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Rare variants in TP73 in a frontotemporal dementia cohort link this gene with primary progressive aphasia phenotypes

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Abstract

Objective: *TP73* was recently reported to cause Amyotrophic Lateral Sclerosis (ALS). ALS and Frontotemporal Dementia (FTD) are considered to be part of a continuum. We aimed to investigate whether *TP73* variants may be associated with FTD.

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Declaration of Interest

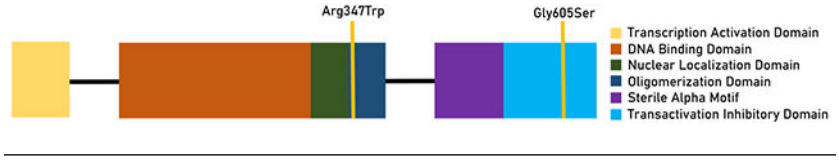
The authors report no conflicts of interest.

Methods: We studied a thoroughly investigated cohort of 65 Portuguese Frontotemporal Dementia patients by Whole-Exome Sequencing. Patients had no other known genetic cause for their disease.

Results: Of the 65 patients studied, two had rare variants in *TP73* (p.Gly605Ser and p.Arg347Trp). Both had MAF<0.001 and are predicted to be pathogenic *in silico.* Both patients showed a phenotype with predominant language impairment, suggestive of non-fluent progressive aphasia.

Conclusion: We show that thoroughly studied patients without other known genetic changes harbour *TP73* rare variants, which are pathogenic *in silico*. This adds evidence to the role of *TP73* in the ALS-FTD spectrum and especially in primary progressive aphasia cases.

Graphical Abstract



Introduction

Overtime, Frontotemporal Dementia (FTD) and amyotrophic lateral sclerosis (ALS) have evolved to be considered to be part of a continuum(1). Much of the support of this association comes from shared neuropathological substrates (mostly TDP43-, but also FUS-positive inclusions), but also from genetic data, as they share many genes as the underlying genetic cause of disease(2), such as *TARDBP, VCP, TBK1, CHCD10, SQSTM1, UBQLN2, CCNF, CHMP2B, OPTN, DTCN1, TUBA4A, hnRNP2B1* and *hnRPNA1*(1) and most importantly, the *C9ORF72* repeat expansion(3). Yet, many of the genes that have been associated with ALS have not been shown to cause FTD(3).

Recently Russell and colleagues (2020)(4) reported *TP73* as a new causative gene of ALS. The authors have analyzed whole exome sequences of ALS patients. They found five rare, nonsynonymous variants in *TP73* in a cohort of 87 sporadic ALS patients and an additional 19 in other independent cohorts of ALS patients, examining a total of 2,940 ALS patients. Then, they showed that these variants lead to dysfunctional apoptosis in mouse myoblast C2C12 differentiation assays, a model used to study other ALS genes in the past. They further showed that the loss of *TP73* leads to loss of number and axon branch length in spinal motor neurons in a zebra fish model.

We aim to investigate the role of *TP73* variants in a cohort of Frontotemporal Dementia patients.

Material and Methods

We conducted a study in a previously reported(5) cohort of 65 FTD patients from our memory clinic, in Centro Hospitalar e Universitário de Coimbra, Portugal. The diagnosis was performed according to the most widely accepted criteria(6,7), and supported by extensive characterization, including CSF biomarkers, when considered adequate. Patients

who developed ALS were excluded. The study was approved by the ethics committee of Coimbra University Hospital and biological samples were obtained following written informed consent from the patients' legal representatives. The study followed the principles of the Helsinki Declaration. Whole-exome sequencing was performed for all samples on a HiSeq2500 with 75-100 bp pair-end reads after library preparation using the SureSelect Exome Capture Kit v4 (Agilent). Exome data processing was accomplished following the GenomeAnalysisTK best practices through executing the alignment with the Burrows-Wheeler Aligner (bwa-mem) v0.7.12 against the hg19 genome assembly, identifying duplicates with samblaster v0.1.21 and recalibrating bases with GenomeAnalysisTK v3.8-1(8). Variant Quality Score Recalibration(9), and annotation with snpEff v4.2 and dbNSFP v2.9 were applied to all variants(10,11). Variants were filtered according to their quality metrics described by Patel and collaborators(12). Pathogenicity of the changes was evaluated *in silico* with CADD (Combined Annotation Dependent Depletion)(13), SIFT (Scale-Invariant Feature Transform)(14), Polyphen 2(15) and Mutation Taster(16). Scores and cut-offs suggested by the software's authors were considered. In CADD, a score higher than 15 was considered as deleterious.

