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The Right Temporal Variant of Frontotemporal Dementia Is Not Genetically Sporadic: A Case Series

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Abstract.
Background: Right temporal variant frontotemporal dementia (rtvFTD) has been generally considered as a right sided variant of semantic variant primary progressive aphasia (svPPA), which is a genetically sporadic disorder. Recently, we have shown that rtvFTD has a unique clinical syndrome compared to svPPA and behavioral variant frontotemporal dementia.
Objective: We challenge the assumption that rtvFTD is a sporadic, non-familial variant of FTD by identifying potential autosomal dominant inheritance and related genes in rtvFTD.
Methods: We collected all subjects with a diagnosis of FTD or primary progressive aphasia who had undergone genetic screening ($n = 284$) and subsequently who had a genetic variant ($n = 48$) with a diagnosis of rtvFTD ($n = 6$) in 2 specialized memory clinics.
Results: Genetic variants in FTD related genes were found in 33% of genetically screened rtvFTD cases; including *MAPT* ($n = 4$), *GRN* ($n = 1$), and *TARDBP* ($n = 1$) genes, whereas only one svPPA case had a genetic variant in our combined cohorts. Additionally, 4 out of 6 rtvFTD subjects had a strong family history for dementia.

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Conclusion: Our results demonstrate that rtvFTD, unlike svPPA, is not a pure sporadic, but a heterogeneous potential genetic variant of FTD, and screening for genetic causes for FTD should be performed in patients with rtvFTD.

Keywords: Dementia, frontotemporal dementia, frontotemporal lobar degeneration, genetic, *GRN, MAPT*, right temporal lobe, *TARDBP*

INTRODUCTION

Frontotemporal dementia (FTD) is a syndrome caused by degeneration of the frontal and/or temporal lobes [1]. Patients with predominant behavioral disturbances and frontotemporal atrophy on neuroimaging are classified as behavioral variant FTD (bvFTD) [2], whereas the language predominant subtypes of FTD are classified under the umbrella of primary progressive aphasia (PPA) and have been associated with left hemisphere atrophy [3].

Over the years, the genetics of FTD have been broadly explored. The autosomal dominant inheritance pattern has been found higher in bvFTD, whereas semantic variant PPA (svPPA) is typically a non-familial sporadic disease [4–7]. Pathogenic variants are most common in the microtubule associated protein tau gene (*MAPT)*, the progranulin gene (*GRN*), and a hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 gene (*C9orf72),* whereas a variety of rare pathogenic variants has been described as well [5].

Currently, diagnostic criteria for a variant of FTD presenting with behavioral changes, memory deficit, and prosopagnosia in the presence of right temporal atrophy (rtvFTD) are lacking [8]. Because of the atrophy pattern, theoretically, rtvFTD is considered a right variant of svPPA [3, 9, 10] and the general assumption is that it is also a sporadic disease.

Only one study focusing on the underlying genetic and pathological features in rtvFTD, showed a positive family history in 45% of the patients with postmortem diagnostic confirmation [11]. Thus, we set out to investigate whether rtvFTD could be potentially a genetic disorder.

METHODS

In this report, out of 636 patients from the Amsterdam dementia cohort (ADC) with a clinical diagnosis of bvFTD ($n = 450$), non-fluent variant PPA ($n = 32$), logopenic variant PPA ($n = 18$), svPPA ($n = 65$), and rtvFTD ($n = 71$) (January 2000–November 2019) [12], we included 148 cases who had undergone genetic screening. Additionally, 136 FTD/PPA patients with genetic screening from the Istanbul University dementia cohort (IUDC) (November 1999-January 2020) [13] were included (total genetically screened patients, $n = 284$). Genetic screening was offered in case of a positive family history or when this was requested by the patient/caregiver. All included patients were screened for a variant in the *GRN* and *MAPT* genes. Additionally, a subset of patients was screened for the hexanucleotide repeat expansion in the *C9orf72* gene ($n = 189$) and/or the variants in other dementia genes with whole-exome sequencing (WES) ($n = 77$) (Supplementary Material 1). In 48 patients, pathogenic variants or variants of unknown significance (VUS) [14] in the FTD related genes were identified and six out of them met the clinical and the radiological characteristics of rtvFTD [8] (Supplementary Figure 1). Of note, in all subjects, the atrophy scores of the right temporal lobe [15–17] were higher (at least 1 grade) than the left temporal lobe and the frontal lobes that were assessed by a well experienced neuroradiologist who was blind to the clinical diagnosis (FB). Additionally, in our sample, the frontal atrophy scores were less than grade-1 [16] and none of the subjects met the diagnostic criteria of svPPA [3], while all of the fulfilled at least two symptoms out of prosopagnosia, episodic memory impairment, and behavioral change [8], even if they had an accompanying left temporal atrophy on the initial MRI. All subjects gave their written informed consent for the use of their clinical and genetic data for research purposes. Details of the genetic and pathological assessment are reported in Supplementary Material 1.

