Whole Genome Sequencing Captures Additional Variants in the Pediatric Neurology Population

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INTRODUCTION

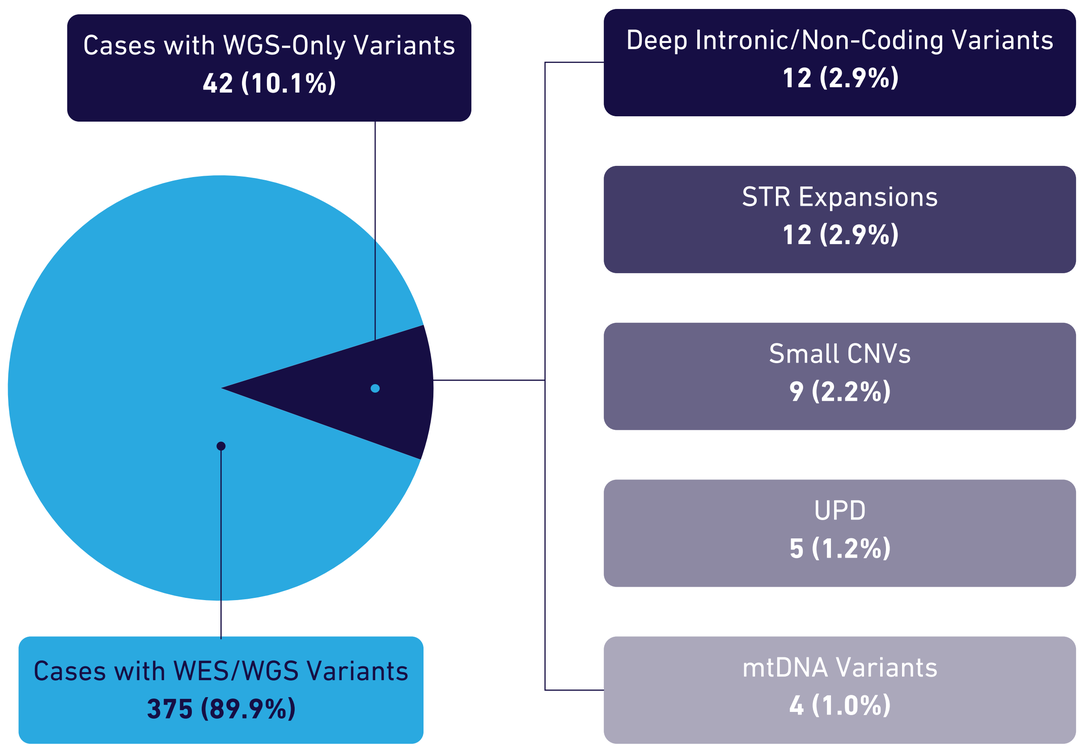
- **Up to 50% of neurology-related indications have a genetic cause[1]**
- Whole genome sequencing (WGS) and whole exome sequencing (WES) offer higher diagnostic yields than traditional sequencing methods such as multigene panels[1]
- **WGS can capture types of variants that WES can miss**, leading to WGS having an increased diagnostic yield even over WES
- There are limited data on the percentage of variants that WGS captures above WES specifically within the pediatric neurology population
- We present our clinical laboratory's experience with WGS-identified findings in the pediatric neurology population

