

Introduction

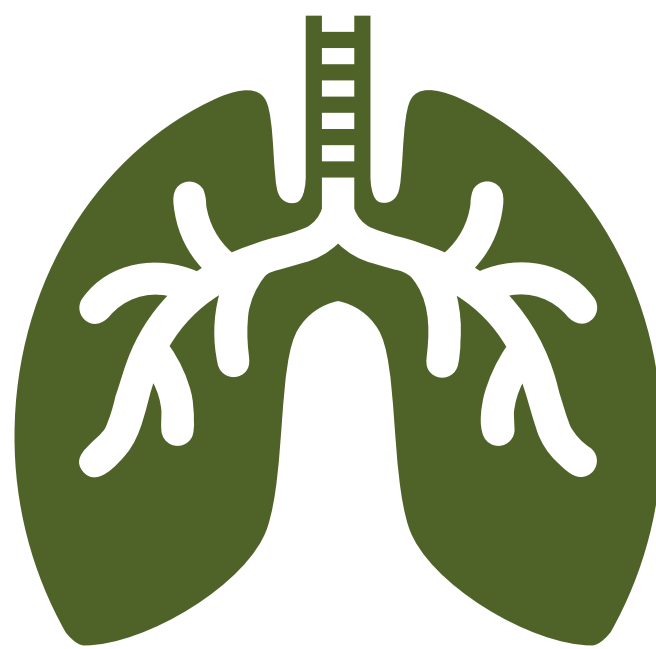
- Prader Willi Syndrome (PWS) is a complex disorder involving defects of imprinting at the paternal 15q11.2-q13 locus.
- Clinical features vary widely but include neonatal hypotonia, transient feeding difficulty, developmental delay/intellectual disability, hyperphagia, and dysmorphic facial features that may not be apparent in infancy.

- The average age of diagnosis varies by source but has been reported to be between 8 weeks to early childhood^{1,2,3}.
- DNA methylation analysis is the gold standard for PWS assessment, but typically takes several weeks to complete.

- Genome sequencing (GS) is a comprehensive genetic testing method that can be performed rapidly. We demonstrate in two cases here that it can detect PWS prior to clear clinical suspicion.**

Case 1

- A term male presented on day of life 1 with encephalopathy, hypotonia, and apnea requiring ventilator support.
- There was a persistent requirement for ventilatory support without a clear cause. Infectious workup was negative.
- Clinical instability prohibited thorough physical exams and additional diagnostic steps.
- Due to the broad differential for these features in the setting of severe clinical instability, rapid trio GS was sent at 6 days of life.



Case 1 Diagnostic Results

RESULTS

POSITIVE FINDINGS

DISEASE	INHERITANCE PATTERN	GENE/VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
15q11.2q13.1 Deletion	Autosomal Dominant	15q11.2q13.1:HG38 chr15:23370904-28318200DEL 4947.3(kb)	Copy Number Variant	Heterozygous	De Novo	Pathogenic

