

IDENTIFICATION OF MATERNAL UNIPARENTAL ISODISOMY OF CHROMOSOME 10 IN A PATIENT WITH MITOCHONDRIAL DNA DEPLETION SYNDROME

Nogueira C¹, Marques JS², Nesti C³, Azevedo A⁴, Di Lullo M⁵, Meschini MC³, Orlicchio A⁵, Videira A⁶, Santorelli FM³, Vilarinho L¹

¹Genetics Department, R&D Unit, National Institute of Health, INSA, Porto, Portugal; ²Unidade de Doenças Metabólicas, Serviço de Pediatria do Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal; ³Molecular Medicine & Neurogenetics, IRCCS Fondazione Stella Maris, Pisa, Italy; ⁴IPATIMUP, University of Porto, Portugal; ⁵Laboratorio di Neurogenetica, IRCCS Santa Lucia, Italy; ⁶ICBAS - Instituto de Ciências Biomédicas de Abel Salazar, University of Porto, Porto, Portugal

INTRODUCTION

Twinkle, the mitochondrial helicase encoded by *C10orf2*, serves a key function in mtDNA replication [1] and its mutations associated with a broad spectrum of clinical conditions characterized by qualitative or quantitative defects of mtDNA, including infantile-onset spinocerebellar ataxia (IOSCA), progressive external ophthalmoplegia, and the hepatocerebral mtDNA depletion syndrome (MDS). The signs in IOSCA demonstrate a fairly distinct pattern. Among these, peripheral neuropathy seems to be the most common presenting feature in *C10orf2* defects [2].

PATIENTS AND METHODS

We studied a Portuguese child, born to unrelated healthy parents, who presented hypotonia and Pierre-Robin sequence with mandibular retrognathism, partial syndactyly of 2nd–3rd fingers, bilateral strabismus, and eyelid asymmetry. The child manifested severe intellectual and developmental disability and nystagmus in the following months. Brain MRI revealed brain atrophy and a thin corpus callosum (Figure 1). Serum lactate levels were increased, OXPHOS activities in a skeletal muscle biopsy were in the low normal range and there was a severe mtDNA depletion in muscle (residual mtDNA levels were 20% of normal age matched controls).

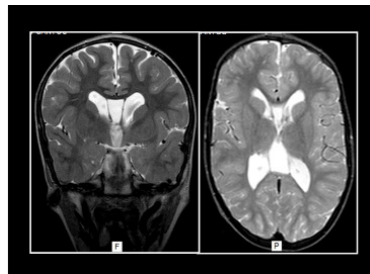


Figure 1. Brain MRI (coronal and axial images). There was decreased intensity in the posterior periventricular white matter and a thinner corpus callosum. No pathological signal changes were seen in the striatum, brainstem and dentate nuclei. F-frontal; P-posterior.

RESULTS

Two “in cis” homozygous splice site mutations in *C10orf2* (c.1593-3T>C + c.1593-5C>T) were identified (Figure 2a), which predicted in silico to activate a new cryptic acceptor site and lead to missplicing. The novel mutations were heterozygous in the mother and the healthy brother whereas the father was wild-type. Once a false paternity and a multi-exon deletion on the paternal allele by MLPA were ruled out, some microsatellite markers and SNPs flanking *C10orf2* on chromosome 10q24 were genotyped and the result was consistent with segmental uniparental isodisomic transmission (UPD) of the maternal chromosome 10 (Figure 2b).

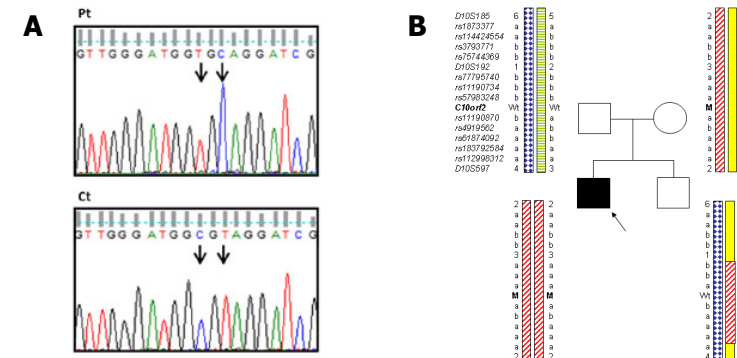


Figure 2. A) Electropherograms of the *C10orf2* gene flanking the homozygous splice site mutations ((c.1593-3T>C + c.1593-5C>T) identified in the patient (Pt). Wild-type sequence in a control (Ct) is also shown. The mutated bases are indicated with an arrow. B) Segregation analysis of polymorphic microsatellite markers and single nucleotide polymorphisms flanking the *C10orf2* gene suggested maternal UPD.

DISCUSSION / CONCLUSION

Our study expands the background of MDS patients with UPD, a similar condition has already been reported for *TYMP* and *DGUOK*, two other causes of MDS [3,4], and illustrates the need to consider UPD in cases of homozygosity of a rare mutation being responsible for recessive disease in non-consanguineous families. We report the first UPD of chromosome 10 in a patient presenting mutations in *C10orf2*.

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