

Prader-willi syndrome: A case report and a Chinese literature review

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Summary

Prader-Willi syndrome (PWS) is a genetic disorder, resulting from lack of gene expression on the paternally inherited chromosome 15. It is important to determine diagnostic methods for PWS for early treatment. In this study, we report a newborn with Prader-willi syndrome. We further summarized the genetic testing results in the Chinese literature and the relevance of high resolution chromosome and genome-wide copy number variation analysis. There is a heterozygosis deletion of a 5 Mb region in the paternal chromosome 15q11.3-q13.3 by genome-wide copy number variation analysis. However, there is no abnormality in high resolution chromosome karyotype analysis. In conclusion, genome-wide copy number variation analysis is an effective and specific diagnosis method, which will provide scientific evidence for the clinical diagnosis and early treatment of PWS.

Keywords: Prader-Willi syndrome, genome-wide copy number variation analysis, high resolution chromosome gene imprinting

1. Introduction

Prader-Willi syndrome (PWS) is a complex genetic disorder, characterized by neonatal hypotonia, delayed development, short stature, childhood obesity, hypogonadism, characteristic facial features, and so on (1). It is a genomic imprinting disorder caused by a deficiency of paternally expressed gene or genes in chromosome 15 (15q11.3-q13.3 region) (2). This region contains genes that are epigenetically imprinted. A recent foreign study has shown that the prevalence of PWS is 1/29,000 in newborns (3).

Although an accurate consensus of clinical diagnostic criteria exist, it is difficult to make the diagnosis on many patients who are too young to manifest sufficient features, particularly at an early age. The clinical symptoms are difficult to diagnose in infants and only become clearer at later ages as the patients develop hyperphagia and morbid obesity. Therefore, further

genetic testing is important to confirm the diagnosis of PWS for all patients. Cytogenetic and molecular genetic diagnosis can confirm PWS at an early stage and provide useful information for the genetic counseling of PWS families. In our study, the child was observed from the prenatal motherhood. We found that there is weak quickening, fewer fetal movements at 39 weeks and intrauterine distress during the pregnancy. The male child was born by cesarean delivery and studied by cytogenetics and genome-wide copy number variation analysis.

2. Case report

The Characteristics of the Object. The male neonatal was clinically suspected to be a PWS patient. This patient is the first child of his parents. There was weak quickening, fewer fetal movements at 39 weeks and intrauterine distress during the pregnancy. Therefore he was born by cesarean delivery and his birth weight was only 2.8 kg. Furthermore, his Apgar score was 3.

Genome-wide copy number variation analysis. Informed consent was obtained from the parents of the patient. The peripheral blood of the patient and his parents were taken for normal chromosome and high

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resolution chromosome G banding (4). Meanwhile, the blood genomic DNA was isolated by the standard phenol/chloroform method and then tested by genome-wide copy number variation analysis using the Illumina HumanCyto SNP-12 Beadchip.

This patient has low muscle tone, little limb activity, low crying and crying like a cat call syndrome, poor sucking force, feeding difficulties and a characteristic face, which are basically according to the clinical diagnosis standards. The characteristics including white skin color, narrow face, small jaw, almond eyes, small mouth, thin upper lip and convex, angle downward, low ear, slightly larger head, small hands and feet compared to the standard, short torso, lack of wrist radian in both ulnar sides of upper limbs, limited outreach, reproductive organs dysplasia, bilateral cryptorchidism, slightly thin limbs and flat belly. However, the intelligence and appearance of his parents are normal and there are no relatives with similar manifestations compared to the patient.

In this study, we found that there was a deletion of a 5 Mb region in chromosome 15q11.3-q13.3 in this patient by genome-wide copy number variation analysis (Figure 1). Furthermore, it was a regional deletion in paternal chromosome 15q11-q13 in this PWS patient, but there were no abnormalities in conventional karyotype and high resolution chromosome analysis.

Through clinical follow-up, after 1 to 3 months, the child had obvious symptoms, including feeding difficulties, poor sucking, poor physical activity, low and weak cry, and drowsiness. After 6-8 months, appetite was improved. Weight was increasing rapidly, but growth in height was slow. At the age of 1, the child had characteristics of the typical face such as narrow forehead, and almond eyes. Weight was gained rapidly, and intelligence quality was low.

3. Discussion

FPWS is a hereditary disease associated with genomic imprinting. The several mechanisms of PWS include: *i*) a paternally derived large deletion of 15q11-q13, accounting for 70% of all patients; *ii*) a maternal uniparental disomy, accounting for approximately 20%-25%; *iii*) a defect in the genomic imprinting mechanism, about 2%-4%; and *iv*) other rare reasons, such as chromosome translocation and microdeletion, less than 1%.

PWS is considered as the most common cause of life-threatening obesity. As a genetic syndrome, there is no effective treatment method for PWS. In the clinic, we should pay attention if the baby has unexplained low muscle tone, weak sucking force, feeding difficulties, and delayed puberty with moderate mental retardation (5). The diagnostic basis for this disease is genetic techniques, which provide an important guiding significance for genetic disease screening and prenatal diagnosis. Therefore, the suspected newborn should have early gene analysis in order to avoid misdiagnosis. In addition, PWS cases do have a significant recurrence risk not only for the relevant parent, but also for certain close relatives, thus it is important to determine the exact molecular defect in addition to the general diagnosis of PWS.

