Advancing Precision Diagnosis through Simultaneous Detection of Diverse Variant Types: Insights from Clinical Whole Genome Sequencing

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INTRODUCTION

Genetic disorders arise from diverse types of molecular variants. Historically, clinical genetic testing assays could only assess for specific types of variants (primarily sequencing-based). This resulted in many patients with complex phenotypes remaining undiagnosed or required to submit to multiple rounds of testing with alternate assays to reach a diagnosis. Whole genome sequencing (WGS) now offers healthcare providers the ability to test for many types of variants with one assay, providing a powerful tool to pinpoint an etiology accurately and more rapidly for these patients, thus avoiding the diagnostic odyssey. Here, we summarize our experience performing clinical WGS at Baylor Genetics to highlight its utility as a first-tier diagnostic test capable of detecting a spectrum of variant types.

METHODS

This is a retrospective evaluation of WGS results at Baylor Genetics. For each patient, the type of variant(s) reported as well as demographic data, clinical history, and diagnostic findings were investigated.

RESULTS

Single nucleotide variations (SNVs) and small indels were the most common variant types in 233 cases with significant findings related to reported phenotype.

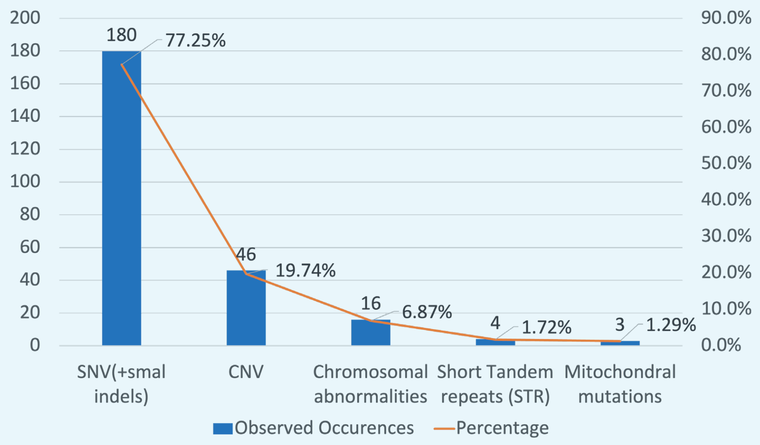

Figure 1: Reported occurrences and percentage of different variant types

Nearly 30% of cases with WGS findings related to phenotypes would not have been captured by assays only focusing on SNV/indels.

Case Type	Numbers	Percentage
Cases with SNV(+small indels) only	164	70.4%
Cases involved other variant types	69	29.6%

Examples of cases solved by variants other than SNV

Variant Type	Major Phenotypes	Variants Detected	Diagnosis
CNV	cleft lip/palate, PDA, ASD, respiratory failure	*De novo* deletion of exons 3-4 in *SPECC1L*	Teebi hypertelorism syndrome-1
Chromosomal	IUGR, dysmorphic features, thrombocytopenia	deletion of 11q23.3q25 and duplication of 16p13.3	Jacobsen syndrome & 16p13.3 microduplication
STR	congenital hypotonia	~2450 CTG repeats in *DMPK*	Congenital myotonic dystrophy-1
Mitochondrial	failure to thrive, chronic muscle weakness	*De novo* Heteroplasmic (~39%) m.14453G>A	*MT-ND6*-related disorders

An example of complex WGS findings: a mosaic monosomy X plus Xq21.31q28 deletion detected by the comprehensive ability of WGS analysis (Figure 2-5)

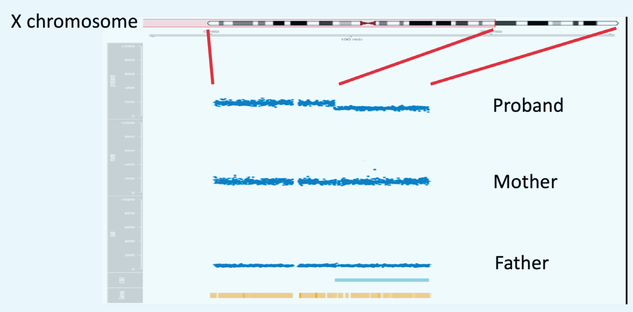

Figure 2: CNV analysis detected a *de novo* Xq terminal deletion in the proband

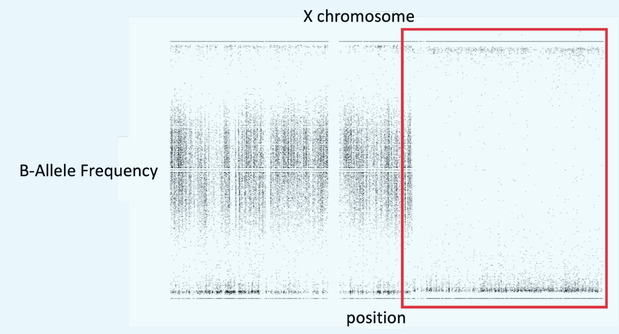

Figure 3: Terminal deletion in chromosome X consistent with the regions of homozygosity (ROH, indicated by red box) detected by WGS on the X chromosome.

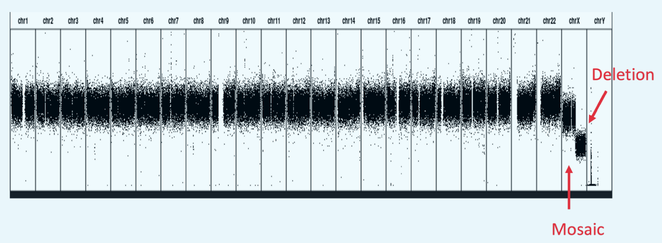

Figure 4: Genome wide review of read depth presentation however revealed a more complex scenario, suggestive of mosaicism for monosomy X in addition to the Xq terminal deletion.

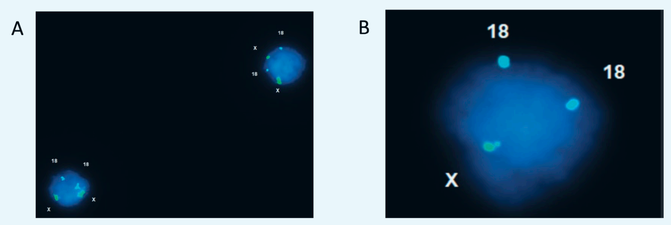

Figure 5: Further confirmatory rapid FISH test with X centromere probes detected 64% cells with two X chromosome (represented in picture A), while 36% cells with monosomy X (represented in picture B). Probe set for simultaneously detecting centromere of chromosome 18 and X were deployed.

CONCLUSIONS

These data affirm the utility of WGS as a comprehensive test for detecting an assortment of molecular variants to make a diagnosis. Many patients with hard-to-diagnose phenotypes are critically ill, and this data supports WGS as an expedient tool which can improve patient outcomes and avoid diagnostic odysseys. The availability of rapid WGS (~5 calendar day TAT) further supports the clinical utility of WGS.