Genome and Exome Sequencing as Diagnostic Tools for Pediatric Leukodystrophies and Genetic Leukoencephalopathies

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Background

- Leukodystrophies (LDs) and genetic leukoencephalopathies (gLEs) are heterogenous, heritable conditions primarily affecting white matter in the central nervous system.[1,2,3]
- There are 30 and 61 canonically recognized LDs and gLEs, respectively; however, the clinical definitions of these conditions continue to expand along with discovery of additional LDs and gLEs, exceeding 300 genes.[1,2,4]
- Preliminary studies have shown increased diagnostic yield of genome sequencing (GS) and exome sequencing (ES) beyond standard of care assessment including magnetic resonance imaging, biochemical testing, and single gene testing.[5,6]
- This study characterizes genetic findings from GS/ES for LD/LE to better understand their diagnostic utility.

Methods

- A retrospective study was conducted to evaluate genetic findings of consecutive children (<18 years old) who underwent GS/ES at our clinical diagnostic laboratory.
- Cases were selected based on a reported clinical suspicion of LD/LE.
- Variants involved in established diagnoses were characterized by variant type, and genetic diagnoses were characterized by phenotype association and inheritance pattern.

Results

Key Point 1:

The combined diagnostic yield of GS and ES was 37.5% with GS having a yield of 39.1% and ES having a yield of 31.3%.

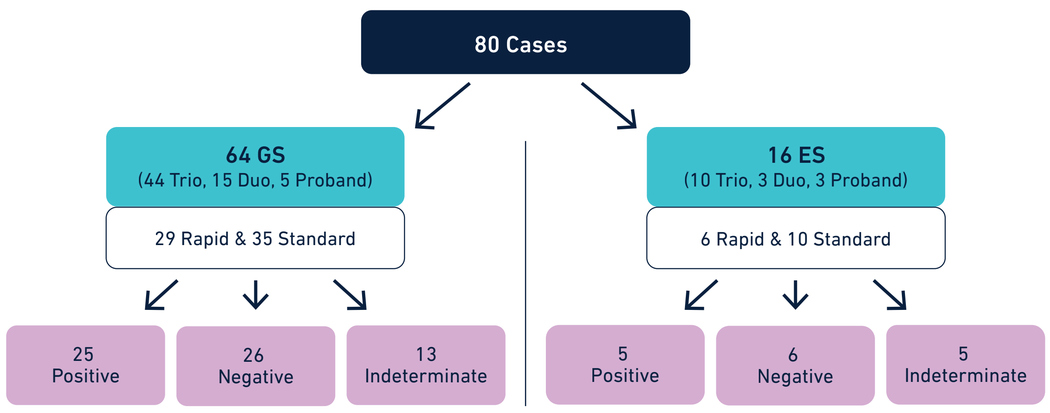
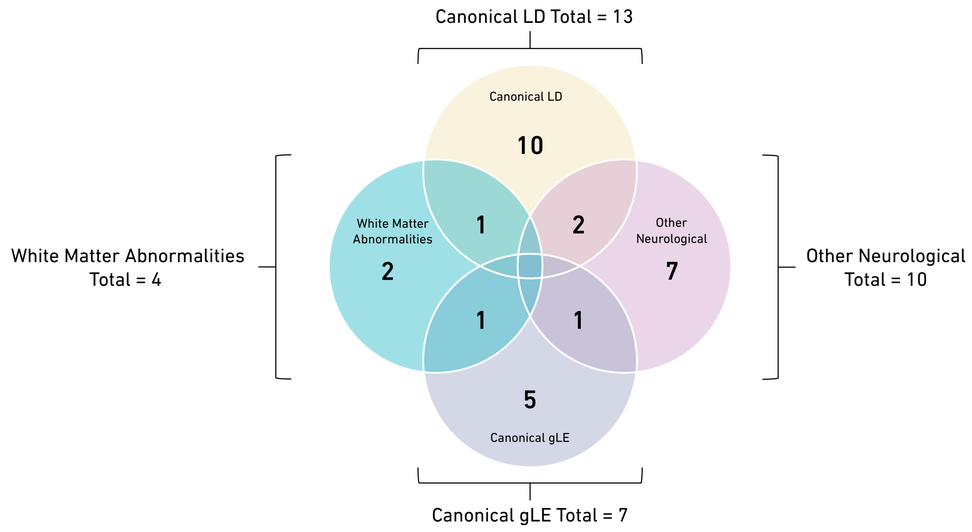


Figure 1. Cohort composition

Key Point 2:

Of the 30 children with positive results, 66.7% (20/30) had a finding in a gene associated with a canonical LD (13/30) or gLE (7/30). Ten had positive results unrelated to LD/gLE, including 2 with findings in a gene in which white matter abnormalities have been reported, 7 with findings in other neurological-related genes, and 1 with findings in a gene unrelated to neurological symptoms.



* Of note, one diagnosis was unrelated to neurological symptoms and therefore is not represented in the Venn diagram.

Figure 2. Phenotypic categories of positive results of both GS and ES

Key Point 3:

13.3% (4/30) of positive cases had variants identified by GS likely to be missed by gene panels or ES. These cases included 2 short tandem repeats (*ATXN1* & *DMPK*) and 4 noncoding variants (*RNU4ATAC* & *RNU7-1*).

Key Point 4:

15 children with positive results had autosomal recessive (AR) conditions. Nine (30.0%; 9/30) children with positive results had compound heterozygous variants in AR genes that were able to be phased due to the inclusion of parental samples. An additional 5 children had autosomal dominant (AD) *de novo* variants.

Identified Canonical LD/gLEs	Gene(s)	Inheritance	# of Cases
X-Linked Adrenoleukodystrophy	*ABCD1*	XL	5
Alexander Disease	*GFAP*	AD	3
Leukoencephalopathy with Vanishing White Matter (Types 3 & 5)	*EIF2B3* & *EIF2B5*	AR	2
Glutaricaciduria Type 1	*GCDH*	AR	2
Sjogren-Larsson syndrome	*ALDH3A2* *	AR	1
Krabbe Disease	*GALC*	AR	1
Aicardi-Goutieres Syndrome Type 9	*RNU7-1*	AR	1
Tay-Sachs disease	*HEXA*	AR	1
LAMA2 -Related Disorders	*LAMA2*	AR	1
ATP7A -Related Disorders	*ATP7A*	XL	1
Mitochondrial DNA Depletion Syndrome 1 (MNGIE type)	*TYMP* ‡	AR	1
Myotonic Dystrophy Type 1	*DMPK*	AD	1

* This case had a homozygous copy number variant (17p11.2 deletion) involving *ALDH3A2*

‡ This case had a compound heterozygous single nucleotide variant and copy number variant (22q13.33 deletion) involving *TYMP* in trans

Table 1. Canonical LD/gLEs identified in the cohort per Vanderver et al. (2015)

Conclusion

- The LD/LE cohort had an overall diagnostic yield by GS/ES of 37.5%, with GS having a higher diagnostic yield than ES.
- Of those with positive results, 96.7% (29/30) had findings that either explained their LD/LE or other neurological symptoms.
- Additionally, 13.3% of positive cases had variants identified by GS likely to be missed by gene panels or ES.
- 46.7% (14/30) of positive results were either due to autosomal recessive compound heterozygous variants or autosomal dominant de novo variants, highlighting the benefit of incorporating parental samples when running GS/ES as compared to other tests.
- Future studies should further explore the clinical utility of genomic sequencing as first-tier testing for LD/LE.

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