Utilizing Advanced Genomic Technologies to Identify Dual Diagnoses

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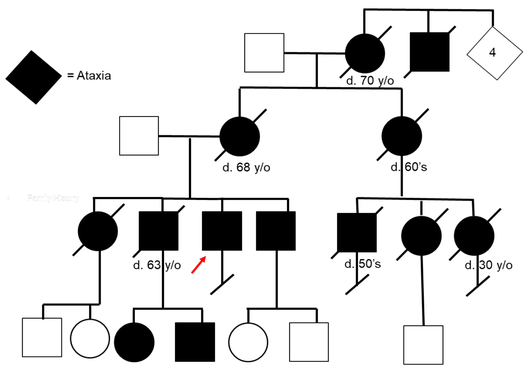
BACKGROUND AND METHODS

Comprehensive understanding of a complex phenotype may be facilitated by the identification of multiple diagnoses in a single patient. However, recognizing a potential dual diagnosis presents clinical challenges, as overlapping phenotypes may be misinterpreted as a monogenic disorder. Moreover, a single diagnosis in a patient with multiple underlying disorders may lead to incorrect assumptions regarding phenotypic variability and a premature end to the diagnostic odyssey. In addition to the clinical challenges of dual diagnoses, the varying types of pathogenic findings that may occur in a single patient present molecular challenges. Identification of dual diagnoses is critical to our understanding of molecular genetics and can benefit patients by leading to opportunities for improved medical management. The ability of whole genome sequencing to interrogate the entire genome for a wide range of pathogenic findings provides an increase in diagnostic yield over that of whole exome sequencing, targeted gene panels and microarray. This advantage also allows for improved identification of multiple diagnoses in a single patient. Here we present data on the incidence of dual diagnoses among patients who received diagnostic whole genome sequencing. Two hundred eighty four cases of comprehensive clinical WGS at a depth of 40X and mitochondrial genome at a depth of 1000X for detection of single nucleotide and copy number variation were evaluated. An additional 331 cases of low-resolution WGS, known as the CNGnome® test, at a depth of 5x for the detection of large-scale copy number variants were evaluated.

DUAL GENOME DETECTION

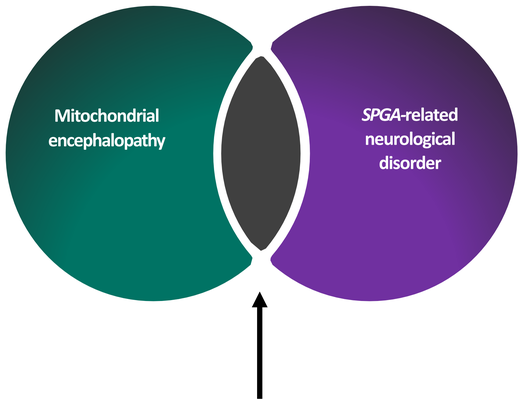
60 year old male with history of:

- Progressive ataxia presenting in 30's
- Intention tremors
- Gait abnormalities
- Dystonia
- Dysarthria
- Sensory polyneuropathy
- Weight loss



NUCLEAR GENOME:
Pathogenic heterozygous variant in *SPG7*

MITO GENOME:
Pathogenic m.7471dupC variant



Blended phenotype of two adult-sent neurological conditions

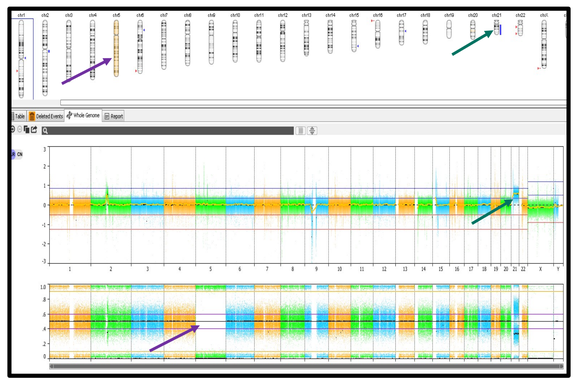
SNV AND CNV DUAL DETECTION

11 year old male with history of:

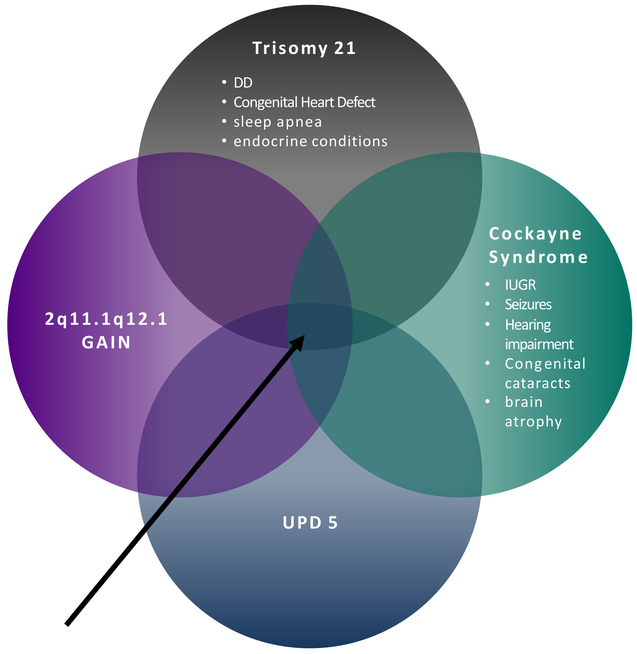
- Sensorineural hearing loss
- Sleep apnea
- Nephrotic syndrome and hypertension
- Severe brain atrophy on MRI
- Significant ID; nonverbal
- Walker to ambulate
- Seizures
- Endocrine anomalies

STRUCTURAL VARIANTS:
Trisomy 21, 2q11.1q12.1 gain, Chrom 5 UPD

SINGLE NUCLEOTIDE VARIANT:
Likely path homo variant in *ERCC8,* Chrom 5



Whole Genome Structural Variant Analysis

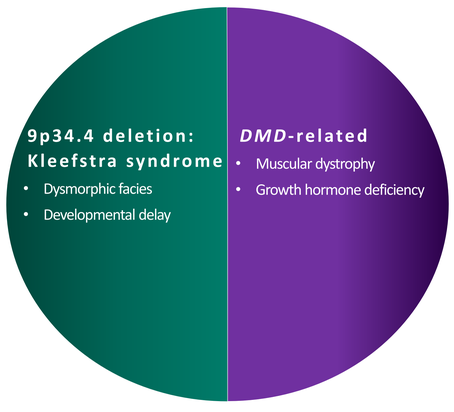


Blended phenotype of multiple disorders

CNV DUAL DETECTION

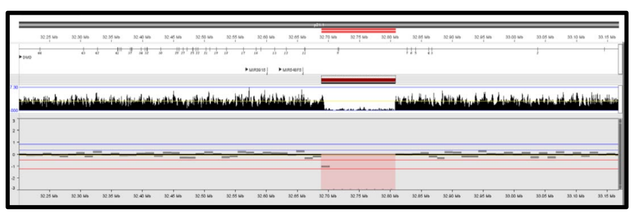
8 year old male with history of:

- Delayed motor development
- Delayed language development
- Growth hormone deficiency
- Muscular dystrophy

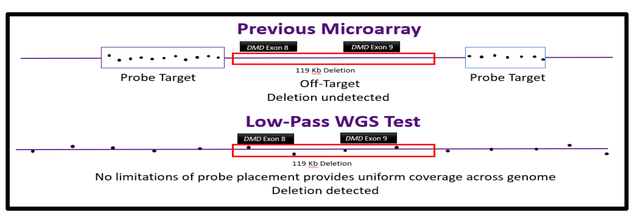


Composite phenotype with distinct features of 2 disorders

COPY NUMBER VARIANTS:
Likely pathogenic 9p34.4 deletion
Pathogenic 119Kb deletion, DMD



DMD exons 8-9



DMD deletion missed on microarray

RESULTS AND DISCUSSION

- Among the 118 cases in which a clinically-relevant diagnostic finding was detected, 3% of cases were identified as having multiple diagnoses. Inheritance patterns ranging from autosomal dominant, X-linked dominant, X-linked recessive, mitochondrial DNA inheritance and autosomal recessive with uniparental isodisomy were represented.
- Disorders resulted from 2 SNVs, a SNV plus aneuploidy, a nuclear DNA SNV plus a mitochondrial DNA SNV and a case of multiple diagnoses resulting from an SNV, CNV, aneuploidy and uniparental isodisomy.
- 50% of patients with multiple diagnoses had a previous analysis that identified one of their diagnoses suggesting that the diagnostic evaluation should not always end with the identification of an initial molecular diagnosis and that genome-wide analysis can still be beneficial in som cases.