Prenatal and Postnatal Diagnosis and Phenotype of 8p23.2p22 Duplication in One Family

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Research article

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Abstract

Background Distal 8p duplication is rare, but clinically significant.

Methods A family has an induced labor fetal (II-2) for increased nuchal translucency (3.5mm) at 12 weeks gestation and detecting a 16.22Mb deletion of 8p23.2p22 by copy number variation sequencing (CNV-seq). Hence, the family requested family analysis and prenatal diagnosis of subject II-3. All family members underwent CNV-seq, karyotyping and *FISH* testing.

Results II-1 and II-3 were found to have a 16.22Mb duplication of 8p23.2p22, containing the 8p23.1 duplication syndrome region, inherited from their father, a carrier with a translocation of 8p22 and 22q13. It's confirmed that duplication site was located on chromosome 22p13 by combining the results of CNV-seq, karyotype and *FISH*.

II-1 is a 7.5 year old boy. At one month old, he was diagnosed with a ventricular septal defect and treated using surgically at age four. His growth and intelligence developed well, and he performed well in school. His primary issue is an inability to distinguish between the flat tongue and warped tongue in speech. II-3 had a normal ultrasonic index until 26 weeks gestation. The family wants keep the pregnancy, providing us with the opportunity to evaluate the effects of 8p23.2p22 duplication in comparison with the brother (II-1).

Conclusion Our study makes a significant contribution to the literature because this relatively rare condition can have significant phenotypical consequences, and an understanding of the inheritance and variability of phenotypes caused by this mutation is essential to an increased understanding of the condition.

Background

The prevalence of 8p23.1 duplication syndrome has been reported to have an incidence of 1/58,000[1]. The 8p23.1 duplication syndrome has a variable phenotype, with three relatively common manifestations: developmental delay, intellectual disability, and malformation of the heart [1–6]. Other phenotypic effects range from delayed speech and language development and abnormal facial shape to behavioral or psychiatric abnormalities[2, 3, 5–7]. The typical genomic region affected involves 3.68 Mb, but a minimal region spanning 776 kb, and containing only eight genes has been suggested by Barber *et al* [1, 8].

The phenotypes vary greatly, from multiple deformities to solely intellectual disabilities. This heterogeneity increased the challenges of evaluating the condition and providing prenatal genetic counseling to families. The Decipher database contains several cases of 8p23.1 duplication. However, there are only three cases (8:10001-12655629, 12.65 Mb) that are close to and smaller than our report (8:160000-16380000, 16.22 Mb). The Decipher IDs are [392337], [395697], and [399307]

(<https://decipher.sanger.ac.uk/>). These cases arise from imbalance from a balanced parental rearrangement, maternal inheritance constitutive in the mother, and unknown.

Here, we report a family with a 16.22 Mb duplication of 8p23.2p22 in both postnatal (II-1) and prenatal members (II-3), with a deletion in the same region in II-2. The chromosomal abnormality of the three members result from their father, a carrier of a balanced translocation of 8p22 and 22p13.

Methods

Molecular cytogenetics

G-banding of chromosomes and fluorescence *in situ* hybridization (FISH) were carried out using standard techniques. FISH was performed using 8pter (TelVysion 8p Spectrum Green), 8qter (TelVysion 8q Spectrum Orange), and 22qter (TelVysion 22q Spectrum Orange), obtained from the Abbott Laboratories.

Molecular Genetics

Chorionic villus analysis or amniocentesis was performed according to previously published procedures[9, 10]. DNeasy Blood and tissue kits (Qiagen) were used to extract the genomic DNA of chorionic villus and amniocytes, which was collected by centrifugation and washed with PBS. Quantitative fluorescence PCR (QF-PCR) was used as quality control to detect DNA contamination. Short tandem repeat (STR) markers were used for chromosome 21 (D21S1435, D21S1411, D21S11), chromosome 18 (D18S1002, D18S391, D18S535, D18S386), chromosome 13 (DXS981, DXS6809, DXS22), and the sex chromosomes X and Y, according to the previously described procedures.

