Ultrarapid Whole Genome Sequencing Facilitates Early Definitive Diagnosis of Rare Genetic Disorders

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1 Introduction

Early definitive diagnosis helps to find any possible treatment options, better disease management and ultimately reduces healthcare burden related to pediatric disorders and other rare genetic disorders. With the recent reduced sequencing costs whole genome sequencing is playing an important role as a first -tier diagnostic test for rare genetic disorders. Ultrarapid whole genome sequencing is launched as the comprehensive diagnostic test with short turnaround time of 5-8 days in our laboratory. Here we present the interesting findings from 248 ultrarapid whole genome sequencing cases.

2 Materials and Methods

This comprehensive testing includes single nucleotide variant (SNV) analysis, copy number variant (CNV) analysis, mitochondrial variant analysis, repeat expansion disorder screening and deletion analysis for spinal muscular atrophy (SMA) in one assay. Whole genome sequencing was performed on genomic DNA using 2X150bp reads on Illumina next-generation sequencing (NGS) systems at a mean coverage of 40X in the target region. Sequence variants were assessed by our analysis and interpretation pipeline, Ordered Data Interpretation Network (ODIN). Copy number variants (CNV) analysis was assessed using Biodiscovery's NxClinical software (BioDiscovery, El Segundo, CA).

3 Results

In a cohort of 248 patients, we performed ultrarapid whole genome sequencing and definitive molecular diagnosis is established in 24.1% (60 of 248) cases tested. With the help of comprehensive coordination between laboratory team, analysis team and reporting team turnaround time of this assay is bring down to 5 days for majority of these tested cases which ultimately helped in providing early definitive diagnosis for pediatric disorders as well as other rare disorders.

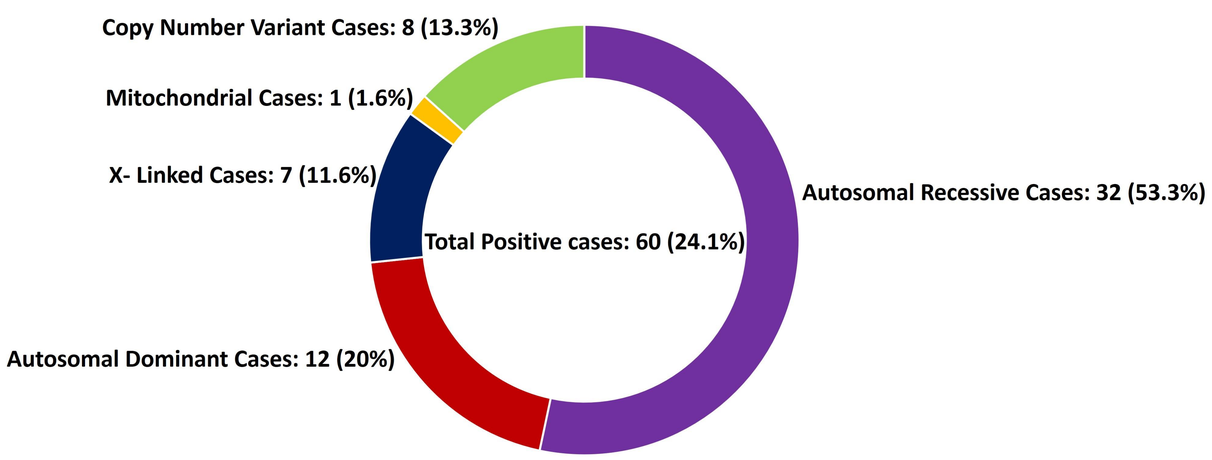

Figure 1. Summary of positive cases identified in ultrarapid WGS cases.

Autosomal recessive disorders identified in 53.3% (32/60) of definitive diagnostic cases including major contributing genes of *ATP7B*, *PEX1*, *ARSA*, *NPC1*, *TH*, *PGM3*, *STAC3*, *DNAJC30*, *TGM1*, *MYL2*, and *GBE1*. Autosomal dominant disorders identified in 20% (12/60) of definitive diagnostic cases including major contributing dominant gene of *SCN2A*, *CAMK2A*, *PTPN11*, *SOX9*, *NSD2*, *KMT2D*, *CREBBP*, *HNF4A* and *DYRK1A*. X-linked disorders identified in 11.6% (7/60) of definitive diagnostic cases including major contributing genes of *MECP2*, *IL2RG*, *FGD1*, *ABCD1*, *DDX3X*, *F8* and *G6PD* (Figure 1&2). Pathogenic copy number variants identified in 13% (8/60) of definitive diagnostic cases (Figure 1&3).

