A genetic revisitation 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 discover 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 mitochondrial DNA (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.

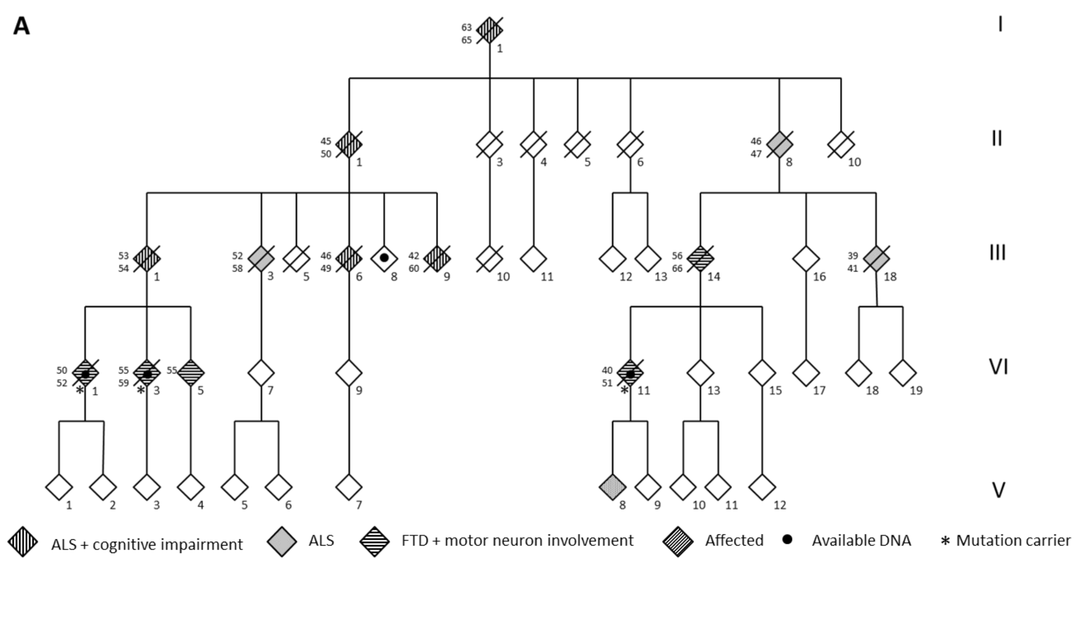
Results

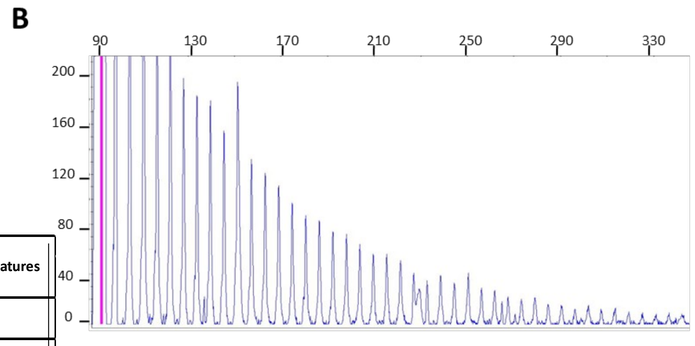
We included 13 affected members (11 f, 2 m) (Fig. A), seven already described [1]. Mean age at onset was 48,2 ± 7,1 y and mean disease duration was 5,5 ± 5,1 y. The diagnosis at presentation was ALS in 8 patients , FTD in 4, schizophrenia in 1. Three patients presented a pure ALS phenotype. In all other cases signs of cognitive impairment coexisted. ALS onset was bulbar in 6 and spinal in 2 patients (table).

