MITOCHONDRIAL M.T4216C (p.Y304H) AND M.A4917G, (p.N150D) VARIATIONS IN A YOUNG PATIENT WITH MATERNALLY INHERITED DIABETES AND DEAFNESS

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Maternally Inherited Diabetes and Deafness (MIDD) is a rare form of diabetes that accounts up to 1-3% of all diabetes. At onset, MIDD is often misdiagnosed as type 1 or type 2 diabetes, depending on the severity of insulin deficiency, or as monogenic diabetes. The absence of autoimmunity and obesity and the presence of maternal heritability, distinguish the latter three forms of diabetes from MIDD respectively. Furthermore MIDD presents typical clinical features, such as bilateral neurosensorial hearing loss and macular alterations, in around 90% and 80% of patients respectively. Other elements indicating the mitochondrial origin of the disease, such as myopathies, heart disease and episodes of lactic acidosis are also sometimes present. MIDD is usually diagnosed by looking for mutation m.A3243G, tRNA $^{Leu(UUR)}$, in mitochondrial DNA, but several other mtDNA variants have been associated with a diabetic phenotype suggestive of MIDD.

The m.T4216C (p.Y304H) and the m.A4917G, (p.N150D) variants, in the in NADH-dehydrogenase gene MT-ND1 and MT-ND2 respectively, are known both as sequence polymorphisms, with 10% and 5% frequency, that detected in patients with Multiple Sclerosis, Type II Diabetes or Deafness. Very few studies have explored the role of these variations, individually or in association, in MIDD patients.

We investigated a young woman affected by diabetes mellitus, neurosensorial hearing loss and maculopathy. These clinical features suggested us a MIDD suspect. Genomic DNA from peripheral blood and buccal cells from patient was extracted and the whole mitochondrial genome sequenced and compared to mitochondrial reference sequence (rCRS NC_012920). In both biological samples we detected the m.T4216C and m.A4917G, homoplasmic variants. This finding supports the knowledge that both these mitochondrial variations could exert synergically a pathogenetic role in MIDD as well as in other diseases. However, due to controversial functional studies, these variations, either individually or together, should be also considered increasing the severity of other pathogenetic mutations.