BAYLOR GENETICS

From Instability to Insight: Genome Sequencing as a Tool for Diagnosing Pediatric Ataxias

Introduction

Ataxia is a neurological symptom characterized by impaired muscle coordination and imbalance. Ataxia may be caused by numerous conditions with onset ranging anywhere from infancy to adulthood. Childhood ataxias can be caused by genetic or non-genetic factors.[1,2] The prevalence of these conditions is around 26 per 100,000 children, with approximately half having a genetic etiology for their ataxia.[3,4] When there is a genetic etiology, this may be referred to as a hereditary ataxia (HA).

As a collective group of conditions, HAs may cause progressive, intermittent, and more rarely, relatively static ataxia.[2] The ataxia may be isolated or accompanied by other neurological symptoms such as developmental delay, cognitive decline, neuropathy, and epilepsy.[2,5] HAs can also have overlapping clinical symptoms with other genetic conditions including Charcot-Marie-Tooth disease (CMT) and hereditary spastic paraplegias (HSPs).[2,6] Many childhood ataxias are inherited in an autosomal recessive (AR) manner, with the most common example being Friedreich ataxia (FRDA).[2,5] However, autosomal dominant (AD), X-linked (XL), and mitochondrial inheritance patterns also have been observed.

Management for many HAs is symptomatic and supportive, although there are some ataxias with specific therapies and interventions. Examples include acetazolamide for episodic ataxia type 2 (EA2), omaveloxolone for FRDA, supplements or dietary restrictions for many metabolic genetic conditions, and arimoclomol, miglustat, and levacetylleucine for Niemann-Pick disease type C.[2,7] This emphasizes the importance of obtaining a diagnosis for patients with HAs.

With up to 500 genes implicated in causing ataxia, genetic testing for HAs can be of benefit when searching for a diagnosis.[8] Various types of genetic variants can lead to ataxia including short tandem repeat (STR) expansions and copy number variants (CNVs). While testing approaches such as STR gene panels and next-generation sequencing (NGS) based approaches, including exome sequencing (ES), can identify a molecular diagnosis in some patients, there are limitations to what they may capture.[9] Varying factors from described cohorts, such as specific phenotype selection and cohorts with high rates of consanguinity, make ascertaining a consistent yield of these tests challenging.

Compared to ES or traditional NGS panel-based testing, genome sequencing (GS) enables a more comprehensive analysis of multiple variant types in a single test. However, limited studies have evaluated the diagnostic utility of GS in this setting, with described cohorts often being small or having had previous uninformative testing.[10-12] Practice recommendations for genetic testing of ataxias published in 2025 support GS that incorporates STR analysis as a first-tier test when an individual is experiencing unexplained symptoms of ataxia.[13]

Here, we describe a cohort of pediatric patients with ataxia tested by Whole Genome Sequencing (WGS) through Baylor Genetics. This study provides additional evidence to support the utility of WGS as a diagnostic tool for ataxia testing.

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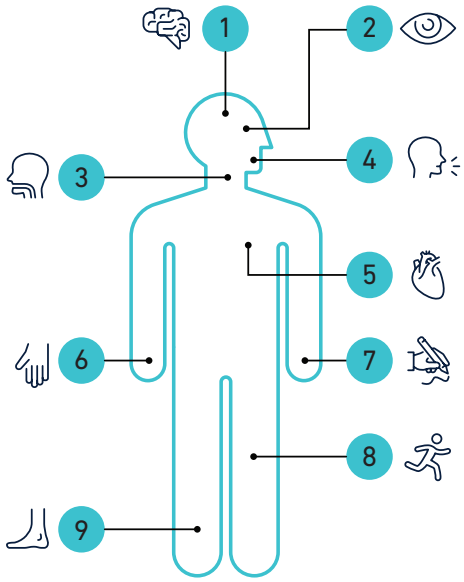


1. Lack of Coordination
2. Eye Movement Abnormalities
3. Trouble Eating and Swallowing
4. Slurred Speech
5. Heart Problems
6. Tremors
7. Deterioration of Fine Motor Skills
8. Gait Abnormalities
9. Difficulty Walking and Poor Balance

Figure 1. Symptoms commonly associated with HAs.