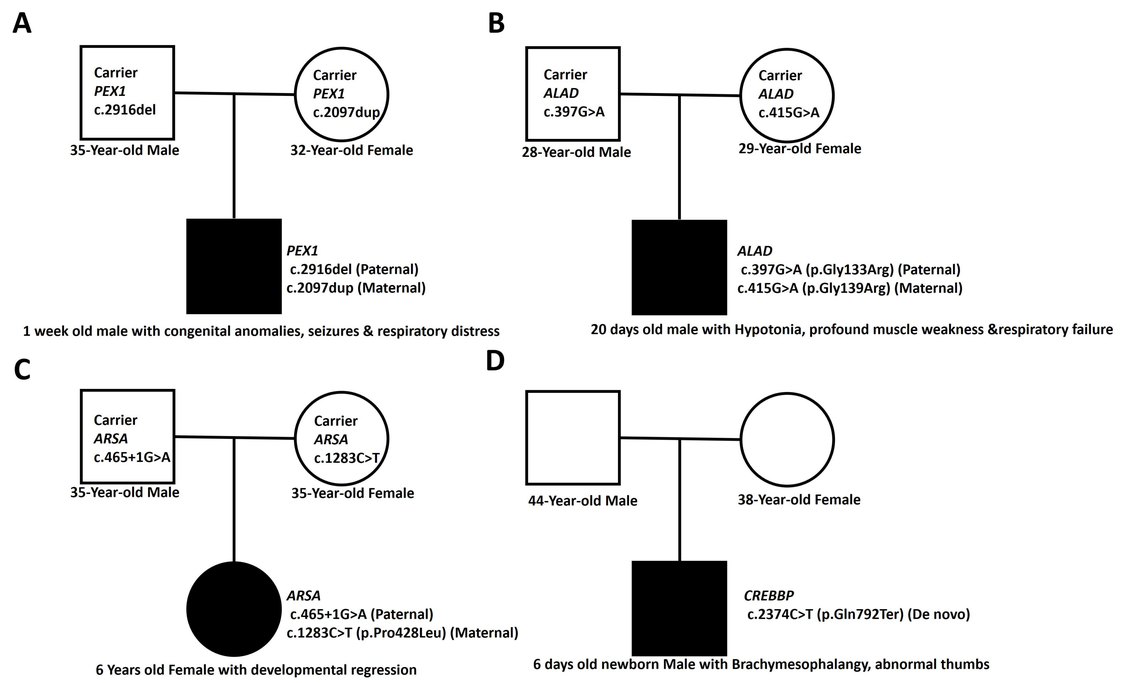

Figure 2. Early definitive diagnosis established with the help of ultrarapid WGS.

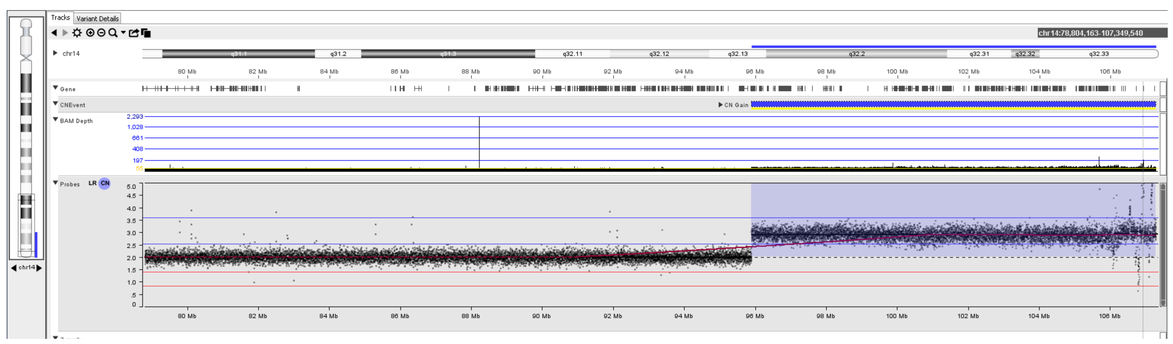

Figure 3. NGS based Copy Number Analysis with the help of ultrarapid WGS. An approximately 11.4 Mb copy number gain of chromosome 14q32.13 - q32.33 was identified in 1 year old male with hypoglycemia induced seizures, hypotonia, multiple congenital anomalies and developmental delay.

4 Conclusions

This comprehensive ultrarapid whole genome sequencing helped to identify different disorders including metabolic disorders, early infantile epileptic encephalopathy disorders, intellectual disability disorders and other rare disorders indicating importance of this test as first -tier diagnostic test. With a streamlined assay workflow turnaround time reduced to 5 days indicating this ultrarapid whole genome sequencing is highly suitable test for pediatric disorders as well as other rare genetic disorder and ultimately helps in early selection of any possible treatment options and better disease management.