Patients underwent a comprehensive baseline neuropsychological assessment composed by cognitive screening tests and the Battery of Lisbon for the Assessment of Dementia (BLAD(17)). This battery includes some tests of the Wechsler Memory Scale (WMS(18)) and assesses the following cognitive abilities: attention (Cancellation Task); verbal initiative (Semantic Fluency), motor and graphomotor initiatives; verbal comprehension (Token Test); verbal and non-verbal reasoning (Interpretation of Proverbs and the Raven's Coloured Progressive Matrices – Ab series); orientation (spatial, temporal and social orientation); visuoconstructive abilities (cube copy; clock drawing test); basic written and mental calculus; immediate memory (Digit Span Forward); visual memory (WMS Visual Reproduction Test); working memory (Digit Span Backward); learning and verbal memory (WMS Verbal Paired-Associate Learning, Logical Memory and Word Recall) and language: fluency (initial interview), object knowledge, verbal comprehension (Token Test), repetition (words, simple and complex phrases), naming, reading and writing (both spontaneous and by dictation).

This study complies with the Declaration of Helsinki and was approved by the regional ethical review board in Coimbra, Portugal (CE-029/2019).

Results

Of the 65 patients studied, two had rare variants in *TP73* (p.Gly605Ser and p.Arg347Trp). As there is evidence that the deltaN isoform is the dominant transcript in the brain(19), aminoacid changes in this isoform (p.Gly556Ser and p.Arg298Trp) are also depicted in table 1. Both had MAF<0.001 and are predicted to be *pathogenic in silico*.

Patient 1 was a male with a dementia starting at the age of 54 years of age and no family history. He was a soldier, without previous medical history. He then developed language problems, with a slow and effortful speech restricted to short and simple phrases, with casual omission of connecting words - agrammatism. Verbal comprehension (complex sentences),

sentence repetition and naming were also impaired. He had troubles in writing (both spontaneous and by dictation) with omission of letters and/or syllables. He had spared object knowledge and reading. He also started having problems in some daily chores, such as tying his shoes. On comprehensive neuropsychological evaluation he showed a severe deficit of frontal functions, and a language profile compatible with a non-fluent progressive aphasia. He also showed moderate visuoconstructive impairment. He had mild hypomimia and right limbs rigidity. MRI showed slight left hemisphere atrophy. On CSF biomarkers (table 2), despite having a reduced amyloid-beta, no changes on Total-Tau or phosphorylated Tau were identified. We found no other coding variants (pathogenic or of uncertain significance) that could explain the phenotype in the genes known to cause FTD, Alzheimer's disease, ALS or other related neurodegenerative disorders. He carried the p.Gly605Ser variant on *TP73*.

Patient 2 was a male of Italian and Swiss ancestry with dementia starting when he was 46 years old. His mother had a history of behaviour changes and started to crawl at the end of her life. She died at the age of 47. He had a history of cervical trauma, with mild motor sequelae. At the age of 46, he started having behaviour changes and trouble in speaking all the three languages he was fluent in (Portuguese, French and Italian). At the time of the first observation (he was 50 years old), he had also been having some gaming addiction. On neuropsychological evaluation, he had moderate impairment of executive functions and some language changes: he presented with speech slowness with a tendency to short phrases and troubles initiating conversations. Sentence repetition and naming were also impaired. He also showed troubles in writing in both Portuguese and French, with omission and change of letters. Object knowledge and reading were preserved. This neuropsychological profile point towards a diagnosis of nonfluent primary progressive aphasia. This left-side predominant impairment was supported by frontal and anterior temporal lobe hypometabolism, with a left predominance, on brain SPECT (single photon emission computed tomography). Cerebrospinal fluid biomarkers revealed normal values of amyloid-β_{42} with increased Total and phosphorylated Tau (table 2). He had pyramidal signs, which are considered to be associated with cervical trauma. EMG showed no signs of motor neuron involvement, up until now (the patient is currently 54 years old). He has progressed very slowly in the last 4 years, in terms of language impairment, but with increased behavioural changes. He is still not mute and shows no extrapyramidal signs. Pyramidal changes (probably associated with the cervical trauma) are stable. MRI showed mild atrophy, with predominant involvement of the left frontal and temporal lobes. We found no other variant that could explain the phenotype in the genes known to cause FTD, Alzheimer's disease, ALS or other coding variants (pathogenic or of uncertain significance) related to neurodegenerative disorders. He carried the *TP73* p.Arg347Trp variant.