CNV-seq was performed as previously described[11]. The CNVs identified (blast with hg19) were used to query public databases, including, DGV (<http://dgv.tcag.ca/dgv/app/home>), gnomAD (<https://gnomad.broadinstitute.org/>), Decipher (<https://decipher.sanger.ac.uk/>), OMIM (<https://www.omim.org/>), UCSC (<https://genome.ucsc.edu/>) and ClinGen (<https://dosage.clinicalgenome.org/>). Pathogenicity was assessed according to the latest guidelines outlined by the American College of Medical Genetics (ACMG)[12]. CNVs were classified as five levels: benign, likely benign, variants of uncertain significance (VUS), likely pathogenic, and pathogenic.

Clinical History

The pregnant woman is 35 years old with a history of three pregnancies. Her first child (II-1), a boy, was delivered after a normal pregnancy. At the age of one month, an ultrasound examination revealed that he has a ventricular septal defect (VSD), and he underwent minimally invasive surgery, with a successful outcome, at age four. He is currently 7.5 years old, and has normal intellectual and growth development, with a height of 128 cm and weight of 28.5 kg. However, a slightly delay of speech and language

development is apparent, in that he cannot distinguish between the flat tongue and warped tongue. This individual did not undergo genetic diagnosis before II-3 received a prenatal diagnosis. The second fetus (II-2) was found to have increased nuchal translucency (3.5 mm) at 12 weeks gestation, and was diagnosed prenatally using chorionic villus sampling and CNV-seq testing. The CNV-seq results showed a 16.22 Mb deletion on 8p23.2p22 (seq[hg19] 8p23.2p22 (160000- 16380000) x1), which is a pathogenic CNV including 8p23.1 deletion syndrome. The common phenotype of the syndrome is heart abnormality, atrioventricular canal defect, congenital diaphragmatic hernia, cryptorchidism, defects in the atrial septum, hyperactivity, and intellectual disability[13–15]. Therefore, the mother chose to terminate the pregnancy following genetic counseling. In her third pregnancy, although the ultrasound phenotype was normal, she came to our center for prenatal diagnosis and family analysis.

Results

The pedigree of the family is shown in Fig. 1A. The CNV-seq results showed that II-3 and II-1 have the same duplications (seq[hg19]8p23.2p22(160000-16380000)x3). Individual II-2 has a deletion of 8p23.2p22 (seq[hg19]8p23.2p22(160000-16380000)x1) (Fig. 1B). The results of both parents are normal (data not shown).

- banding analysis showed an addition to chromosome 22 in II-1 and II-3 (46,XN,add(22)), and a suspected balanced translocation of 8p22 and 22p11.2 in the father (I-1, 46,XY,t(8;22)(p22;p13)), all of which were confirmed using *FISH*(Figs. 2 and 3). The karyotype of the mother is normal (data not shown).

Discussion

As the father is the carrier of a balanced translocation (t(8;22)(p22;p13)), all three offspring inherited unbalanced chromosome abnormalities: II-2 an 8p23.2p22 deletion, and II-1 and II-3 8p23.2p22 duplications. The 16.22 Mb of 8p23.2p22 contains 81 protein-coding genes, including a large *defensin* cluster (23), and a haploinsufficiency gene *GATA4*. *GATA4* is related to atrial septal defect 2, atrioventricular septal defect 4, tetralogy of Fallot, and ventricular septal defect 1, in an autosomal dominant manner [OMIM,600576]. The 8p23.2p22 region contains 8p23.1 deletion syndrome and duplication syndrome. Barber *et al*/reported that the prevalence of 8p23.1 duplication syndrome is 1/58,000, which is the reciprocal of the 8p23.1 deletion syndrome [1] .

The common features of the 8p23.1 deletion syndrome are abnormalities of the heart, atrioventricular canal defect, congenital diaphragmatic hernia, cryptorchidism, defects in the atrial septum, hyperactivity, and intellectual disability [13–15]. In a prenatal case report, Guimiot showed maternal transmission of an interstitial 8p23.1 deletion of about 5.6 Mb to the fetus, which had a normal phenotype according to ultrasound at 20 weeks gestation, while the mother presented with moderate intellectual disability and underwent cardiac surgery for a ventricular septal defect [16]. Faivre reported a fetus with a diaphragmatic hernia at ultrasound, diagnosed with 8p23.1 deletion at 22 weeks gestation[17]. In this study, the second fetus with 8p23.2p22 deletion, was only found to have increased nuchal translucency

(3.5 mm) at 12 weeks of gestation, and labor was later induced. The prenatal phenotype of individuals with a 8p23.1 deletion, as determined by ultrasound, may vary greatly.

