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Abstract Topic:- Molecular and cytogenetic diagnostics

Abstract Title:- The role and superiority of Whole Genome Sequencing in inherited neuropathies.

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Aims:-Genetics of inherited neuropathies is often complex as it could be monogenic causing either isolated peripheral neuropathy or as a part of a multi-system disease. Genotype – phenotype correlation becomes important in understanding the pathomechanism of hereditary neuropathies in the era of newer upcoming therapies and advanced genetic evaluations may be warranted when routine genetic test is inconclusive.

Methods:- Whole genome sequencing (WGS) was performed in two ambulant males with clinically suspected inherited neuropathy, 19-year-old and 5-year-old respectively. They presented with progressive distal muscle weakness and wasting in the lower limbs from early childhood. Nerve conduction studies showed a generalized neuropathy in the older proband and motor axonal neuropathy in the younger one. Both tested negative for deletions and duplications in PMP22 gene by Multiplex Ligation Probe Assay (MLPA) and subsequent whole exome sequencing failed to reveal an abnormality.

Results:- WGS of the 19-year young man revealed a compound heterozygous variant in the SPTBN4 gene: NM_020971.2:c.3481G>A (possibly damaging) and NM_020971.2:c.4716G>C (benign). These variants are known to cause neurodevelopmental disorder with hypotonia, neuropathy and deafness. WGS of 5-year-old boy showed a mutation in the GDAP1 gene in the heterozygous state which has been previously described with neuropathy in both autosomal dominant and recessive inheritance. The proband's father was a carrier of the same variant but his nerve conductions were normal.

Conclusions:- WGS is a useful tool in identifying disease-causing variants especially where there is a well described disease phenotype but a negative exome. Detailed phenotyping is crucial before proceeding to WGS to arrive at disease-causing variants to aid clinical management.

Keywords:- Whole exam and whole genome