Baylor Genetics' WGS Reporting Includes:

- Phenotype-driven reporting of diverse variant types across the genome, many of which might be missed by other testing methods such as ES
  - Single nucleotide variants (SNVs)
  - Copy number variants (CNVs)
  - Insertion/deletion variants (indels)
  - Intronic variants
  - Non-coding variants
  - Mitochondrial genome (mtDNA) variants
  - Short tandem repeats (STRs) in 58 genes
- Detection of de novo variants and uniparental disomy (UPD) when both parents are included in sequencing
- Reflex RNA sequencing and optical genome mapping (OGM) when qualified findings are identified, to enhance variant classification
- Optional reporting items include ACMG recommended secondary findings, incidental findings unrelated to patient phenotype, and findings in genes with no known disease association
- One complimentary provider-initiated reanalysis to provide more answers by leveraging future genomic understanding

The Study

We performed a retrospective review of consecutive WGS cases performed at Baylor Genetics involving children under the age of 18 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.

There were 305 children with ataxia who underwent WGS that were reviewed. Around 25% (77/305) of the cohort underwent rapid WGS and around 75% (228/305) underwent standard WGS. The majority of cases were trios (66.9%). The mean age at time of testing was 7.8 years, and 55.1% were male.

305 Children with Ataxia Underwent WGS

204 (66.9%) of WGS Cases Included a **Complete Trio**

Median Age at Time of Testing was 7.8 Years

77 Children Underwent **Rapid WGS** While 228 Underwent **Standard WGS**

Figure 2. Cohort overview.

WGS Diagnostic Yield and Phenotypic/Genotypic Representation Among the Cohort

The diagnostic yield of WGS was 34.1%, with 104 children having at least one genetic diagnosis associated with their clinical indication, 78 (25.6%) having indeterminate results, and 123 (40.3%) having negative results. Of the positive results, there were six children with two primary diagnoses (5.8%) and two children with three diagnoses (1.9%), leading to a total of 114 diagnoses. The diagnostic yield was similar between males (57/168; 33.9%) and females (47/137; 34.3%), as well as for rapid WGS (26/77; 33.8%) and standard WGS (78/228; 34.2%). Trio WGS had a higher diagnostic yield of 37.3% (76/204) as compared to duo and proband-only WGS which had a combined diagnostic yield of 27.7% (28/101).

Of the 114 positive diagnoses, 57.0% (65/114) were related to a gene or chromosomal region associated with ataxia and 10.5% (12/114) to a neuromuscular presentation. Examples of ataxia-associated genes included *ATXN2* and *FXN* while neuromuscular related genes included *PMP22* and *DMPK*. Of children with positive diagnoses, 77% (80/104) had a finding in a gene or chromosomal region unique within the cohort, translating to 76.3% (87/114) of diagnoses. Examples of recurrent findings included 4 diagnoses of *CACNA1A*-related disorders and 2 diagnoses of CMT type 1A (CMT1A).

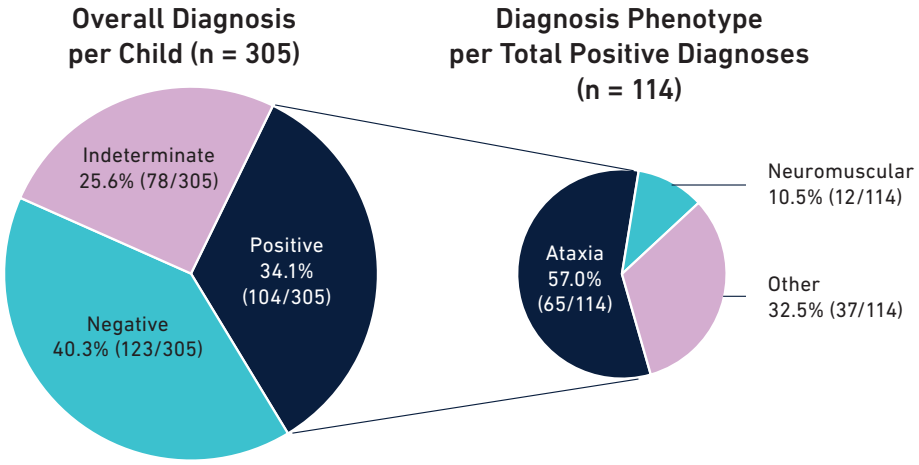


Figure 3. Diagnostic yield of WGS per child and phenotypic representation among all positive diagnoses.

