Diagnostic Yield of Whole Genome Sequencing for Patients with Neurodevelopmental Delays

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BACKGROUND

- Neurodevelopmental disorders (NDD) are a broad set of disorders associated with syndromic and non-syndromic autism spectrum disorder, intellectual disability, and/or developmental delay.
- Genetic testing for NDD can inform medical management, prognosis, family planning, and clinical trial eligibility[1].
- Whole genome sequencing (WGS) is increasingly being adopted as a first-tier diagnostic tool for patients with NDD, in accordance with guidelines from the American College of Medical Genetics and Genomics (ACMG)[2].
- The information available about the diagnostic yield of WGS for patients with NDD is growing but still relatively limited.
- In this study, we reviewed the diagnostic yield of WGS for patients presenting with various NDDs.

METHODS

Study Design: Retrospective review of WGS results

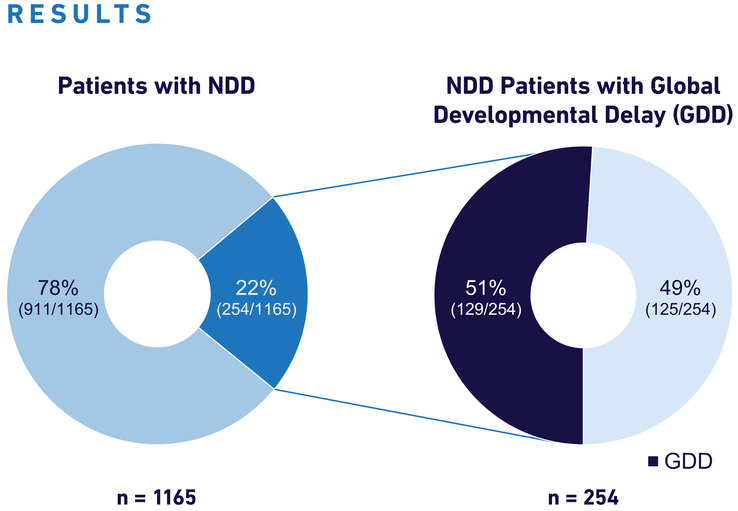
Inclusion Criteria:

- Recent consecutive WGS cases completed at one clinical laboratory
- Clinical indication includes those associated with neurodevelopmental disorders

Analysis: We reviewed the clinical and genetic data to determine:

- The **frequency of phenotype-related positive results** (defined as pathogenic and likely pathogenic) detected by WGS as well as detection of high-suspicion variants of uncertain significance (VUS)
- The **variant types** identified by WGS

RESULTS



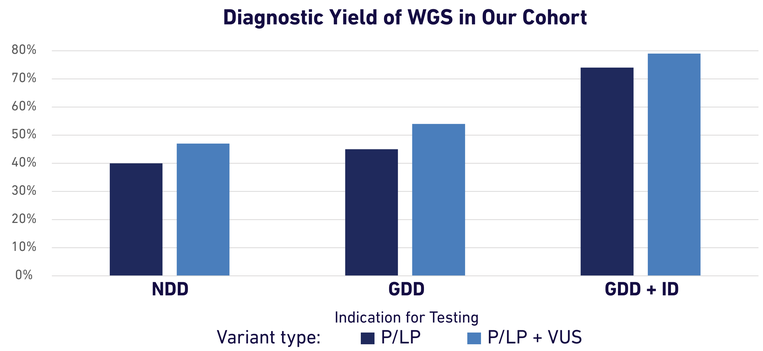
QUICK FACTS

Most patients (97%) had at least one non-neurological symptom.

Copy number variations accounted for almost 10% of diagnoses (24/254, 9.4%)

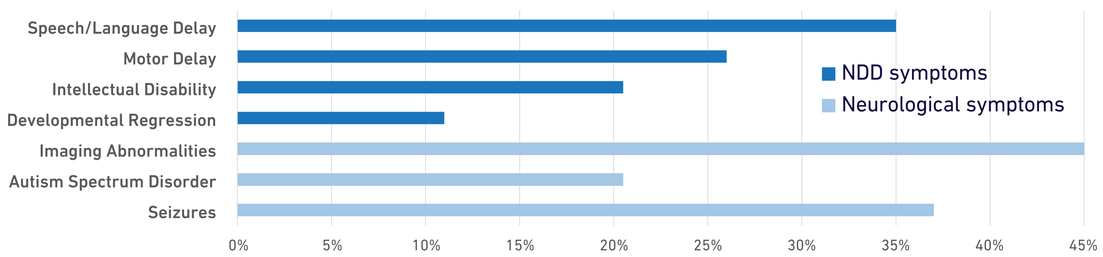
Other diagnoses included two patients with Angelman syndrome, and one patient each with Turner syndrome, Prader-Willi syndrome, and Duchenne/Becker muscular dystrophy. Two patients had *ATXN2* expansions associated with spinocerebellar ataxia 2. One patient had uniparental disomy associated with Temple syndrome.

Diagnostic Yield of WGS in Our Cohort



Diagnostic yield was higher when high-suspicion VUS were included. Yield was also higher for patients with global developmental delay and intellectual disability.

Additional symptoms included:



CONCLUSIONS

WGS identified a genetic diagnosis in nearly half of patients with NDD. Several variant types were detected, many of which can often be missed by other standalone genomic technologies. The diagnostic yield was higher in patients with both global developmental delay and intellectual disability, with nearly 80% of this cohort testing positive.

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References:
1 Genetic Testing in Neurodevelopmental Disorders. PMID: 33681094
2 Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). PMID: 34211152