Prenatal diagnosis of PWS is difficult. For the doctor it is very difficult to assess the risk of PWS occurrence during pregnancy for the delivery of PWS child couples (6). In order for better genetic counseling, we should carry out ultrasound images to analyze fetal movements during pregnancy. In this study, the activity of the child was weak in his mother's womb before birth. We should further take villi or amniotic fluid cells for molecular diagnosis.

Molecular genetic tests are able to definitively diagnose PWS and allow early diagnosis of the

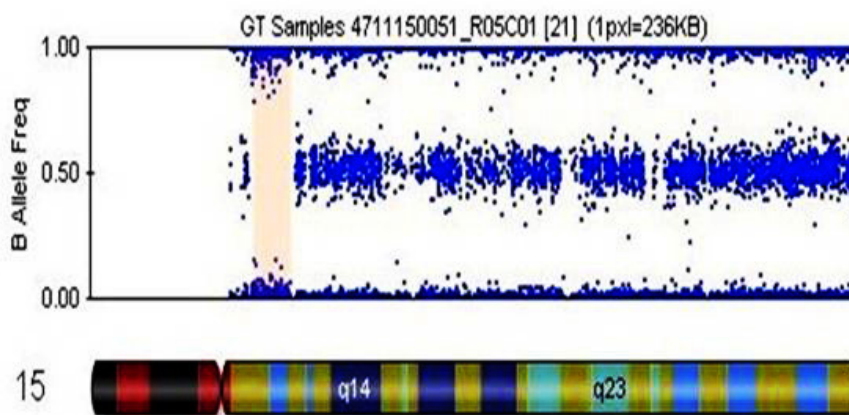


Figure 1. This figure shows a schematic diagram of chromosome 5. Red areas shown are the deletion region (2120838726210229), of 5 Mb, located in 15q11.3-13.3.

Table 1. The Method of Molecular Genetic Tests Reported in China

Methods	Number of reports	Location	Result of testing
Bisulphate sequencing	1	chromosome 15q11.2	Abnormal methylation of the CpG islands
Fluorescence in situ hybridization (FISH)	1	chromosome 15q11.2	Small deletion
Methylation-specific PCR (MSPCR)	9	chromosome 15q11-13	Small deletion
Multiplex ligation dependent probe amplification (MLPA)	2	chromosome 15q11-13	Small deletion
Short tandem repeat linkage analysis (STR)	1	chromosome 15q11-13	Small deletion

syndrome. So far, detection methods for PWS include high resolution banding (HRB), fluorescence in situ hybridization (FISH), methylation-specific PCR (MSPCR), multiplex ligation dependent probe amplification (MLPA), short tandem repeat (STR) linkage analysis, microsatellite analysis, Southern blots, and so on (7,8). Shen *et al.* found abnormal methylation of the CpG islands in the *SNRPN* gene locus in a PWS patient using bisulphate sequencing (7). Che *et al.* recently reported a PWS case using FISH, which showed a gene deletion in chromosome 15 q11.2 (9). Furthermore, a previous study showed that FISH and MSPCR when applied to 4 clinically suspected PWS patients and molecular pathogenesis of them had paternal micro-deletions of 15q11-q13 or maternal uniparental disomy of chromosome 15 (10). However, FISH cannot detect uniparental disomy or imprinting mutations. MSPCR is a sensitive, efficient, specific and convenient assay for detecting PWS. Recently, Gao *et al.* diagnosed a PWS patient with MSPCR and suggested that the clinician should diagnose suspected PWS patients with a methylation test and assure timely intervention (11). Previous studies showed that only MSPCR could detect deletion, uniparental disomy and imprinting defects. Therefore, 99% of PWS could be diagnosed by MSPCR (12-14). Compared to MSPCR, MLPA assays can be applied to clarify the pathogenesis and provide a scientific basis for clinical diagnosis (15). MLPA's high sensitivity and specificity for deletion detection is the same as the "gold standard", such as FISH analysis or Southern blot based methylation analysis. Moreover, a recent study showed that short tandem repeat (STR) linkage analysis can identify the molecular defect of PWS cases quickly and accurately (16). With more STR loci analyzed and their polymorphism information content obtained, this linkage analysis method could be used for a potential diagnosis in PWS cases. In addition, Li *et al.* established a linkage analysis method for Chinese patients. This method can detect both deletion and uniparental disomy, thus providing valuable information for genetic counseling and the opportunity to analyze the relationship between the PWS genotype and phenotype (17). In our study, we found that genome-wide copy number variation analysis is an

effective and specific diagnostic method for PWS (Table 1).

With improved recognition and availability of testing methodologies, PWS is being diagnosed earlier, often in the first few months of life. Earlier diagnosis allowing for earlier access to developmental resources, recombinant human growth hormone therapy, and anticipatory guidance, has significantly improved the long-term health and developmental outcomes of children with PWS (18).

In conclusion, we found that genome-wide copy number variation analysis is an effective and specific diagnostic method, which will provide a guide for the clinical diagnosis and early treatment of PWS. Early diagnosis and comprehensive care of PWS patients have improved outcomes. However, areas where further research is needed include the etiology and management of PWS.

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