The Clinical and Genetic Landscape of Epilepsy in Individuals with Dual Diagnoses

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BACKGROUND

- Whole Genome Sequencing (WGS) is a **comprehensive** test that investigates the genome to identify pathogenic variants.
- WGS enables the **simultaneous detection of multiple variant types**.
- Previous studies have shown that **2-7%** of individuals undergoing WGS receive a **dual molecular diagnosis**.[1]
- The clinical and genetic landscape of specific indications associated with dual diagnoses remains underexplored.
- This study **examined WGS results from patients with dual diagnoses and epilepsy**.

METHODS

Study Design: Retrospective review of WGS results

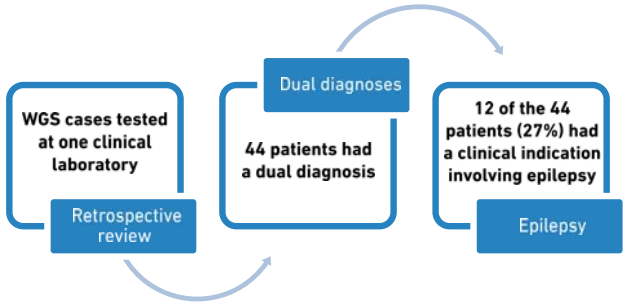
Inclusion Criteria:

- WGS completed at one clinical laboratory
- Clinical indication includes epilepsy
- Dual diagnosis (2 or more molecular diagnoses) by WGS

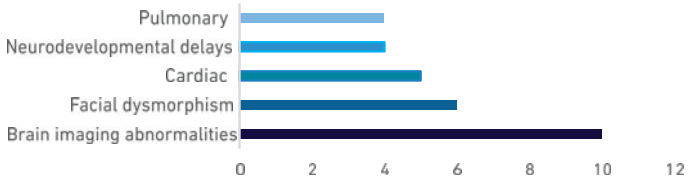
Analysis:

- Reviewed clinical indications and genetic results (specific gene, variant type, inheritance pattern) for all patients with epilepsy and dual diagnosis
- Assessed epilepsy gene panels from 9 commercial laboratories to determine if patients with dual diagnoses and epilepsy would receive a complete diagnosis through panel testing

RESULTS



All patients exhibited a multisystemic phenotype



There were 24 unique variants across 12 patients

5 patients	• Both findings in genes with established epilepsy association
6 patients	• 1 finding in a gene with established epilepsy association • 1 finding in a gene associated with non-epilepsy clinical features
1 patient	• Both findings in genes with preliminary evidence supporting epilepsy association

Only 1 of the 12 patients would receive a complete genetic diagnosis through panel testing

Patient ID	Gene 1	Gene 2	Both findings are on all 9 panels?
1	10q22q23 duplication	*BRWD3*	No
2	*ANKRD11*	16p12.2 deletion	No
3	*DMD*	*CACNA1A*	No
[illegible]	[illegible]	16p13.11 microduplication	No
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

6 genes were included in ongoing research studies at the time of the study

Gene	Included on all 9 panels?
ANKRD11	No (present on 8/9)
NSD1	No (present on 5/9)
SIN3A	No (present on 3/9)
SETD2	No (present on 4/9)
DNM1	Yes
TANGO2	No (present on 6/9)

Conclusions:

- Panel testing would provide a complete diagnosis for **only one of the 12 patients** with a dual diagnosis identified through WGS.
- A complete diagnosis could impact medical management and eligibility for clinical research studies.
- The phenotypic complexity amongst patients with epilepsy and the specific gene findings from their dual diagnoses highlight

References: (1) Chau, M, et al. (2023, November 1-5). Not just one: the utility of whole genome sequencing for making a dual molecular diagnosis. American Society of Human Genetics, Washington, DC.

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