A Diverse Set of Case Presentation Highlight the Power of Whole Genome Sequencing – What Next?

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BACKGROUND

- The progression of high throughput sequencing technologies in the past decades has promoted whole genome sequencing (WGS) as the most comprehensive method to scrutinize the entire human genome to identify sequencing and structural variants in coding and non-coding regions of the genome.
- Emerging data have demonstrated that WGS has become the first test to be considered for critically sick children and WGS trio analysis helped clinical diagnosis. Additionally, WGS has been used as a screening tool that allows healthy individuals to learn their potential risks of developing medically actionable conditions as well as carrier status.
- WGS conducted in our laboratory showed a diagnostic yield ranging from 38% to 48% in adult and pediatric patients, respectively (ACMG 2021 abstract).
- Despite the strengths of WGS in clinical testing and research, the weakness of WGS including misalignment due to repetitive sequences, limited knowledge to fully understand variants of uncertain significance cannot be neglected.

RESULTS

Case 1
- 20-year-old South Asian male
- Distal muscle weakness, myopathy, muscle atrophy, hyperCKemia, Gait difficulty
- Clinical suspicion of Nonaka myopathy

Case 2
- 2-year-old female
- Cerebellar ataxia, cerebellar atrophy, leukodystrophy, con-rod dystrophy, vision loss, developmental delay and intellectual disability
- Negative SNV and CNV by WGS
- ATXN7 GCA repeat expansion of 48-66 through WGS screening. Confirmatory test is required.

Case 3
- 5-years old female
- Limb girdle weakness, positive Gower’s sign, idiopathic gait dysfunction, femoral anteversion, hypermobility, proximal muscle weakness
- Neuromuscular panel is negative
- WGS screening revealed homozygous deletion of SMN1 exon 7, confirmed by MLPA

Case 4
- 6 months old female
- Retinoblastoma and extra-ocular features
- RB1 negative
- WGS detected a pathogenic mtDNA variant that was missed by WES due to low coverage

Case 5
- Family with two similarly affected preteen sisters
- Spastic diplegia, diplegic cerebral palsy, developmental delay, intellectual disability, midbrain lesion, macrocephaly, encephalopathy.
- Multiple variants reported by WES and microarray and yet non-diagnostic
- Two variants in trans in the newly defined HPDL gene associated with neurological disorder detected by WGS quad analysis, in both sisters

CONCLUSION

- Albeit the advantages of WGS to capture multiple types of genetic variation, provide complete picture of the individual's genetic makeup, large data set and variant/gene of uncertain significance also leads to difficulties in interpreting the test results.
- It necessitates to integrate genomic data with other levels of information including transcription, translation, epigenomics and metabolism, to delineate disease-causing mechanisms and genotype-phenotype correlation.