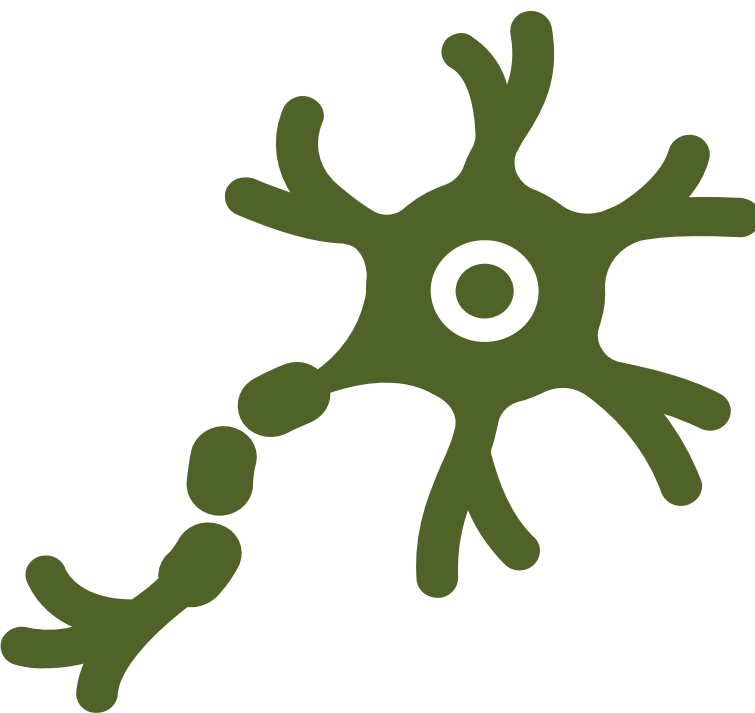
RESULTS SUMMARY

A de novo heterozygous pathogenic deletion in chromosome bands 15q11.2q13.1 was detected. The genome data indicate this deletion occurred on the paternal allele, suggestive of a diagnosis of Prader-Willi syndrome.

Time to diagnosis: 8 days

Case 2

- A term male first presented at 10 weeks old with hypotonia and failure to thrive.
- Persistent poor oral motor skills since birth and global developmental delay were both observed.
- Physical exam showed nonspecific dysmorphic craniofacial features and profound global hypotonia .
- Due to the broad differential for neuromuscular genetic etiologies and the potential for identifying an actionable cause, rapid trio GS was sent at 11 weeks of life.



Case 2 Diagnostic Results

RESULTS

POSITIVE FINDINGS

DISEASE	INHERITANCE PATTERN	GENE/VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
15q11.2q13.1 Deletion	Autosomal Dominant	:chr15:23304900-28293509DEL 4988.61(kb)	Copy Number Variant	Heterozygous	De Novo	Pathogenic

RESULTS SUMMARY

Heterozygous De Novo Pathogenic Copy Number Loss involving chromosome bands 15q11.2q13.1 detected. Genome sequencing analysis also shows this copy number loss variant is on paternally inherited chromosome 15. This finding is consistent with a diagnosis of Prader-Willi syndrome in this individual.

Contiguous Regions of Homozygosity (ROH) greater than 5 Mb was detected in chromosome 15, which is consistent with the copy number loss observed in 15q11.2q13.1. Coordinates of the ROH region are listed below.
chr15:2306956-28456900

Time to diagnosis: 5 days

Discussion

- While neonatal hypotonia can be a strong clinical indicator of PWS, other features are highly variable and can obscure diagnosis.
- In some cases, more expansive and rapid testing is indicated.

- GS is emerging as the optimal test choice in patients with critical illness and complex features due to its comprehensive interrogation of single gene disorders, copy number variants, and added utility in parental allele identification.

- We demonstrated in two unique cases that rapid GS was able to provide a timely diagnosis of PWS that directly impacted clinical management while simultaneously ruling out other causes of their neurological deficits.**

References

- [1] Trifirò, G., Livieri, C., Bosio, L., Gargantini, L., Corrias, A., Pozzan, G., Crinò, A., & Genetic Obesity Study Group of the Italian Society of Paediatric Endocrinology and Diabetology (2003). Neonatal hypotonia: don't forget the Prader-Willi syndrome. Acta paediatrica (Oslo, Norway : 1992), 92(9), 1085–1089. <https://doi.org/10.1080/08035250310004810>
- [2] Lioni, T., Reid, S. M., White, S. M., & Rowell, M. M. (2015). A population-based profile of 160 Australians with Prader-Willi syndrome: trends in diagnosis, birth prevalence and birth characteristics. American journal of medical genetics. Part A, 167A(2), 371–378. <https://doi.org/10.1002/ajmg.a.36845>
- [3] Ahakoud, M., Daha Belghiti, H., Nedbour, A., Bouramtane, A., Chaouki, S., Bouguenouch, L., & Ouldim, K. (2023). The Diagnosis and Genetic Mechanisms of Prader-Willi Syndrome: Findings From a Moroccan Population Study. Cureus, 15(4), e37866. <https://doi.org/10.7759/cureus.37866>