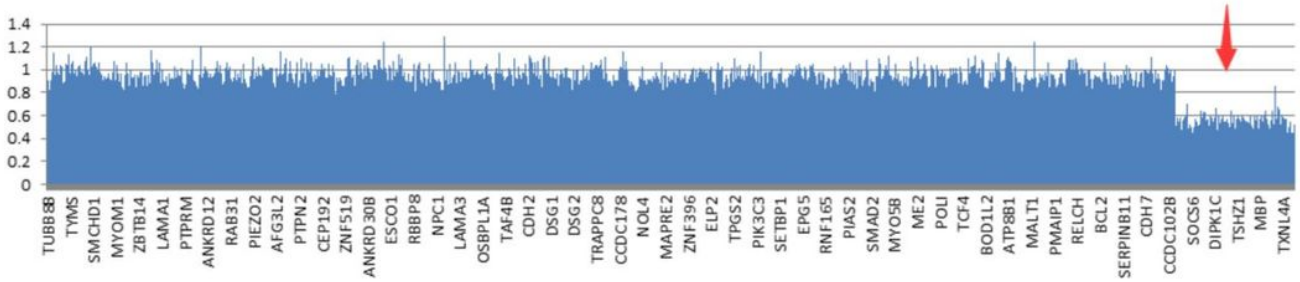

Figure 2

NGS of the Child showed a 10.44Mb copy number loss at 18q22.2q23.

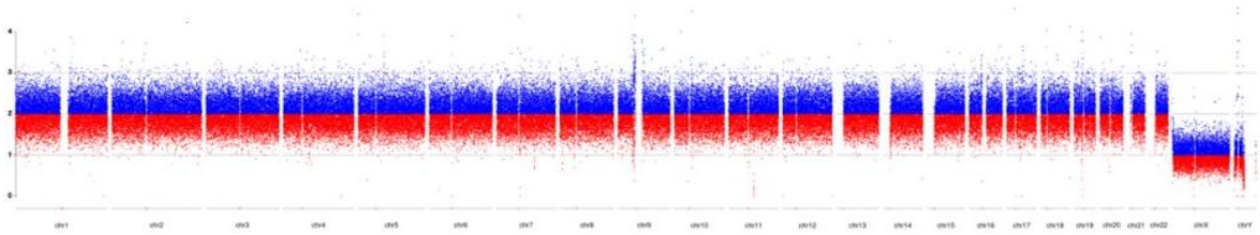

Figure 3

No 18q22.2q23 deletion was found by CNV analysis and verification of the father.

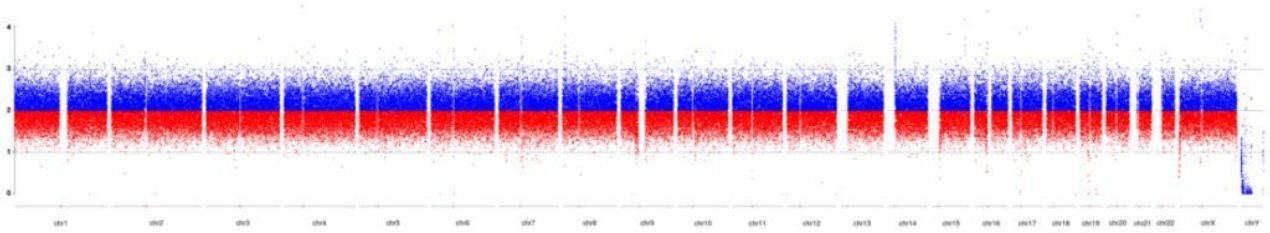

Figure 4

No 18q22.2q23 deletion was found by CNV analysis and verification of the mather.