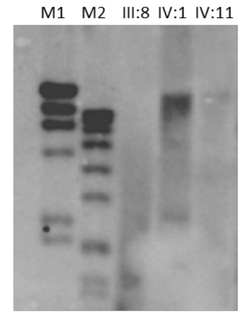
FTD presented as behavioral variant. In two patients psychotic symptoms were the disease presentation. Motor neuron disease signs consisted mainly of UMN signs with pseudobulbar palsy and only one case met criteria for probable ALS. Age at onset (48,2 ± 7,5 vs 51,2 ± 6,6 y), disease duration (4,8 ± 5,5 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, offspring 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 MAPT, PRNP, LRRK2, ATXN3, HTT, ATN1, PSEN1 and PSEN2 gene mutations, along with 11778, 3460, 14484 mtDNA mutations screening were negative.







Subject	Gender	Age of onset (y)	Survival (y)	age cognitive (y)	age motor (y)	Initial presentation	primary diagnosis	presence of FTD feature	presence of ALS feature	ALS features at onset (site of onset)	Cognitive involvement features						Other clinical features
											Depression	*Delusions/ Psychosis*	*Memory impairment*	*Aphasia*	*Frontal syndrome*	*Voracity*	
I:1	F	63	2	65	63	bulbar symptoms	ALS	x		bulbar, LMN	-	**	NA	-	NA	-	
II:1	F	45	5	45	45	bulbar symptoms	ALS	x		bulbar, LMN	-	-	**	-	-	-	
II:8	F	46	1	/	46	lower limbs weakness	ALS			lower spinal, LMN	-	-	-	-	-	-	
III:1	M	53	1	53	53	bulbar symptoms and memory deficit	ALS	x		bulbar and upper spinal, LMN	-	-	++	+	-	-	hypoacusia
III:3	F	52	6	/	52	bulbar symptoms	ALS			bulbar, LMN	-	-	-	-	-	-	dystonia and tremor
III:6	F	46	3	46	48	bulbar symptoms	ALS	x		bulbar, LMN	-	**	-	-	**	-	
III:9	F	42	18	NA	42	diffuse weakness	ALS	x		upper spinal, LMN	NA	NA	NA	NA	NA	NA	
III:14	F	56	10	56	NA	delusions	bvFTD		x	pseudobulbar	-	++	+		++	+	
III:18	F	39	3	/	39	bulbar symptoms	ALS			bulbar, LMN	-	-	-	-	-	-	parkinsonian features, nystagmus
IV:1	M	50	2	50	51	frontal syndrome	bvFTD		x	psuedobulbar	-	-	+		++	++	
IV:3	F	55	4	55	55	memory impairment and aphasia	bvFTD		xx	pseudobulbar	-	-	++	++	+	+	epilepsy; parkinsonian features and cerebellar signs
IV:5	F	55	-	55	NA	frontal syndrome	bvFTD		x	pseudobulbar	-	-	+	+	++	-	cerebellar sings
IV:11	F	40	11	40	43	schizophrenia	bvFTD		x	bulbar and spinal, UMN	+	++	+	++	+	+	hypoacusia,parkinsonism, myoclonus, dystonia

Figure – **A:** The pedigree of the family indicating inheritance, predominant clinical syndrome, age at onset and at death of affected individuals. Diamond symbols are for anonymity reasons. **B:** PCR products of RP-PCR reaction visualized by GeneMapper software. Electropherogram is zoomed to 200 relative fluorescence units to show stutter amplification. One expanded repeat carrier (IV:11) from family is shown. **C:** Southern blotting of two expanded repeat carriers and one non-carrier from family members. Lane 1 (M1) shows DIG-labeled DNA Molecular Weight Marker II (Roche Life Science), lane 2 (M2) DIGlabeled DNA Molecular Weight Marker VII (Roche Life Science).

Table – Clinical features of affected individuals. Y= years; ALS= amyotrophic lateral sclerosis; FTD= frontotemporal dementia; bvFTD= behavioral FTD; LMN= lower motor neuron; UMN= upper motor neuron; NA= not available;(++)= initial main feature; (+)= minor feature at onset; (**)= late manifesting main feature; (*)= minor late feature; (-)= absent.

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

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