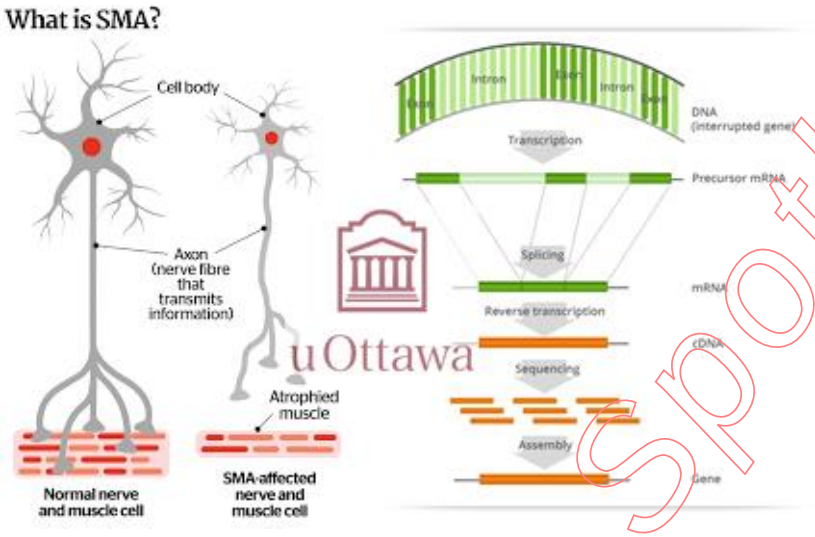
Genetic Science Spotlight

University of Ottawa diagnosis strategy confirms of spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) by Whole Transcriptome Sequencing



A study from University of Ottawa suggested that a Whole Transcriptome Sequencing may be used to diagnose spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) where mutations may also affect mRNA splicing sites. SMA-PME is a neurological condition that causes muscle weakness and wasting) and a combination of seizures and uncontrollable muscle jerks. A patient with a sporadic and atypical form of SMA presented to the regional Neurogenetics Clinic for evaluation identified a single variant in ASAH1 (NM_004315.4: c.458A>G; p.Tyr153Cys) and was classified as a variant of unknown significance. However, it was highly regarded to be the causal mutation to his phenotypes due its rarity in control cohorts and predicted deleterious protein function on the Polyphen-2 and SIFT. A subsequent leukocytes RNA was sequenced to a read depth of 63 million reads on an Illumina NextSeq500, using a combination of 150 base pair paired end and 75 base pair paired end technology revealed a highly significant and atypical ASAH1 isoform not explained by c.458A>G (pC;p.Lys168Asn) and provided a molecular diagnosis of autosomal recessive spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME). A Sanger sequencing was performed to assess for a second ASAH1 variant. A c.504A>C, p.Lys168Asn (NM_004315.4) variant located at the 3' end of exon 6 (-2bp from the splice junction) was identified where protein function prediction algorithm did not predict it to be damaging. The second mutation identified is likely to be the cause of the differential in splicing effect. The patient was concluded to carry biallelic ASAH1 mutations, c.504A>C (p.Lys168Asn) and c.458A>G (p.Tyr153Cys). This study suggests that Whole Transcriptome Sequencing may become a promising new tool in diagnosis of recessive conditions especially when only one pathogenic mutation is identified with the other remains unknown, and could play a key role in interpreting variants of unknown significance by establishing any splicing effects in a gene of interest, aiding in the identification of splice-impacting DNA mutations.

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