# Not just one: the utility of whole genome sequencing for making a dual molecular diagnosis

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## TAKEAWAYS

- Whole genome sequencing (WGS) identifies multi-locus findings in over 5% of patients
- These findings comprise multiple types of variants, some of which next-generation sequencing (NGS) panels or whole exome sequencing (WES) alone would not capture
- WGS offers a comprehensive testing solution that can readily provide a complete diagnosis of a patient's phenotype and enable better clinical understanding of rare disease

## BACKGROUND

- Whole genome sequencing (WGS) offers a comprehensive solution for genetic investigation by capturing a wide range of genomic variations in a single test
- Conventional phenotype-driven and stepwise genetic testing can be costly, time-consuming, and may yield inconclusive results
- The genetic investigation paradigm often stops at the point of identifying a single diagnosis, potentially overlooking additional underlying genetic etiologies
- WGS is recommended as a first- or second-tier test by the American College of Medical Genetics and Genomics (ACMG) for patients with multiple congenital anomalies (MCA), developmental delay (DD), and intellectual disability (ID)
- Limited data exist on the frequency of patients receiving multiple genetic diagnoses pertaining to their phenotype

## OBJECTIVES

- To understand the frequency, type, associated indication, and other characteristics of multiple genetic diagnoses made by WGS

## METHODS

- WGS results from 1,382 consecutive individuals who were referred for investigation of genetic conditions at Baylor Genetics were evaluated
- The molecular findings and characteristics of the variants contributing to multiple diagnoses were examined

## RESULTS

- Reportable multi-locus findings were detected in 78 cases (5.6%), including:
  - 26 cases with dual molecular diagnoses (pathogenic or likely pathogenic variants)
  - 1 case with an actionable secondary finding (SF)
  - 1 case with a reportable finding in another locus [2 variants in an autosomal recessive (AR) locus or 1 variant in an autosomal dominant (AD) locus]
  - 1 case with triple molecular diagnoses
  - 37 cases with one diagnosis with reportable finding(s) in another locus
  - 7 cases with one molecular diagnosis and one reportable variant in an AR locus
  - 7 cases with one molecular diagnosis and an actionable SF
- Among the 24 cases with dual diagnoses, the most common clinical indications included:
  - MCA (n=21)
  - DD/ID (n=7)
  - Seizures (n=3)
  - Failure to thrive (n=4)
- Parental samples were available in 13 cases with dual diagnoses which revealed that *de novo* findings accounted for at least one of the diagnostic variants in 11 trios

## FIGURE 1

**WGS and Rapid WGS yielded single and multiple reportable findings**

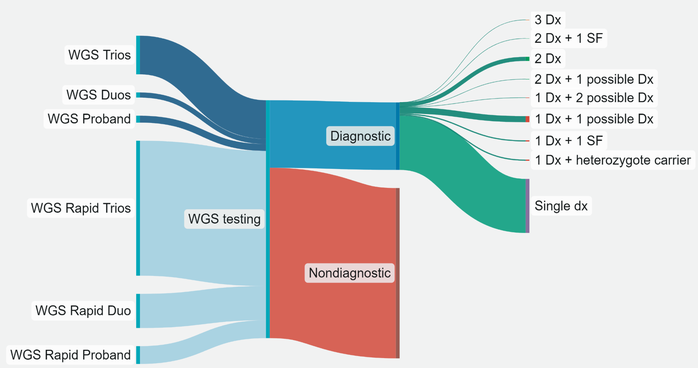
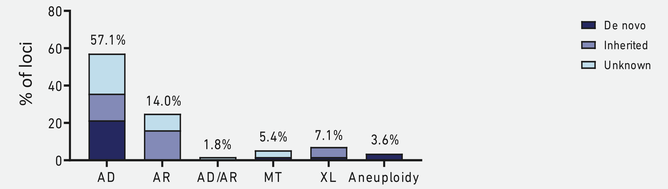



**Figure 1:** The proportion of WGS and Rapid WGS yielding single and multiple molecular diagnoses. Dx, diagnosis(es). SF, secondary findings based on the ACMG v3.2 gene list. A possible diagnosis is defined by one VUS in an autosomal dominant disease-causing locus or one pathogenic/likely pathogenic variant in addition to a VUS in an autosomal recessive disease-causing locus.

## FIGURE 2

**A Mode of inheritance of disease-causing loci contributing to multiple diagnoses**




**B Characteristics of the variants contributing to multiple diagnoses**

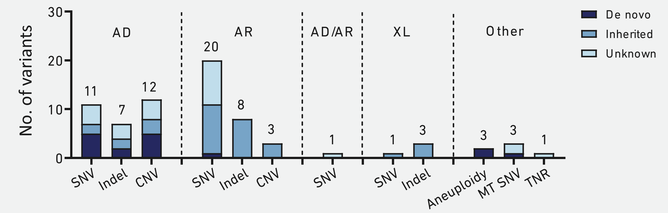
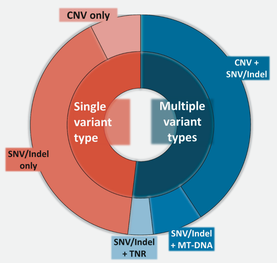



**Figure 2:** A & B. The mode of inheritance of the loci and variant types contributing to multiple molecular diagnoses in 27 cases. AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; MT, mitochondrial; SNV, single nucleotide variant; Indel, small insertions and deletions; CNV, copy-number variant; TNR, triplet repeat expansion.

## FIGURE 3




**Combination of variant types contributing to multiple diagnoses**

**Figure 3:** Approximately half of the multiple diagnoses involved a combination of different variant types. WGS or multiple lines of testing would be required to reach these multiple diagnoses.

## CONCLUSIONS

- This study demonstrates the utility of WGS to provide reportable multi-locus findings involving multiple types of variants
- WGS can expedite resolution of diagnostic odysseys and aid in optimizing management of critically ill patients with complex phenotypes in the NICU, PICU, and other settings
- Recognition of the clinical effects of multiple variants at more than one locus will also improve understanding of rare disease

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