COMPLEX III DEFICIENCY IN A PORTUGUESE FAMILY: EXPANDING THE CLINICAL PHENOTYPE

Célia Nogueira[1], Claudia Nesti[2], Maria Chiara Meschini[2], Rosalba Carrozzo[3], José Barros[4], Maria José Sá[5], Luísa Azevedo[6], Filippo M. Santorelli[2], Laura Vilarinho[1]

[1]National Institute of Health, Genetics Department, Neonatal Screening, Metabolism and Genetics Unit , Oporto, Portugal; [2]Molecular Medicine & Neurogenetics, IRCCS Stella Maris, Pisa, Italy; [3]IRCCS Bambino Gesù, Rome, ItaLY [4]Neurology Unit, Centro Hospitalar do Porto, Oporto, Portugal; [5]Neurology Unit, Centro Hospitalar S. João, Oporto, Portugal; [6]IPATIMUP, Population Genetics, Oporto University, Oporto, Portugal

INTRODUCTION

Defects of mitochondrial complex III (CIII) are a relatively rare cause of mitochondrial dysfunction. The complex catalyzes the electron transfer from reduced coenzyme Q to cytochrome c and is composed of 11 subunits, one of which (*MT-CYB*) is mtDNA encoded [1]. Mutations in *MT-CYB* and in assembly factor *BCS1L* account for the vast majority of cases with low CIII, and are associated with a wide range of neurological disorders [2].

The gene coding for human tetratricopeptide 19 (*TTC19*) produces a poorly characterized protein thought to be involved in the correct assembly of CIII. Recently, mutations in *TTC19* have been described in three unrelated Italian kindred in association with a severe neurodegenerative disease [3].

PATIENTS AND METHODS

Patients

We studied a consanguineous Portuguese family (Fig.1A) where a severe neurometabolic disorder occurred in four siblings (three men and one woman) in association with a slowly progressive disorder characterized by dystonia of hands and feet, ataxic gait, severe olivo-ponto-cerebellar atrophy documented at brain MRI (Fig.1B), and relentless psychiatric manifestations. Variability in age at onset and disease course was observed.

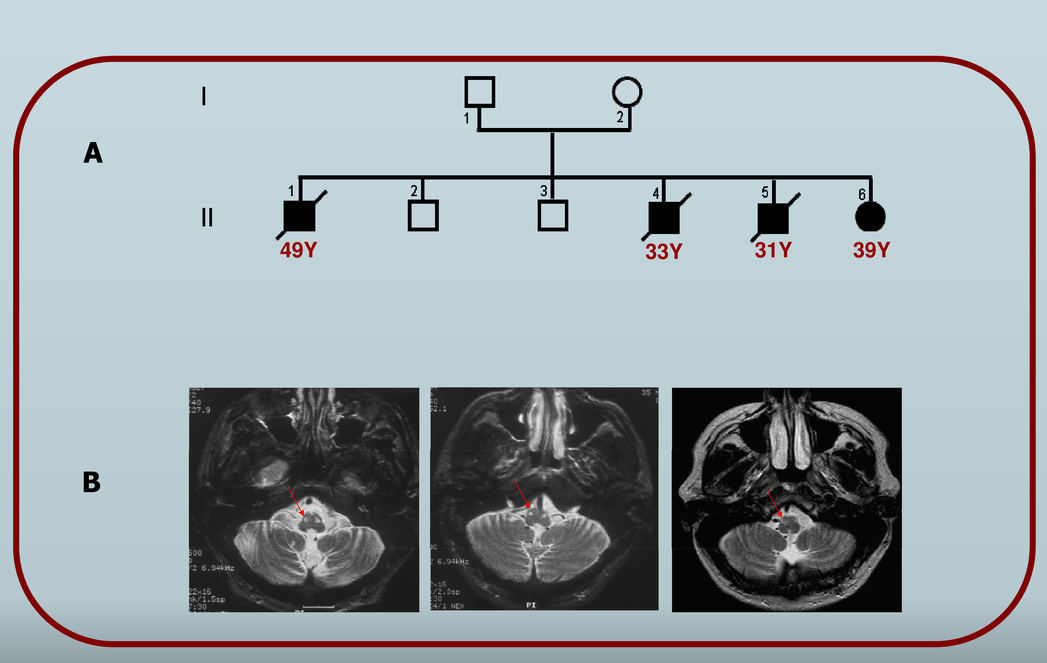

Figure 1 – A) Portuguese family pedigree. **B)** Brain MRI of the affected patients.

Methods

The enzymatic activity of CIII was determined in muscle using a reported spectrophotometric method. Sequence analysis of genomic DNA was performed to identify disease-causing mutations in *TTC19*. Western blotting in muscle homogenate and skin fibroblasts appraised the amount TTC19 protein using a commercially available anti-TTC19 antibody.

