Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is a rare Mendelian disorder characterised by central nervous system hypomyelination. PMD typically manifests in infancy or early childhood and is caused by mutations in proteolipid protein-1 (PLP1). However, variants in several other genes including gap junction protein gamma 2 (GJC2) can also cause a similar phenotype and are referred to PMD-like disease (PMLD). Whole-exome sequencing in two siblings presenting with clinical symptoms of PMD revealed a homozygous variant in the arginyl-tRNA synthetase (RARS) gene: NM_002887.3: c.[5A>G] p.(Asp2Gly). Subsequent screening of a PMD cohort without a genetic diagnosis identified an unrelated individual with novel compound heterozygous variants including a missense variant c.[1367C>T] p.(Ser456Leu) and a de novo deletion c.[1846_1847delTA] p.(Tyr616Leufs*6). Protein levels of RARS and the multi-tRNA synthetase complex into which it assembles were found to be significantly reduced by 80 and 90% by western blotting and Blue native-PAGE respectively using patient fibroblast extracts. As RARS is involved in protein synthesis whereby it attaches arginine to its cognate tRNA, patient cells were studied to determine their ability to proliferate with limiting amounts of this essential amino acid. Patient fibroblasts cultured in medium with limited arginine at 30 °C and 40 °C, showed a significant decrease in fibroblast proliferation (P<0.001) compared to control cells, suggestive of inefficiency of protein synthesis in the patient cells. Our functional studies provide further evidence that RARS is a PMD-causing gene [1)].

Epilepsy regroups a common and diverse set of chronic neurological disorders that are characterized by spontaneous, unprovoked, and recurrent epileptic seizures. Epilepsies have a highly heterogeneous background with a strong genetic contribution and various mode of inheritance. X-linked epilepsy usually manifests as part of a syndrome or epileptic encephalopathy. The variability of clinical manifestations of X-linked epilepsy may be attributed to several factors including the causal genetic mutation, making diagnosis, genetic counseling and treatment decisions difficult.

Lyahyai et al., report the description of a Moroccan family referred to the genetic department with X-linked epileptic seizures as the only initial diagnosis.

Knowing the new contribution of Next Generation Sequencing (NGS) for clinical investigation, and given the heterogeneity of this group of disorders they performed a Whole-Exome Sequencing (WES) analysis and co-segregation study in several members of this large family. They detected a novel pathogenic PLP1 missense mutation c.251C > A (p.Ala84Asp) allowing to make a diagnosis of Pelizaeus-Merzbacher Disease for this family.

This report extends the spectrum of PLP1 mutations and highlights the diagnostic utility of NGS to investigate this group of heterogeneous disorders [2)].

Scala M, Traverso M, Capra V, Vari MS, Severino M, Grossi S, Zara F, Striano P, Minetti C. Pelizaeus-Merzbacher Disease due to PLP1 Frameshift Mutation in a Female with Nonrandom Skewed X-Chromosome Inactivation. Neuropediatrics. 2019 May 28. doi: 10.1055/s-0039-1688954. [Epub ahead of print] PubMed PMID: 31137068.

1)

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