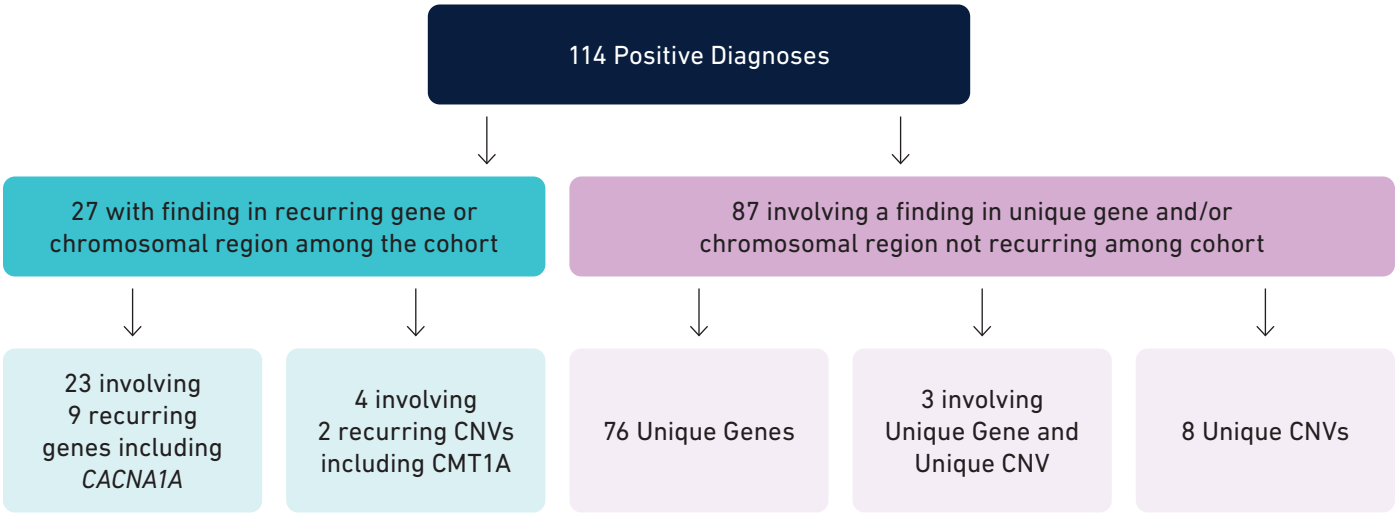


Figure 4. Uniquely occurring versus recurring genes and CNVs among positive diagnoses in the cohort.

WGS Detects Diverse Variant Types with Varying Inheritance Patterns

There were a total of 139 variants related to positive diagnoses in this cohort. Of these variants, 79 were single nucleotide variants (SNVs), 30 were small insertions or deletions (indels), 15 were CNVs, 11 were STRs, and 4 were mitochondrial DNA (mtDNA) variants. Regarding inheritance patterns, out of the 114 diagnoses, 62 were associated with AD inheritance, 38 with AR, 5 with mixed AD and AR associations, 5 with XL, and 4 with mitochondrial inheritance. Of the 76 children who had positive trio testing, 38 (50%) were confirmed to have de novo variants, and 15 (19.7%) had phasing of AR variants performed to confirm a trans configuration. This highlights the importance of GS allowing the incorporation of parental samples.