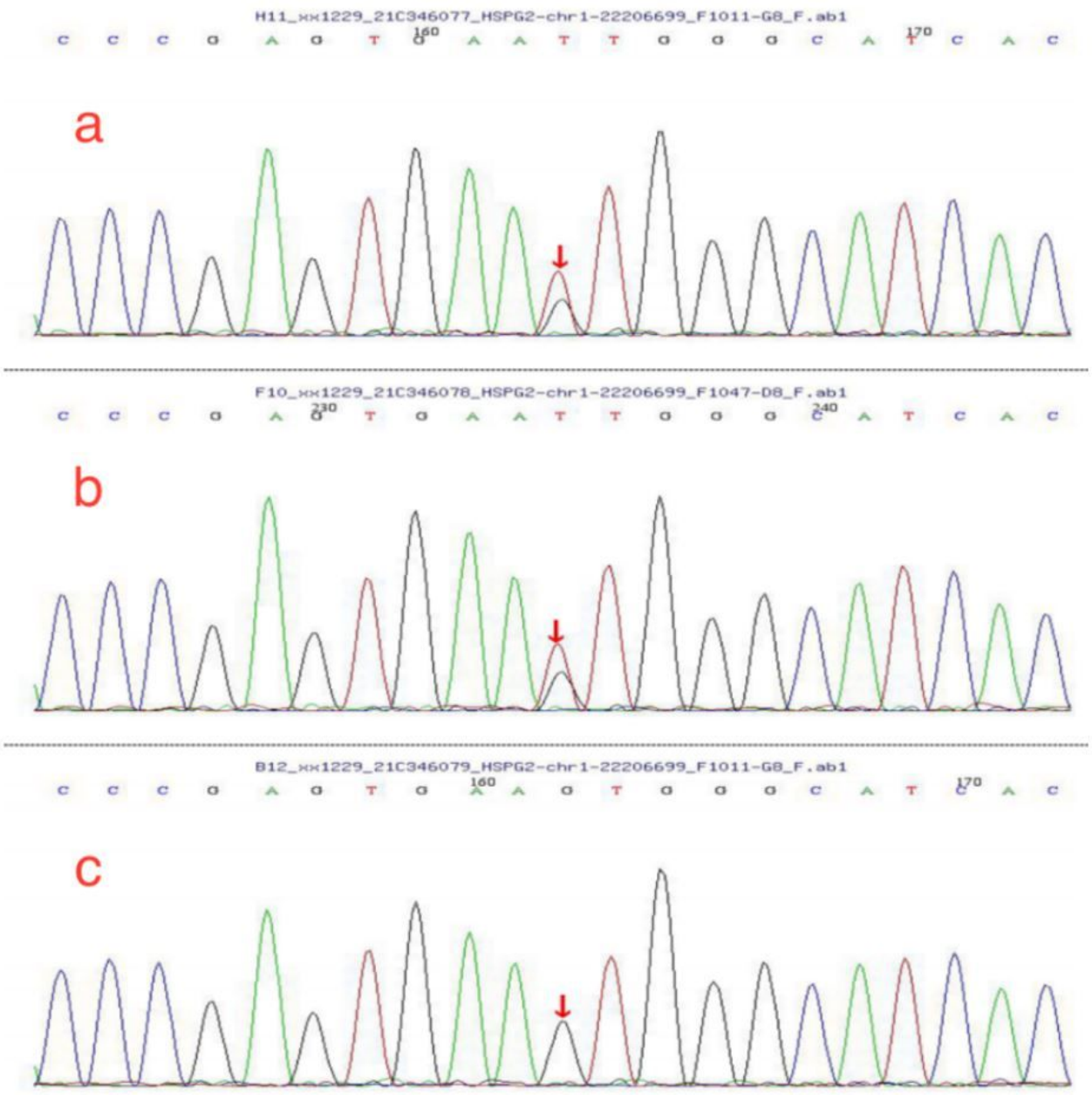

Figure 5

a:Mutation information *HSPG2* (chr1: 22206699, c.2244c > A, exon 17, p.H748Q) in children; b:The variation came from the father; c:The mother had no variation in the site.

