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 kindreds in association with a severe neurodegenerative disease [3].

PATIENTS AND METHODS

Patients

We studied a consanguineous Portuguese family (Fig.1A) in which 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.

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_967delTGCC/p.A321fs*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).

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].

REFERENCES