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# Unveiling a rare genetic aberration: A case study of Prader-Willi syndrome (PWS) with atypical 15q11.2-q13.3 deletion

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## Abstract

Prader-Willi Syndrome (PWS) is a rare genetic disorder resulting from the absence of expression of genes in the 15q11–q13 region on the paternally derived chromosome 15. The present case report describes the chromosomal anomalies suspected to be present in a neonate, detected using Chromosomal Microarray analysis, an advanced platform for genetic analysis. Whole blood sample of the patient was analysed to reveal a pathogenic deletion spanning the region 15q11.2–q13.3; a rare and extended deletion involving breakpoints BP1 to BP5. The identification of this atypical deletion underscores the importance of precise genetic characterization in PWS diagnosis. Early detection through cutting-edge genetic testing enables timely intervention and management of associated abnormalities, highlighting the significance of integrating advanced genomic analysis into clinical practice. The current study contributes to the growing understanding of PWS genetics and emphasizes the need for comprehensive genetic evaluation in patients with suspected PWS.

## Introduction

Prader-Willi Syndrome (PWS) is a rare, complex neurogenetic disorder resulting from the absence of expression of paternally inherited genes in the proximal long arm of chromosome 15, specifically the 15q11–q13 locus (Bittel et al., 2005). PWS and Angelman Syndrome (AS) are attributable to distinctive chromosomal abnormalities triggering developmental disorders resulting from defects in imprinted genes on the 15q11–q13 chromosomal segment. Causative factors of PWS include type I and II paternal deletions (50%), maternal uniparental disomy (43%), imprinting defects (4%) or translocations (<1%). Seldom, atypical deletions which are smaller or larger than the typical forms have been noted in literature (Horsthemke et al., 2008; Buiting, 2010).

Genetic abnormalities may contribute to recurrent miscarriages and congenital anomalies, warranting testing of both parents and fetal or placental tissue (Kacprzak et al., 2016). Chromosomal microarray (CMA) offers high-resolution detection of submicroscopic genomic deletions or duplications, termed copy number variants (CNVs), according to The American College of Obstetricians and Gynecologists report. This report of a neonate highlights a case of early detection of an atypical, extended deletion in the 15q11.2–q13.3 region involving breakpoints BP1 to BP5 associated with PWS using CMA platform.

## Case Report

*Clinical manifestation*

A 11 days old male, born late preterm (35+1 weeks of gestation), via emergency caesarean section due to abnormal doppler findings, was small for gestational age- weighing 1.755 kg.The baby cried immediately after birth. Apgar score was undocumented. Vital signs included heart rate of 156/minute , respiratory rate of 56/minute, and a blood pressure of 56/44 mmHg. Poor respiratory efforts prompted the usage of positive pressure ventilation (PPV) to ensure optimal oxygen delivery. Chest examination revealed hyperinflation on the right, reduced movements, and decreased air entry. The neonate exhibited hypotonia, absent spontaneous movement, undescended testes, hypoplastic scrotum, retrognathia, long fingers, hammer toes, bilateral pes cavus, and diminished deep tendon reflexes. Chest X-ray confirmed a right-sided pneumothorax. Neurological examination revealed muscle power to be 2/5 in the upper and 3/5 in the lower limbs, with poor foot dorsiflexion.

*Maternal history*

The mother, aged 29 years, with an obstetric score of G2P1L1, has a healthy 2 year old female child. The present pregnancy (non-consanguinous) was spontaneous, and included regular antenatal checks. Scans revealed ventriculomegaly and polyhydramnios. There was no maternal history of genetic disorders or neuromuscular diseases in the family.

*Clinical management*

Respiratory distress with right-sided pneumothorax was managed with intercostal drainage (ICD) for 48 hours. The patient was put on ventilator support owing to shallow breathing, increased repiratory rate, acidosis and low blood oxygen levels. On examination, the baby was noted to be hypotonic, with no spontaneous

movements and no eye opening. Enlarged ventricles and hyperintensity in the corona radiata were confirmed by a neurosonogram. Upon strong suspicion of a genetic abnormality, a Chromosomal Microarray Test was opted for.

## Material and methods

Genomic DNA was extracted from EDTA-anticoagulated whole blood and DNA quantification was performed using the Qubit HS DNA assay (Qiagen Kit). Microarray analysis employed the Affymetrix Cytoscan Optima platform, which includes over 148,450 SNP (Single Nucleotide Polymorphism) probes. The DNA underwent enzymatic digestion, ligation, amplification, hybridization to the array, staining, and scanning. Data was analyzed using Chromosome Analysis Suite (ChAS) software with sensitivity and specificity of 98.6% and 99%, respectively, ensuring accurate detection of genomic variations.

## Results and Discussion

Chromosomal Microarray analysis revealed a pathogenic interstitial deletion in chromosome 15 with ISCN arr[hg19] 15q11.2q13.3(24,017,423-32,216,234)x1 as per the International System for Human Cytogenomic Nomenclature.

Typical PWS deletion ranges from 15q11.2-q13 (Figure 1). The present case showed a large interstitial deletion involving breakpoint BP1 to breakpoint BP5, measuring approximately 8.2MB in the q11.2-q13.3 region of chromosome 15, covering different coding regions, non-imprinted regions along with snoRNAs: KLF13, FAN1, CHRFAM7A, PWRN1, NPAP1, IPW, PWRN2, PWAR5, PWAR1, NDNL2, MIR211, SNORD116-1, SNORD115-1, TRPM1, SNRPN, TJP1, UBE3A, GABRA5, GABRB3, HERC2, APBA2, ATP10A, OTUD7A, OCA2, GABRG3 (Fig. 2). The deletion covers critical genomic regions typically associated with Prader-Willi syndrome (PWS), including the SNRPN and SNORD116-1/SNORD115-1 clusters, which play pivotal role in regulating gene expression and chromatin structure. The large interstitial deletion indicated a complex genomic rearrangement with potential implications for gene dosage, expression and phenotypic outcomes.

