P659: Whole-genome sequencing as a first assay has the potential to shorten diagnosis time for neurodevelopmental disorders

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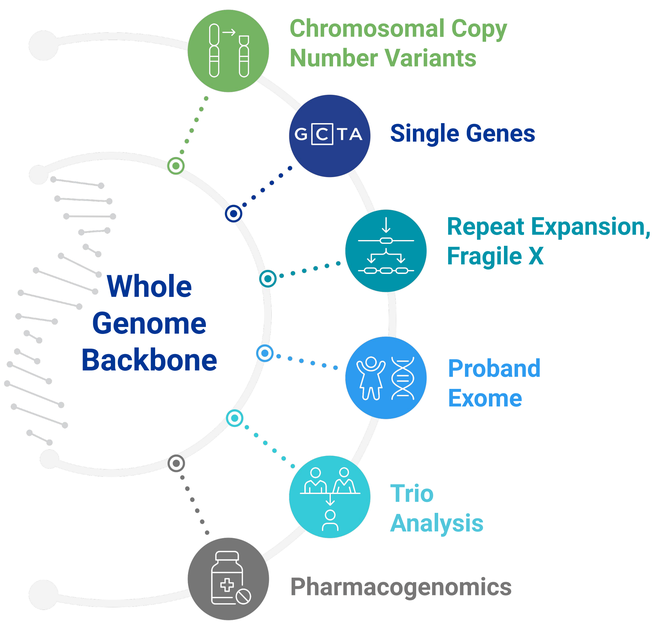
BACKGROUND

- Millions of children in the United States have developmental delay, intellectual disability or autism (ID/DD/ASD).
- A genetic diagnosis can aid in the assessment of prognosis, recurrence risk or treatment plans
- **The conventional testing paradigm leaves many children with ASD/DD/ID without a genetic diagnosis or left in a long diagnostic odyssey**
- Whole-genome sequencing (WGS) can be used to detect multiple variant types including: single nucleotide variants (SNVs), small insertions and deletions (ins/del), and copy number variants (CNVs)

METHODS

Figure 1. Potential of whole-genome sequencing

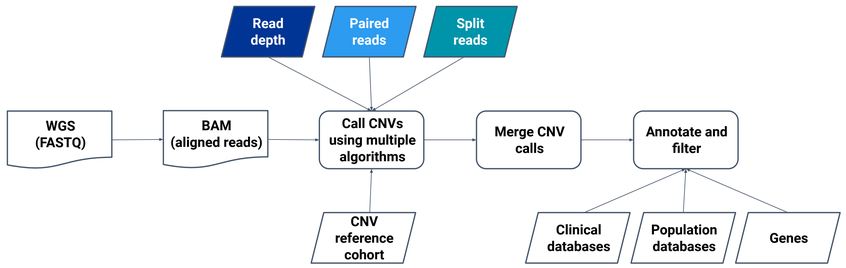


- We developed a pipeline leveraging information from read depth, paired reads and split reads to call CNVs from ~30X WGS (**Figure 2**)
- Recall and precision for benchmark SNV and ins/del detection were assessed across NA12878 (3 replicates) and NA24385.
- Recall for benchmark CNV detection was assessed across NA24385
- **106 known microdeletions/duplications** (≥50kb) previously identified using chromosomal microarray (CMA) in 101 positive cell lines and clinical samples
- Samples without known large CNV undergo proband "exome" analysis

Whole-genome sequencing can provide a more comprehensive genetic analysis for patients with neurodevelopmental disorders

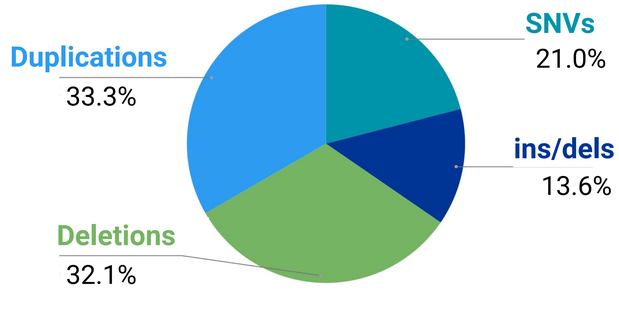
Figure 2. CNV calling workflow

A. Overview of CNV calling pipeline



B. Example heterozygous deletion in WGS data. Dark blue dotted line, region with reduced read depth. Red, reads with larger than expected insert size. Multi-colored, soft clipped reads (i.e. part of read that does not map to reference genome)

C. Distribution of variant types in positive control and clinical samples. We assessed the ability of WGS to detect previously identified variants implicated in disease.



RESULTS

WGS offers the potential to replace multiple tests (green arrow below)and shorten time to diagnosis.

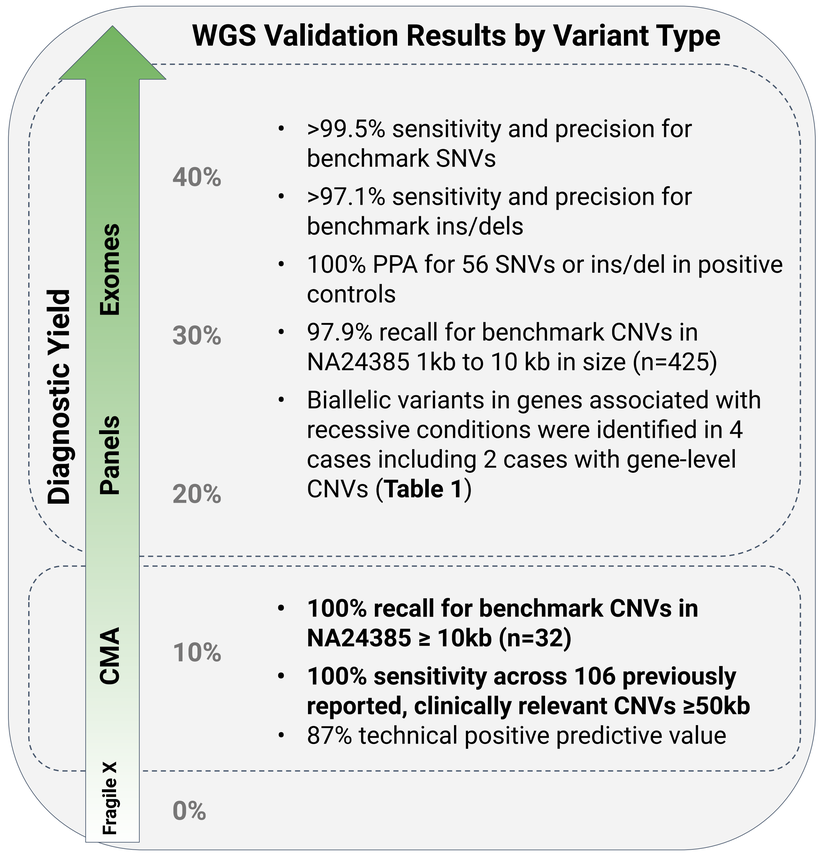


Table 1. Biallelic variants identified during phenotype- driven analysis. These variants would not be detectable by CMA but are identified by WGS

Gene	Variant 1	Variant 2
GAA	c.-32-13T>C	exon 18 deletion
CLN3	p.E295K	1 kb deletion
LIG4	p.R814*	p.G469E
GBA	p.N370S	p.R120Q

CONCLUSIONS AND FUTURE DIRECTIONS

- **WGS can provide information on large CNVs, SNVs, and gene-level CNVs to replace CMA and whole-exome sequencing**
- Ongoing work includes development of clinical algorithms to detect additional structural variants and short tandem repeats (STRs) from WGS

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