A Rare Novel Copy Number Variation of Xp22.33-p11.22 Duplication is Associated with Congenital Heart Defects

Juan Zhang, Qing-Qing Wu, Li Wang, Li-Juan Sun

Department of Ultrasound, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing 100026, China

Key words: Congenital Heart Defects; Copy Number Variations; Chromosomal Duplication; Prenatal Ultrasonic Diagnosis

Congenital heart defect (CHD) is the most common fetal defects. Copy number variations (CNVs) were demonstrated to be involved in the etiology of CHDs. We report three cases from a family diagnosed as CHDs with a rare novel duplication of Xp22.33-p11.22.

A 30-year-old woman, gravida 2 para 0. Her first pregnancy at 2012 was diagnosed to be dichorionic twin pregnancy and her second pregnancy at 2014 was a singleton pregnancy. After a routine ultrasound scan at 22 week's gestation, all the fetuses were diagnosed with critical CHDs. The first fetus (male) exhibited tetralogy of Fallot, atrial septal defect, persistent left superior vena cava, and coronary sinus dilatation while the examination of the second fetus (male) revealed atrioventricular septal defect and hypoplastic left heart syndrome. The third fetus (female) was also diagnosed with an atrioventricular septal defect and hypoplastic left heart syndrome. The parents decided to terminate the pregnancy.

All the fetuses received prenatal diagnostic testing. Conventional G-band karyotype analysis revealed normal karyotypes of the fetuses. Then the chromosomal microarray analysis was performed to detect the pathological CNVs. There is a rare novel 52.9 Mb CNV of chromosome Xp22.33-p11.2 duplication in the three patients. Conventional G-band karyotype analysis and chromosomal microarray analysis on the parents showed they are normal individuals. All the clinical features and prenatal diagnostic testing results of the three fetuses were shown in Figure 1. This study was approved by the Ethics Committees of Beijing Obstetrics and Gynecology Hospital, Capital Medical University. The pregnant woman provided written informed consent to participate in this study.

Pathological CNVs contribute to human genetic variation which is accounting for congenital malformations; a large-scale study revealed the detection rate of genetic aberration in CHD was approximately 8–13%.[1] It is known that chromosome Xp duplication syndrome contributes to mental retardation and speech delay.[2] No powerful evidence for the association of duplication of Xp22.33-p11.22 with CHDs can be found from the literature. Our study revealed a rare novel Xp22.33-p11.22 duplication might contribute to the severe CHDs of the cases.

In the present study, the 52.9 Mb Xp22.33-p11.22 duplications encompasses 256 OMIM genes. The potential mechanism might

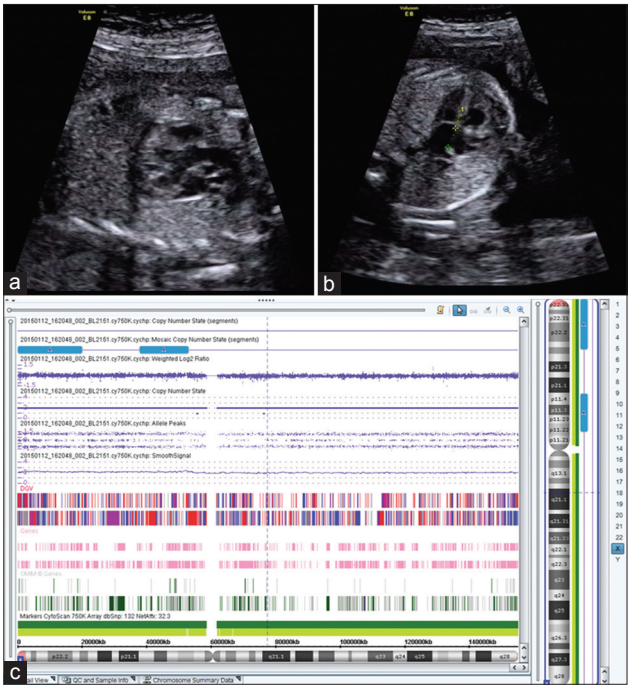

Figure 1: The abnormal findings of ultrasound screening and chromosomal microarray analysis. (a) Left ventricular outflow tract view shows aortic overriding and ventricular septal defect; (b) The four-chamber view shows atrioventricular septal defect; (c) Chromosomal microarray analysis of patient 3. The result reveals a 52.9 Mb duplication of Xp22.33-p11.22 (168,551–53,101,386).

Address for correspondence: Dr. Qing-Qing Wu, Department of Ultrasound, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, No. 251 Yaojiayuan Road, Chaoyang District, Beijing 100026, China
E-Mail: wuqq2013@163.com

Received: 12-07-2015 **Edited by:** Li-Shao Guo
How to cite this article: Zhang J, Wu QQ, Wang L, Sun LJ. A Rare Novel Copy Number Variation of Xp22.33-p11.22 Duplication is Associated with Congenital Heart Defects. Chin Med J 2015;128:2829-30.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.167369

be explained by the copy number alteration of the dosage-sensitive gene(s) while gene disruption, triplosensitivity, and gene fusion at breakpoints may also be the underlining mechanisms of duplications CNVs.[1,3]

In addition, this nonconsanguineous marriage consecutively produced 3 similar genetic aberrations while the parents in our study showed normal karyotype and normal chip results. These results suggested that the duplication of Xp22.33-p11.22 might be a de novo mutation of the parents' germ cells. Since the father cannot transmit an X chromosome to the male fetuses, the mother may produce the mutation in her germline. Xp duplication in males is often inherited from maternal. This CNV may be a *de novo* mutation during the meiosis of the oocyte.[4]

In consideration of the illegitimacy of antenatal fetal gender authentication without medical purposes in China, the chromosome aberrations of the sex chromosome are usually ignored. Our study adds a new dimension to the etiology of CHDs.

Financial support and sponsorship

This work was supported by grants from the National Natural Science Foundation of China (No. 81071159), Beijing Municipal Science and Technology Commission (No. Z141107002514006) and Beijing Municipal Administration of Hospital Clinical Medicine Development of Special Foundation (No. XMLX201310).

Conflicts of interest

There are no conflicts of interest.

References

1. Hillman SC, Mc Mullan DJ, Hall G, Togneri FS, James N, Maher EJ, *et al.* Use of prenatal chromosomal microarray: Prospective cohort study and systematic review and meta-analysis. Ultrasound Obstet Gynecol 2013;41:610-20.
2. Salaria M, Burgess T, Setyapranata S, Winship I. Phenotype in novel Xp duplication. Am J Med Genet A 2012;158A:2342-6.
3. Newman S, Hermetz KE, Weckselblatt B, Rudd MK. Next-generation sequencing of duplication CNVs reveals that most are tandem and some create fusion genes at breakpoints. Am J Hum Genet 2015;96:208-20.
4. Samuels ME, Friedman JM. Genetic mosaics and the germ line lineage. Genes (Basel) 2015;6:216-37.