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 (TTCT19) produces a poorly characterized protein thought to be involved in the correct assembly of CIII. Recently, mutations in TTCT19 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.

RESULTS
A marked reduction of CIII (33% of age-matched normal controls, on average) was identified in the four affected patients. A novel homozygous TTCT19 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).

DISCUSSION / CONCLUSION
This is the fourth kindred presenting mutations in TTCT19. 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.

REFERENCES