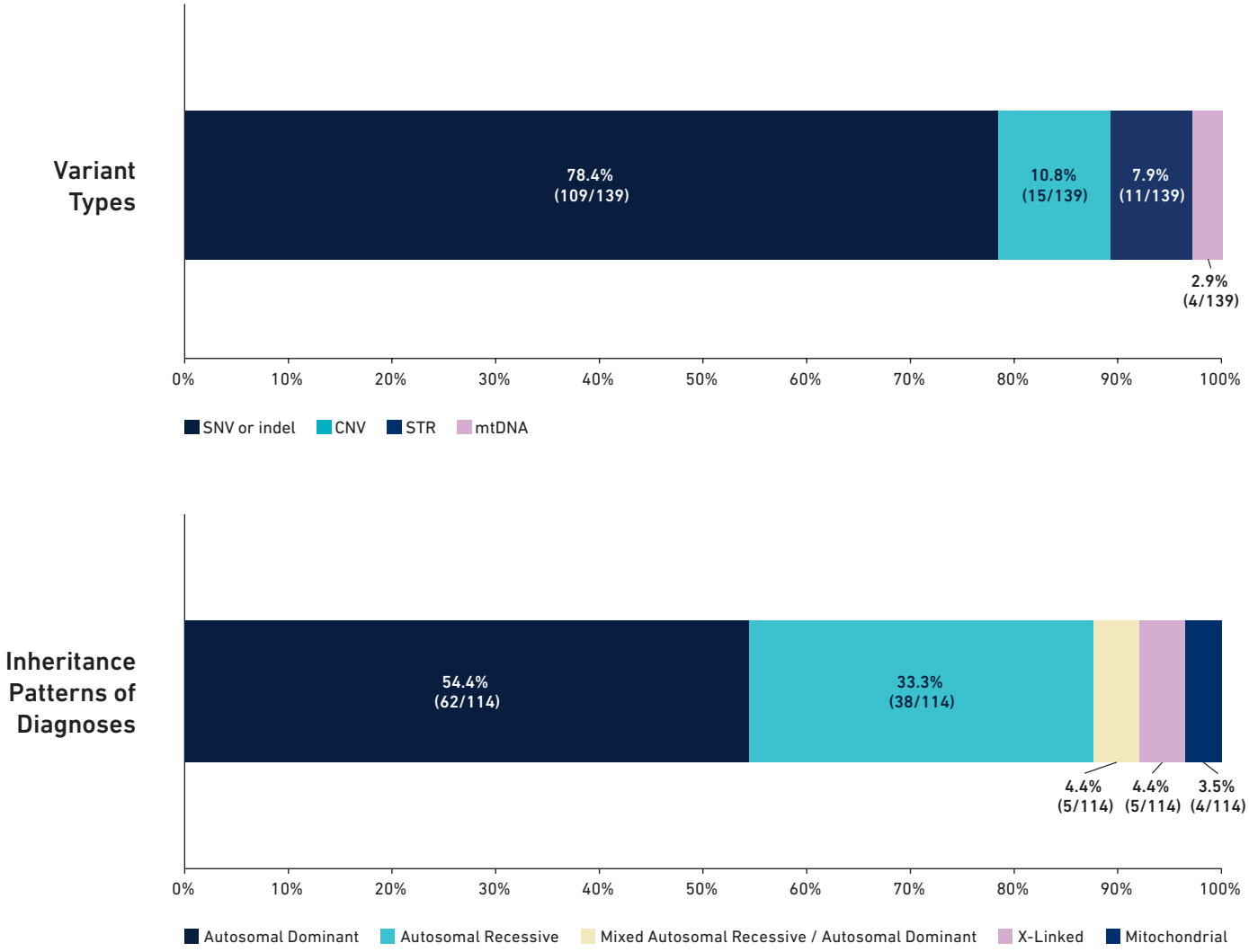


Figure 5. Inheritance patterns and types of variants among the positive diagnoses.

WGS Identifies Traditionally Elusive Variant Types and Illuminates the Full Diagnostic Picture

Of the 104 children with positive diagnoses, 18 (17.3%) had a variant that may have limited to no coverage on ES. This included the 11 children identified to have pathogenic STR expansions, with 3 children diagnosed with FRDA due to biallelic pathogenic GAA repeat expansions in the *FXN* gene and 4 children diagnosed with spinocerebellar ataxia type 8 due to pathogenic repeat expansions in the *ATXN80S* gene. Four children had a likely pathogenic or pathogenic mtDNA variant identified, including a child with a 98% heteroplasmic variant in *MT-TK* (m.8344A>G) predominantly associated with myoclonic epilepsy with ragged-red fibers (MERRF). Additionally, 2 children were diagnosed with an AR condition due to compound heterozygous variants with one variant being a deep intronic variant more than 20 bp from the exon-intron boundary. One case involved *TRNT1* (see Case Study section for more details) and the other involved *NUBPL*, leading to a diagnosis of mitochondrial complex I deficiency nuclear type 21 (MCI1DN21). Separately, another child was diagnosed with an AR condition due to compound heterozygous variants associated with acute recurrent myoglobinuria, with the detection of a SNV and 1.76 kb, single exon deletion within the *LPIN1* gene.