RESULTS

A marked reduction of CIII (33% of age-matched normal controls, on average) was identified in the four affected patients. A novel homozygous *TTC19* mutation: c.962_967delTGGC/p.A321Afs*8 (Fig.2A) predicting a frameshift and early protein truncation was also detected in the four patients. The mutation was heterozygous in parents and in two healthy siblings, and absent in ethnically-matched controls. The protein was undetectable by Western blot analysis (Fig.2B). Using 2D-BNGE, we also immunodetected lower–molecular-weight spots that reacted with α-Core2 antibody, suggesting impaired assembly of CIII (Fig.2C).

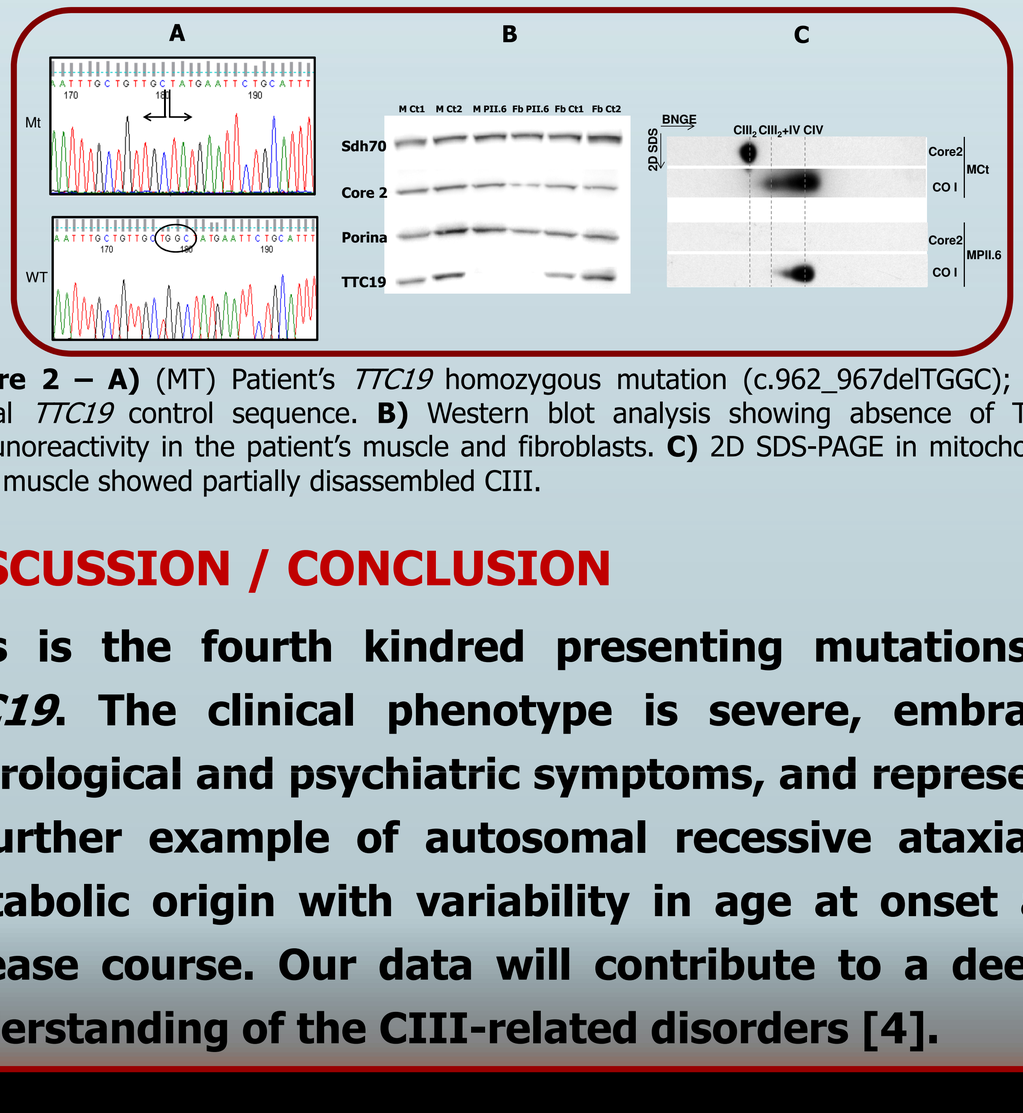

Figure 2 – A) (MT) Patient's *TTC19* homozygous mutation (c.962_967delTGGC); (WT) Partial *TTC19* control sequence. **B)** Western blot analysis showing absence of TTC19 immunoreactivity in the patient's muscle and fibroblasts. **C)** 2D SDS-PAGE in mitochondria from muscle showed partially disassembled CIII.

DISCUSSION / CONCLUSION

This is the fourth kindred presenting mutations in *TTC19*. The clinical phenotype is severe, embraces neurological and psychiatric symptoms, and represents a further example of autosomal recessive ataxia of metabolic origin with variability in age at onset and disease course. Our data will contribute to a deeper understanding of the CIII-related disorders [4].

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