Discussion

TP73 encodes p73, a member of the p53 family(20). This family of genes encodes transcription factors that play key roles as regulators of proliferation, differentiation, cell death, stem cell renewal, and cell fate commitment(21). However, mice where different isoforms of p73 have been deleted show, rather than enhanced tumor susceptibility (as it happens with p53), abnormalities of the nervous system, particularly the central nervous system(22). In fact, it has been shown that old p73+/− mice display reduced motor and

cognitive function, brain atrophy, and neuronal degeneration(23). The loss of p73 has an impact at the level of neuronal circuits, leads to altered neurotransmitter profile and impairs dendritic arborisation(22). All p53 family genes contain the same modular domain structure, including an amino-terminal transactivation domain, a DNA-binding domain and a carboxy-terminal oligomerization domain. The p73 gene contains 15 exons and transcription can be initiated from two N-terminal promoters, generating the transactivating isoforms and amino-terminal truncated proteins, which may display distinct biological activities.

The variant p.ARg347Trp is located in the highly conserved oligomerization domain, such as two of the variants reported by Russell et al.(4) (p.Arg362Gln and p.Leu380Val). Changes in this domain may impair the oligomerization that occurs with the protein with anormal function(24). This may lead to reduced functioning of p73 and neuronal damage. The variant p.Gly605Ser is located in the transactivation inhibitory domain, possibly impairing the transcriptional activity mediated by the N-terminal transactivation domain, leading to changes in the transcription of other genes. *TP73* is, for example, involved in the maintenance of neural stem self-renewal and differentiation throughout the regulation of SOX-2, Hey-2, TRIM32 and Notch. *TP73* has also been linked to the regulation of the differentiation and function of postmitotic neurons by regulating the expression of p75, NTR and GLS2(22).

Our study suffers from some limitations. First, by performing whole-exome sequencing, we could not exclude the presence of large-scale chromosomal rearrangements or repeat expansions (we only excluded *C9ORF72* repeat expansions). Secondly, we could not confirm the definite pathogenic nature of the variants reported. Thirdly, we do not have pathological confirmation of the diagnosis. However, it is important to start delineating the variability observed for *TP73* in disease in order to differentiate benign rare variants from those causing or associated with disease. Adding to the findings of Russell et al, rare variants in *TP73* are relatively frequent in our cohort (3.08%) of FTD, supporting the role of *TP73* in the ALS-FTD pathogenesis. Interestingly, both our patients had a predominant language involvement, with changes suggestive of non-fluent progressive aphasia, in a possible continuum with the motor phenotype of ALS. This adds evidence to the role of *TP73* in the ALS-FTD spectrum and especially in primary progressive aphasia cases.

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Data availability

Partial or complete data may be shared upon request to the corresponding author.

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Table 1:

TP73 rare variants found in our cohort. Scores for *in silico* tools and frequency on gnomAD are reported.

	Genomic position (zygosity)	Variant*	Isoform DeltaN Variant	rs	gnomAD MAF	CADD	SIFT	Polyphen2	Mutation Taster
Pt 1	Chr1: 3649545G>A (het)	p.Gly605Ser	p.Gly556Ser	rs752396818	0.00004729	19.79 (Deleterious)	0.008 (Damaging)	0.056 (Benign)	1.000 (Disease Causing)
Pt 2	Chr1: 3644746C>T (het)	p.Arg347Trp	p.Arg298Trp	rs750085774	0.000008920	23.5 (Deleterious)	0.000 (Damaging)	1.000 (Probably Damaging)	1.000 (Disease Causing)

* variants are reported for the canonical transcript ENST00000378295.4.

Pt: Patient; Het: heterozygous; rs: reference SNP; MAF: Minor Allele Frequency; CADD: Combined Annotation Dependent Depletion; SIFT: Scale-Invariant Feature Transform. gnomAD MAFs correspond to non-Finnish Europeans.

Table 2:

Demographic, clinical, radiological, neuropsychological and CSF biomarkers characterization of the two patients.

	Sex, Age of onset	Phenotype	Family History	ApoE	$A\beta_{42}$[1]	Tau[2]	P- Tau[3]	MRI
Pt1	M, 54	Language	-	ε3ε3	413.1	212.3	23.9	Mild left hemisphere predominant frontotemporoparietal atrophy
Pt2	M, 46	Language + behaviour	Mother	ε3ε3	855.3	155.7	28.3	Mild left frontotemporal atrophy

Pt: Patient; ApoE: Apolipoprotein E; $A\beta_{42}$: Amyloid-Beta$_{42}$; P-tau: Phosphorylated Tau; MRI: Magnetic Resonance Imaging; M: male; F: female.
1 – Normal values >542pg/mL; 2 - Normal values<212pg/mL; 3 - Normal values<32pg/mL.