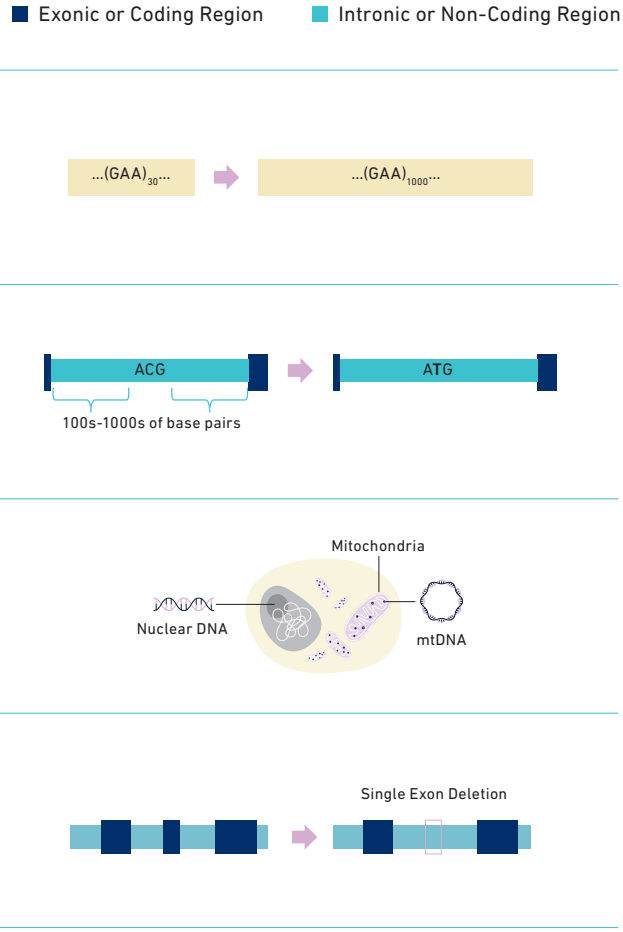
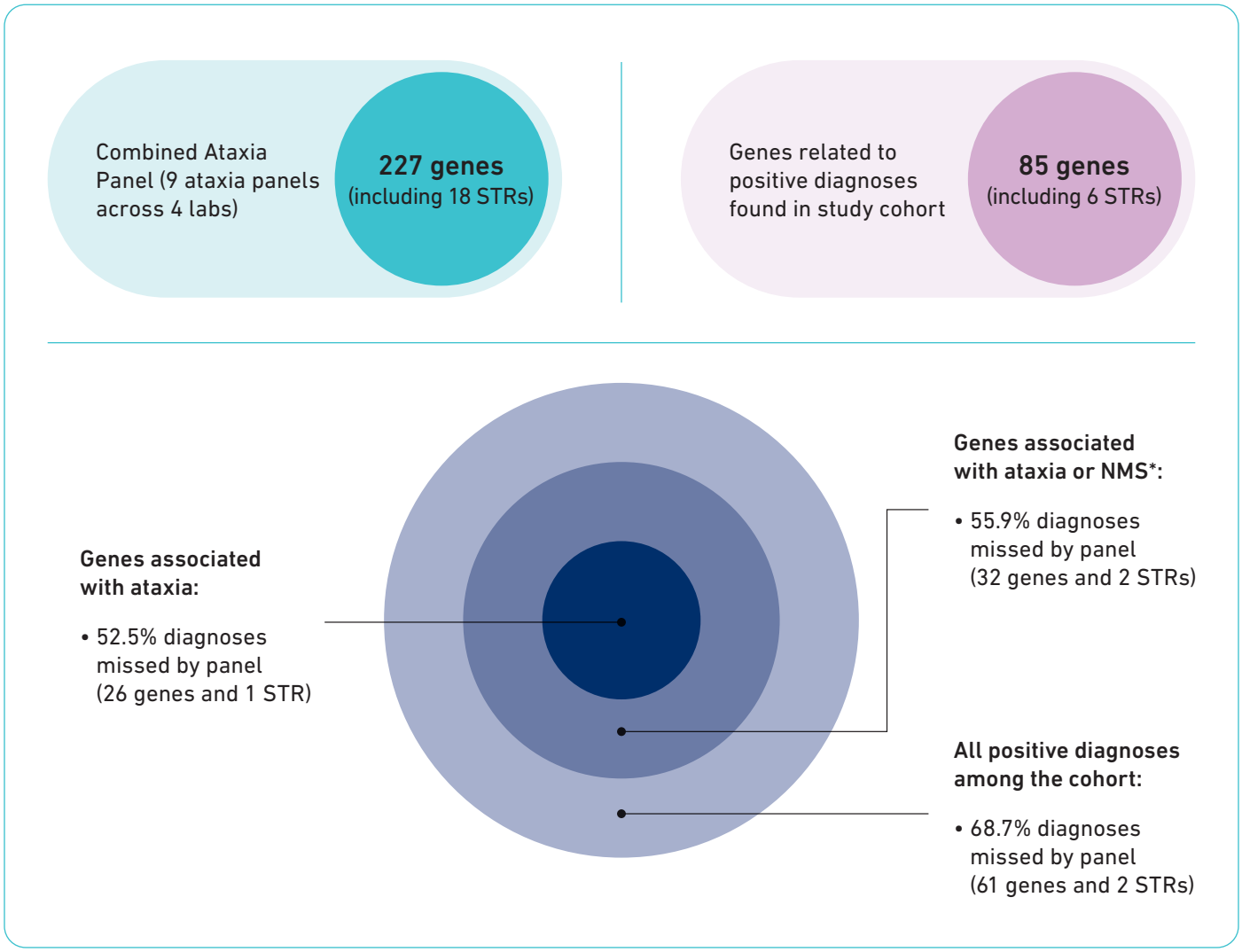