PWS is an uncommon genetic disorder characterized by hypothalamic dysfunction, resulting in physical, endocrine, and neurological disorders, in addition to hyperphagia (Bantim et al., 2019; Bailleul-Forestier et al., 2008). Diagnosis is based on specific clinical features, confirmed by genetic testing. Typical PWS deletions manifest as a large type I deletion (involves BP1-BP 3; ~6MB) or a smaller type II deletion (covers 2 distal BPs – BP2-BP3; ~5.6MB). Atypical larger deletions are rare and involve more distal breakpoints BP4 and BP5. The current report illustrates an atypical PWS with an expanded deletion of 15q11.2-q13.3 and loss of expression of paternal genes in this region. This results in loss of expression of genes responsible for neurodevelopment, along with behavioural changes, hypotonia, hypogonadal, dental caries, skeletal abnormalities. PWS presents with neonatal hypotonia, hyperphagia, obesity, global developmental delay, mild intellectual disability, hypogonadism, and a distinctive behavioral phenotype, which includes temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive behavior. Due to the deletion enveloping 15q distal breakpoints BP4 or BP5, instead of the typical BP3, additional cardiac, renal, neurological abnormalities, palatal defects,

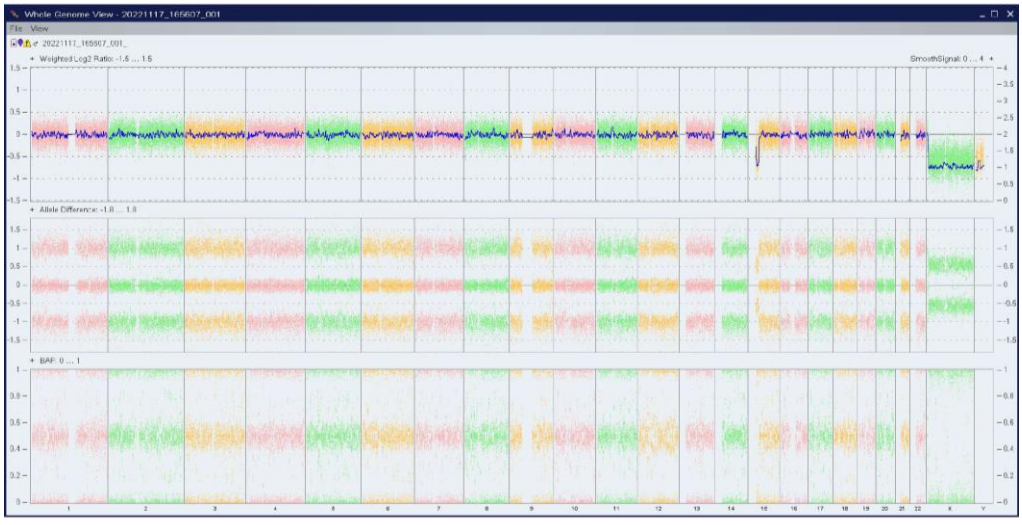

**Figure 1.** Whole chromosome Allelic View

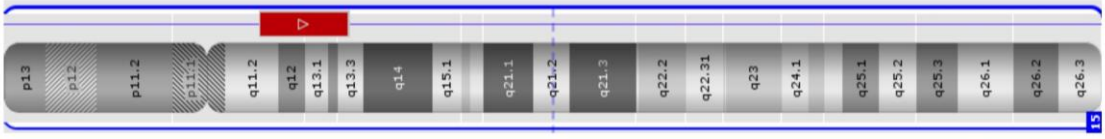


**Figure 2.** Chromosome 15 view with interstitial deletion region

etc., were observed, reiterating the clinicogenetic correlation. These findings suggest that the larger deletion may contribute to a more severe and variable phenotype, underscoring the importance of precise genetic characterization in PWS diagnosis.

In addition, it highlights the significance of chromosomal microarray in detecting atypical deletions and underscores the need for long-term follow-up and management of individuals with PWS, particularly those with rare and expanded deletions.

The clinical and genetic findings in this case contribute to the growing body of literature on the genotype-phenotype correlations in PWS and have implications for genetic counseling, clinical management and research into the molecular mechanism underlying this complex disorder.

## Conclusion

PWS is a complex, heterogeneous disease that has a profound effect on the lives of affected individuals and their families. The implementation of advanced genetic testing methodologies, such as Chromosomal microarray (CMA), enables early detection and precise diagnosis, thereby facilitating timely interventions with employment of a meticulous multidisciplinary approach and significantly improving patient outcomes. By leveraging cutting-edge technologies, clinicians can provide targeted care and improved mangement strategies, ultimately enhancing the quality of life for individuals affected by PWS.

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## Authors' contributions

**S. Ramalingam:**

Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Roles/Writing – original draft; and Writing – review & editing.

**G. Srividya:**

Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Roles/Writing – original draft; and Writing – review & editing.

**K. Jayaswathi:**

Writing – review & editing.

**V. Jayaraj:**

Supervision; Roles/Writing – original draft.

**M. Mariyappa:**

Conceptualization, Funding acquisition; Project administration; Resources; Supervision;and Writing – review & editing.

## Conflict of interest

No conflict of interest was declared by the authors.

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