The common features of the 8p23.1 duplication syndrome are abnormal facial shape, behavioral and psychiatric abnormalities, delayed speech and language development, intellectual disability, and malformation of the heart and great vessels [2, 6]. However, the genetic heterogeneity of 8p23.1 duplication syndrome varies considerably. Barber *et al*/reported four probands with 8p23.1 duplications inherited from their normal parent. The size of the 8p23.1 duplication of the probands ranged from 438 kb to 802 kb, and the main phenotype was delayed development[1]. The minimal region of overlap was 776 kb from 10,167,881 to 10,943,836. Also, a considerable number of *de novo* cases are present in the Decipher data base. On cases of single CNVs, seven cases (3.05 Mb to 5.24 Mb) were selected (Decipher ID [255954],[300950],[322283],[258439],[290136],[262163],[356962]) (<https://decipher.sanger.ac.uk/search?q=8%3A160000-%2016380000#consented-patients/results>), the phenotype of the first five cases includes abnormalities of cardiovascular system, such as VSD or bicuspid aortic value, the nervous system, including mild global developmental delay, moderate expressive language delay, and intellectual disability, and abnormal facial shape. The other two cases had no clinical phenotype. Glancy and colleagues reported a duplication of 8p23.1p23.2 between 3,539,893 to 10,323,426 associated with speech delay, autism and learning difficulties[18].

Here, we reported two cases of 16.22 Mb duplications of 8p23.2p22 in one family. The first child (II-1) of the family is a 7.5 year old boy with normal growth and intellectual development and slightly delayed speech and language development. At the age of one month, ultrasound revealed that he has a VSD, and was followed by successful minimally invasive surgery at age four. He is currently in the first grade of elementary school and performs well. The genotype of II-3 is the same as that of II-1. II-3 did not have any apparent ultrasonic abnormality until 26 weeks of gestation. Due to the heterogeneity of 8p23.1 duplication syndrome and a lack of similar reported cases, it is difficult to evaluate the fetus' further phenotype. However, the mother is strongly motivated to keep the fetus. Following genetic counseling, she still intends to give birth on the expected date, 2020-07-17. This situation provides an excellent opportunity for observation of the growth and development the child after birth.

Conclusion

We reported a family that having a 16.22 Mb duplication of 8p23.2p22 associated with slightly delayed speech and language development postnatally (II-1), and the same duplication in a prenatal fetus (II-3) with a normal ultrasonic index. The same deletion is present in II-2, all arising from their father, a carrier of a translocation of 8p22 and 22q13. Our study makes a significant contribution to the literature because this relatively rare condition can have significant phenotypical consequences, and an understanding of the inheritance and variability of phenotypes caused by this mutation is essential to an increased understanding of the condition.

Abbreviations

CNV, copy number variation;

CNV-seq, CNV sequencing

VSD, ventricular septal defect

FISH, fluorescence *in situ* hybridization

Declarations

Ethics approval and content to participate

All subjects provided informed consent for prenatal genetic investigation, and the II-1 is a 7.5-years-old boy, who' consent to participate was obtained from his parents. And the research was approved by the Zhengzhou University Ethics Committee (approval #KS-2018-KY-36).

Content to publication

Written informed consent was obtained from the parents of the patient for publication of this article. The parents consent for the publication of their medical data and images.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

None declared.

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Authors' contributions

XK, PS, CW designed the study. YZ performed the experiments and analyzed the data. PS, CW and XK drafted the manuscript and all authors contributed to editorial changes.

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Figures

Figure 1

The pedigree of the family and the CNV-seq results of II-1,II-2, and II-3. The parent results is normal and not showed.

Figure 2

The G-band karyotype of I-1,II-1, and II-3. The mother 'result is normal and not showed, and the II-2 sample is chronic villi and not done the G-band experiment.

A

Figure 3

The representative FISH results in I-1, II-1, and II-3.