Figure 6. Variants found among the cohort with limited to no coverage on ES.

WGS Outperforms NGS and STR Panels

Genetic testing for HAs frequently includes NGS and STR gene panels. A comparison of genes on 9 ataxia panels offered among 4 clinical laboratories against the findings in this cohort was performed. First, a theoretical combined ataxia panel was created with 227 genes, including 18 genes with STR analysis, by merging the 9 ataxia panels. This panel was then compared to the genes found among our study cohort to determine the number of diagnoses it may or may not have detected. Diagnoses involving CNVs were excluded from this analysis as detection of CNVs may vary among NGS panels. Accounting for all 99 non-CNV positive diagnoses among the cohort, there were 61 genes and 2 STRs not represented on the combined ataxia panel. This corresponds to 68.7% (68/99) of diagnoses that may not have been detected through a standard ataxia NGS or STR gene panel. Taking an increasingly conservative approach, including only genes with ataxia association, 52.5% (31/59) of diagnoses may have been missed by an ataxia NGS or STR panel, including one diagnosis due to an STR in *CSTB*, related to progressive myoclonic epilepsy type 1 (EPM1).



* Neuromuscular symptoms

Figure 7. Theoretical detection of study cohort positive diagnoses through the combined ataxia panel.

WGS Can Lead to Identification of Treatments or Interventions

While many HAs are managed supportively, some have specific treatments or interventions available. Of the 104 children with positive diagnoses, 22 (21.2%) children had a finding in a gene associated with some level of treatment guidance suggesting either a certain medication, diet, supplement, or procedure. Specific to ataxia, there were findings in 15 children involving genes with ataxia in the phenotypic spectrum that also had associated treatments or interventions. Examples included *FXN* causing FRDA, *CACNA1A* causing *CACNA1A*-related disorders which can include episodic ataxia type 2 (EA2), and *NKX2-1* causing *NKX2-1*-related disorders. Of note, some of the treatments or interventions were addressing symptoms outside of ataxia such as epilepsy or cardiac symptoms, as seen with *SCN8A* causing *SCN8A*-related disorders.

