The Utility of Genome Sequencing as a Diagnostic Tool for Children with Ataxia

Xiaonan Zhao, PhD, FACMG[1,2], Wilson C.W. Wu, PhD, FACMG[1,2], Morgan Driver, PhD, MS, CGC[1], Elizabeth Fieg, MS, CGC[1], Robert Rigobello, MS, CGC[1], Matthew B. Walsh, MMSc, CGC[1], Jason Chibuk, MS, CGC[1], Linyan Meng, PhD, FACMG[1,2], Fan Xia, PhD, FACMG[1,2]

1. Department of Molecular & Human Genetics, Baylor College of Medicine, Houston, USA.
2. Baylor Genetics Laboratory, Houston, TX, USA.

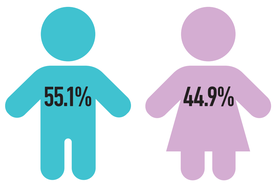
P581

Introduction

- Ataxia is a neurological condition characterized by a lack of muscle coordination resulting in gait instability, impaired fine motor skills, and difficulty with balance and speech.[1]
- Ataxia can be acquired or inherited, with a heterogeneous group of these disorders including short tandem repeat (STR) disorders, mitochondrial genome disorders, and copy number variants.[1]
- Compared to exome sequencing (ES) or traditional panel-based testing, genome sequencing (GS) enables a more comprehensive analysis of multiple variant types in a single test, allowing for higher diagnostic yields for genetically and phenotypically heterogenous conditions such as ataxia.
- However, the diagnostic utility of GS in pediatric cohorts with ataxia is still being assessed and is not well-described in the literature.
- Here, we describe our clinical laboratory experience with GS and testing individuals with ataxia.

Results

305 children with ataxia

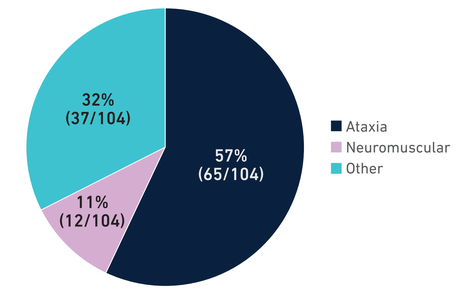


Mean age at testing: 7.8 years

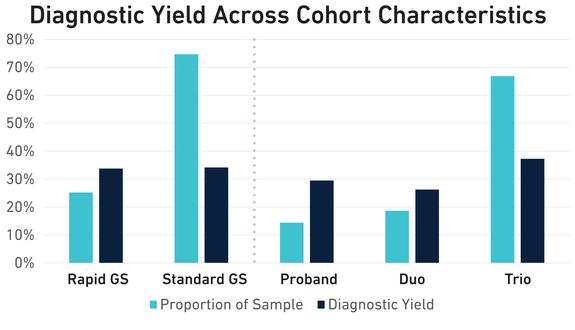
34.1% (104/305) patients received a positive diagnosis

Six children had two primary results and two children had three results, for a total of **114 positive results**

Approximately 70% of patients had a positive result for a condition with ataxia or other neuromuscular phenotype. The remaining positive results were diagnostic for other aspects of the patient phenotype.



Diagnostic Yield Across Cohort Characteristics



Diagnostic yield was similar between rapid (26/77, 33.8%) and standard GS (78/228, 34.2%).

Trio GS made up most of the cohort and exhibited higher diagnostic yield (76/204, 37.3%) compared to proband (13/44, 29.5%) and duo GS (15/57, 26.3%).

Methods

- We performed a retrospective review of consecutive GS cases from our clinical diagnostic laboratory involving children under 18 years old with a clinical indication of ataxia.
- Patient characteristics, clinical indication, test type, test result, and gene(s) and variant(s) identified for each case were reviewed.
- Diagnostic yields were assessed, and descriptive statistics were used to describe cohort and variant characteristics.

17.3% (18/104) positive cases involved the detection of a variant with limited to no coverage on ES

STR Expansion – 11 cases

- 4 cases: pathogenic *ATXN8OS* repeat expansions (spinocerebellar ataxia, type 8)
- 3 cases: biallelic pathogenic *FXN* GAA repeat expansions (Friedreich ataxia)
- 1 case each: pathogenic repeat expansions in *ATXN2*, *ATXN7*, *CSTB*, and *DMPK*

Mitochondrial Genome Variant – 4 cases

- Likely pathogenic or pathogenic variants in *MT-TK*, *MT-TS1*, *MT-TF*, and *MT-TE*

Deep Intronic Variant – 2 cases

- RNA sequencing helped reclassify *TRNT1* c.343-795C>G from a variant of uncertain significance to likely pathogenic, leading to a diagnosis of sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay
- *NUBPL* c.815-27T>C associated with mitochondrial complex I deficiency, nuclear type 21

Single Exon Deletion – 1 case

- *LPIN1* exon 18 deletion and single nucleotide variant in trans, causing autosomal recessive acute recurrent myoglobinuria

Other recurrent diagnoses included four diagnoses of *CACNA1A*-related disorders and two diagnoses of Charcot-Marie-Tooth disease, type 1A.

Conclusions

- Our findings highlight the importance of GS as a diagnostic test for children with ataxia, with more than one-third of children having at least one positive GS result.
- 17.3% of positive results involved variants that have limited to no coverage on exome sequencing such as short tandem repeats and mitochondrial genome variants.
- Additionally, 7.7% cases had more than one molecular diagnosis. This highlights the diagnostic utility of GS to capture findings targeted approaches might miss.

Presented at the American College of Medical Genetics & Genomics (ACMG) Annual Meeting, Mar 10-14, 2026, Baltimore, MD USA.

References:

1. Sumbramony, S.H., Burns, M., Kugelmann, E.L., & Zingariello, C.D. (2022). Inherited Ataxias in Children. Pediatric Neurology, 131, P54-62. doi:10.1016/j.pediatrneurol.2022.04.004