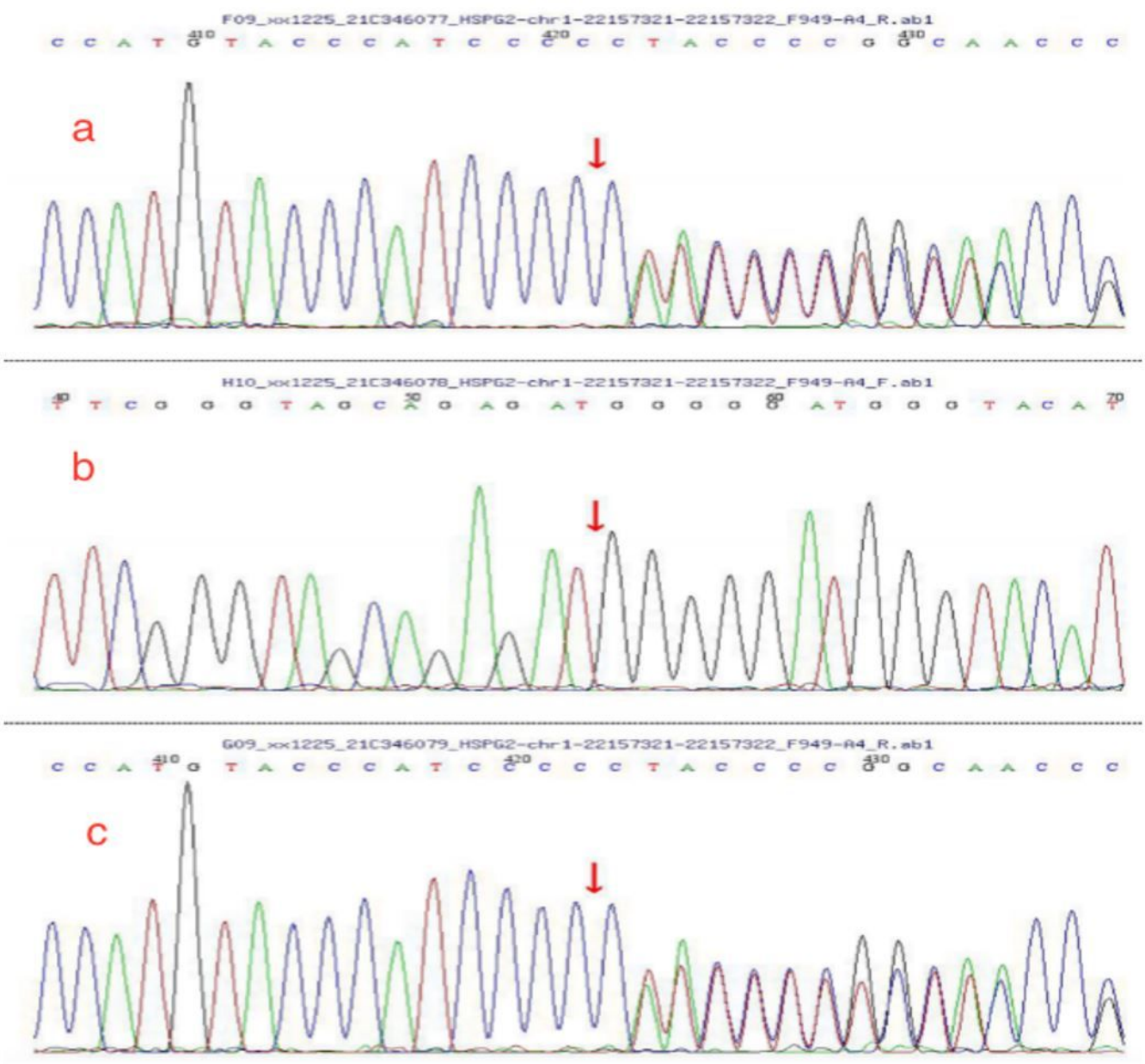

Figure 6

a:Mutation information *HSPG2* (chr1:22157321-22157321, c.11671+154insA, Intron) in children; b:The father had no variation in the site; c:The variation came from the mother.