Gene	Treatment Guidance‡
***FXN* (FRDA)**	Omaveloxolone has been shown to slow the progression of FRDA and is approved for individuals > 16 years old.[14]
***CACNA1A*-related disorders (EA2)**	Acetazolamide may be considered to treat episodes of ataxia.[7]
***NKX2-1*-related disorders**	Tetrabenazine, deutetrabenazine, or valbenazine to control chorea. Levodopa has been reported to improve chorea in children with gait abnormalities and can be considered as a first-line therapy in children with gait impairment.[15]
***SCN8A*-related disorders**	Several studies suggest a favorable response to sodium channel blockers in specific *SCN8A*-related epilepsy phenotypes including DEE and SeLFIE.[16]

‡ This is information is not intended as medical advice but rather highlights potential treatment options associated with certain genetic conditions
* DEE = developmental and epileptic encephalopathy, SeLFIE = self-limited familial infantile epilepsy

Table 1. Examples of genes found in study cohort with available treatment guidance.

Case Study

WGS was completed for a child with personal history of ataxia, developmental delay, hypotonia, and vision loss. Family history was unremarkable for ataxia or neurologic disease. Over the course of the diagnostic workup, multiple rounds of tests and procedures were completed prior to GS including a muscle biopsy. Additionally, several genetic tests were completed including a chromosomal microarray, panel testing, and ES. Despite extensive testing, etiology remained unclear.

Trio WGS revealed compound heterozygous variants in *TRNT1*: a heterozygous likely pathogenic variant, and a heterozygous deep intronic variant of uncertain significance (VUS). *TRNT1* encodes a protein that is essential to the proper functioning of transfer RNA (tRNA). The gene is associated with AR sideroblastic anemia-B-Cell immunodeficiency periodic fever developmental delay syndrome (SIFD) which is characterized by early onset severe shortage of red blood cells, recurrent fevers in the absence of infection, immunodeficiency, and developmental delay with variable neurodegeneration. Additional features include hearing and vision loss, hypotonia, ataxia, and cardiomyopathy.[17]

RNA-Sequencing (RNA-Seq) was then pursued for the deep intronic variant in an attempt to clarify the potential pathogenicity of the variant. RNA-Seq results showed that this variant results in partial retention of intron 3, causing an out-of-frame RNA transcript. This additional functional data allowed for the reclassification of the variant from a VUS to a likely pathogenic variant, consistent with the diagnosis of SIFD.

The combination of GS and RNA-Seq technologies allowed for the detection and characterization of the deep intronic variant needed to confirm this patient's diagnosis. Achieving this diagnosis not only provides the family with an explanation for their child's symptoms, but it also informs the medical management of the patient. Treatment options for SIFD include intravenous immunoglobulin (IVIG) replacement, etanercept, blood transfusion, and bone-marrow transplantation.[17] Knowing the molecular diagnosis may also allow future opportunities for research or clinical trials if studies become available. Additionally, having this information equips the family with knowledge for future or current family planning decisions.

Conclusion

More than one-third of children with ataxia had positive WGS results with nearly 68% of diagnoses relating to a condition involving ataxia or a neuromuscular phenotype. The remaining positive results were diagnostic for other aspects of the patients' phenotypes.

- Our findings highlight the importance of GS as a diagnostic test for children with ataxia, as 7.7% of children had more than one molecular diagnosis and 17.3% of positive results involved variants that may have limited to no coverage on exome sequencing such as STRs, deep intronic variants, and mtDNA variants.
- GS also allows inclusion of more genes than allotted by NGS or STR panels — 52.5% of diagnoses found in an ataxia-related gene may not have been represented on an NGS or STR panel. GS allows a diagnosis to be found more quickly and with fewer rounds of testing.
- HAs may have overlapping clinical features that make it hard to distinguish between other conditions including HSPs and CMT. In our cohort, 2 children were found to have CMT1A and one child had spastic paraplegia type 35. Having broader testing through GS allows for coverage of differential genetic diagnoses.
- Timely diagnosis is important among HAs as some have specific treatments or screening recommendations available that may impact medical management.

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