METHODS

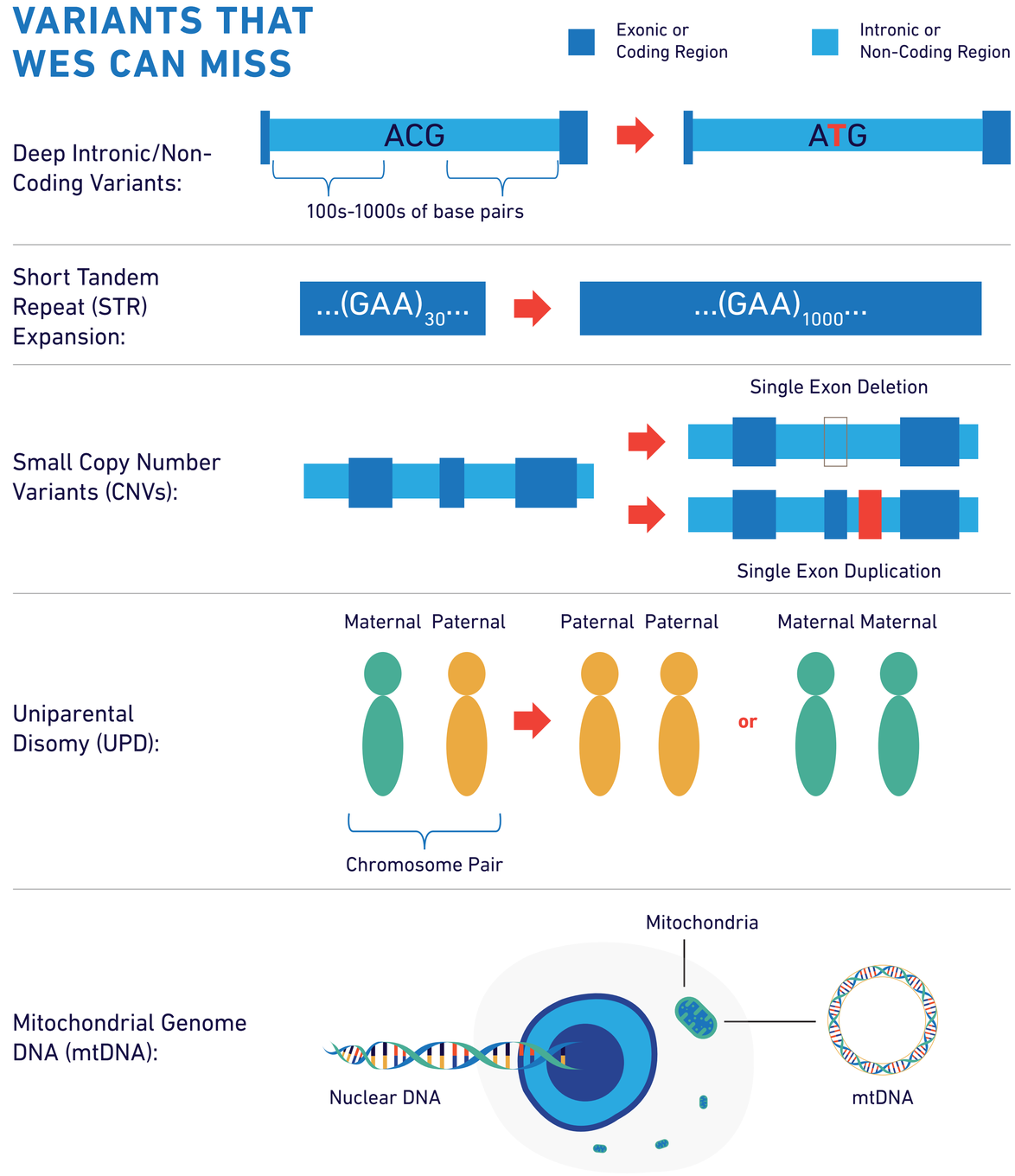
- Retrospective review of consecutive pediatric patients (<18 years) with at least one neurology-related indication that had a positive clinical WGS (one or more pathogenic or likely pathogenic variants associated with their phenotype) at our laboratory
- These results were further evaluated to determine which variants would be expected to be captured by WGS but not by WES or other targeted sequencing methods

RESULTS

- Within the pediatric neurology cohort reviewed, 417 received a positive result by WGS
- Among positive cases, **42 (10.1%) had a positive result for variant(s) not expected to be captured by WES**



VARIANTS THAT WES CAN MISS



Variant Type	Gene/Variant	Condition	Limitations of WES/ Other Testing
Deep Intronic/ Non-Coding Variants	*RNU4-2* - n.64_65insT *RNU4-2* is a non-coding gene	ReNU syndrome **(newly described)**	Most WES and panels only assess variants within coding regions or exon/intron boundaries (~20bp from exons)
STR Expansions	*FXN* - ~880/~1200 GAA repeats	Friedreich ataxia	Sequencing generally cannot accurately capture the number of tandem repeats – other assays like PCR or Southern blot needed
Small CNVs	*CASK* - duplication of exon 3 (31.5 Kb)	Intellectual disability disorder	Sequencing often can capture CNVs 3 exons or greater in size, but can miss smaller ones
Uniparental Disomy (UPD)	Maternal UPD 15	Prader-Willi syndrome	Need to sequence or use another assay on proband and parental DNA to identify UPD
Mitochondrial Variants	*MT-TK* - n.69G>A, homoplasmic	MELAS/Leigh syndrome	Many WES and panels do not include mitochondrial genome testing

- In addition, 73 (17.5%) cases had other findings that might not be fully captured by panel testing that could guide results interpretation:
  - 63 (15.1%) with Contiguous CNVs – If a CNV involves multiple genes, a panel might only capture one involved gene and miss others
  - 10 (2.4%) with Long Regions of Homozygosity – Increases suspicion for recessive disorders or for uniparental disomy (UPD)

CONCLUSIONS

- WGS identifies variant types that might be missed by WES, multigene panels, or other tests in over 10% of cases
- Deep intronic and non-coding variants will be important to capture as more information about the pathogenicity of these variants and more genetic conditions relating to them become available
- These results highlight the comprehensive of WGS as a single test approach for diagnosis in the pediatric neurology setting

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Reference:
1) Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics . Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay: Clinical Report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219.