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GenomeNext™
CASE STUDY
OCA2

Whole Genome Sequencing Unravels Complex Structural Rearrangement Undetectable by Exome Sequencing

CASE STUDY

Clinical Scenario

- 6-month-old female presents with a clinical diagnosis of oculocutaneous albinism[1]
- Prior workup included albinism panel testing at two different clinical laboratories, with deletion/duplication included in the second panel
- Both panels indicated carrier status for oculocutaneous albinism II as a result of a heterozygous *OCA2* pathogenic variant (c.1465A>G (p.Asn489Asp))

Clinical Features

Hypopigmentation

Nystagmus

Genetic Testing

Provider ordered **GenomeNext**

Whole-genome sequencing (WGS) performed to check for a potential missed pathogenic variant in *OCA2*

RESULT DETAILS

- Identified a second pathogenic variant in trans with the previously identified pathogenic *OCA2* variant (c.1465A>G (p.Asn489Asp)).
- Second pathogenic variant was a complex copy neutral rearrangement: a deletion and inverted reinsertion of exons 3-19 within intron 1.
- This complex rearrangement accounts for 2-3% of pathogenic *OCA2* variants.[2] It is undetectable by exome sequencing because it is a deep intronic rearrangement (all breakpoints are in introns) that maintains a copy number neutral exonic sequence.

Using WGS to Provide More Answers

Identification of a second pathogenic variant confirmed the genetic basis of the clinical diagnosis.

Family used this information to pursue in-vitro fertilization and perform preimplantation genetic testing for a subsequent pregnancy.

Points For Your Practice

Recognize that traditional exome sequencing detects up to 85% of pathogenic variants[3] but frequently misses complex structural rearrangements.

Consider utilizing WGS as a first-tier diagnostic tool or a follow-up for negative exome results to achieve more comprehensive variant detection across both coding and non-coding regions.

Based on information from an actual patient case; individual identifiers have been modified to protect patient privacy

References
1. Berger SI, Pitsava G, Cohen AJ, et al. Increased diagnostic yield from negative whole genome-slice panels using automated reanalysis. Clin Genet. 2023;104(3):377-383. doi:10.1111/cge.14360
2. Loftus SK, Lundh L, Watkins-Chow DE, et al. A custom capture sequence approach for oculocutaneous albinism identifies structural variant alleles at the OCA2 locus. Hum Mutat. 2021;42(10):1239-1253. doi:10.1002/humu.24257
3. https://www.illumina.com/techniques/sequencing/dna-sequencing/targeted-resequencing/exome-sequencing.html

1 Enterprise, Aliso Viejo, CA 92656 USA Toll Free +1.866.262.7943 Fax +1.949.900.5501 **ambrygen.com**

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