A genetic reevaluation of the first reported Italian family with FTD/ALS related to C9Orf72 repeat expansion mutation

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Introduction and objectives

The familial association of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) has been observed for decades but only in 2011 the discovery of the repeat expansion (RE) on C9ORF72 gene allowed to identify one of its most common genetic causes. In 1969 Dazzi and Finizio described a large Italian kindred affected by an autosomal dominant form of ALS with high penetrance, female predominance, frequent bulbar onset and high frequency of cognitive disorders [1]. Here we expand their original contribution and define the molecular basis of the first Italian kindred described with the association of ALS and FTD (FTDALS1).

Materials and methods

The family includes 44 members. A genealogical study was performed by reviewing medical records and by interviewing all available family members. Genomic DNA (gDNA) was isolated from subjects III:8, IV:1, IV:3 and IV:11 (Promega). Mutational screening of MAPT, PGRN, PRNP, LRRK2, ATXN3, HTT, ATN1, SOD1, PSEN1, PSEN2 genes, and of 11778, 3460, 14484 mtDNA nucleotides was performed. C9orf72 RE mutations were determined in 10 ng of gDNA using the 2-step strategy previously described [2]. The C9orf72 RE was confirmed by southern blotting.

Results

We included 13 affected members (11 f, 2 m) (Fig. A), seven already described [1]. Mean age at onset was 48.2 ± 7.1 y and mean disease duration was 5.5 ± 5.1 y. The diagnosis at presentation was ALS in 8 patients , FTD in 4, schizophrenia in 1. Three patients presented a pure ALS phenotype. In all other cases signs of cognitive impairment coexisted. ALS onset was bulbar in 6 and spinal in 2 patients (table). FTD presented as behavioral variant. In two patients psychotic symptoms were the disease presentation. Motor neuron disease signs consisted mainly of UMN signs with pseudobulbar palsy and only one case met criteria for probable ALS. Age at onset (48.2 ± 7.5 vs 51.2 ± 6.6 y), disease duration (4.8 ± 5.5 vs 6.7 ± 4.4 y) and age at death (53.1 ± 7.5 vs 57 ± 6.9 y) were lower in ALS patients in comparison with those with FTD, although the difference was not significant. On average, offsping tended to have a lower age at onset compared to their parents. Other clinical features were Parkinsonism, tremor, dyskinetic movements, focal dystonia and myoclonus, cerebellar signs, deafness, optic atrophy and epilepsy with a possible neuronal migration defect. A C9orf72 RE was found in subjects IV:1, IV:3 and IV:11 (Fig. B and C). Search for possible neuronal migration defect.

Discussion

The clinical features of our family are similar to those previously reported [3,4]. Additional features were deafness, optic atrophy and epilepsy related to a possible neuronal migration defect. However, no evidence of causative linkage exists to date between these clinical manifestations and the C9orf72 RE mutation.

Conclusions

We establish that one of the first pedigrees where FTD was demonstrated to be associated with familial ALS is linked to a C9orf72 RE and that it synthesizes all the clinical features described for FTDALS1. Moreover, our report strengthens the role of the C9orf72 RE, demonstrating the segregation of the mutation in the family.

References