RESULTS

Demographic, clinical features are displayed in Table 1, and detailed case histories are reported in Supplementary Material 2.

In our combined cohorts, genetic variants in FTD related genes were found in 33% of genetically screened rtvFTD subjects (6 out of 18 genetically screened rtvFTD), whereas only one svPPA (1 out of 18 genetically screened svPPA) subject had a genetic variant.

Table 1
Demographic and clinical data

Institution	Case 1 ADC	Case 2 ADC	Case 3 ADC	Case 4 ADC	Case 5 IUDC	Case 6 ADC
Age (y)	59	64	58	53	63	58
Sex	Male	Female	Male	Female	Male	Female
Handedness	Right	Right	Right	Right	Right	Right
Symptom duration (y)	2	8	4	1	1	11
MTA (Right/left)	4/1	4/2	2/1	3/2	4/2	3/1
PET	N.A.	N.A.	Right temporal hypo-perfusion	N.A.	N.A.	N.A.
Gene	GRN	MAPT	MAPT	MAPT	MAPT	TARDBP
Variant	Gln130 Serfs*125	Ser305Thr	Ser352Leu	Arg406Trp	Pro301Leu	Ile383Val
Pathogenicity	Pathogenic [37]	Likely pathogenic [38]. *Other variants in this codon reported as pathogenic* [39–42]	Unknown significance [43]. *Heterozygous in our patient, homozygous in the reported patient*	Pathogenic [44].	Pathogenic [45].	Unknown significance [28–30]. *No data about pathogenicity in the reported patients*
Pathological confirmation	N.A.	N.A.	Suggestive for primary tau mutation	N.A.	N.A.	N.A.
Modified Goldman score	2	1	4	1	1	3
APOE	E3E3	E3E3	E3E4	E3E4	N.A.	N.A.
CSF, pg/mL*						
$A\beta_{42}$	1073	1101	716	1270	N.A.	1574
Tau	326	353	717	512	N.A.	311
P-tau	38	54	70	80	N.A.	37
Cognitive Tests						
MMSE	26/30	28/30	23/30	28/30	29/30	29/30
FAB	16/18	-	14/18	18/18	N.A.	18/18
VAT-A				4/12	N.A.	10/12
RAVLT delayed recall	-	-	-	8/30	N.A.	22/30
VAT naming	12/12	12/12	10/12	12/12	N.A.	10/12
TMT A	41” (A)	77,6” (LA)	-	52” (A)	N.A.	32” (A)
TMT B	88” (A)	192,7” (LA)	-	71” (A)	N.A.	70” (A)
VOSP-Dot Counting	10/10	10/10	10/10	10/10	N.A.	10/10
VOSP-FL	20/20	20/20	-	19/20	N.A.	-

ADC, Amsterdam Dementia Cohort; IUDC, Istanbul University Dementia Cohort; MTA, mesial temporal atrophy; PET, positron emission tomography; *APOE*, Apolipoprotein E; CSF, cerebrospinal fluid; $A\beta_{42}$, amyloid-β 42; P-tau, phospho tau; MMSE: Mini-Mental State Examination; FAB, Frontal assessment battery; TMT, Trail making test; VAT, Visual association test; RAVLT, Dutch version of the Rey Auditory Verbal Learning Test; VOSP, Visual objective and space perception; FL, Fragmented letters; L, Low; VL, Very low; HA, High average; LA, Low average; A, Average.
*Cutoff value for CSF $A\beta_{42}$ indicating Alzheimer’s disease pathology is <550 pg/mL, Tau >375 pg/mL, P-tau>52 pg/mL.

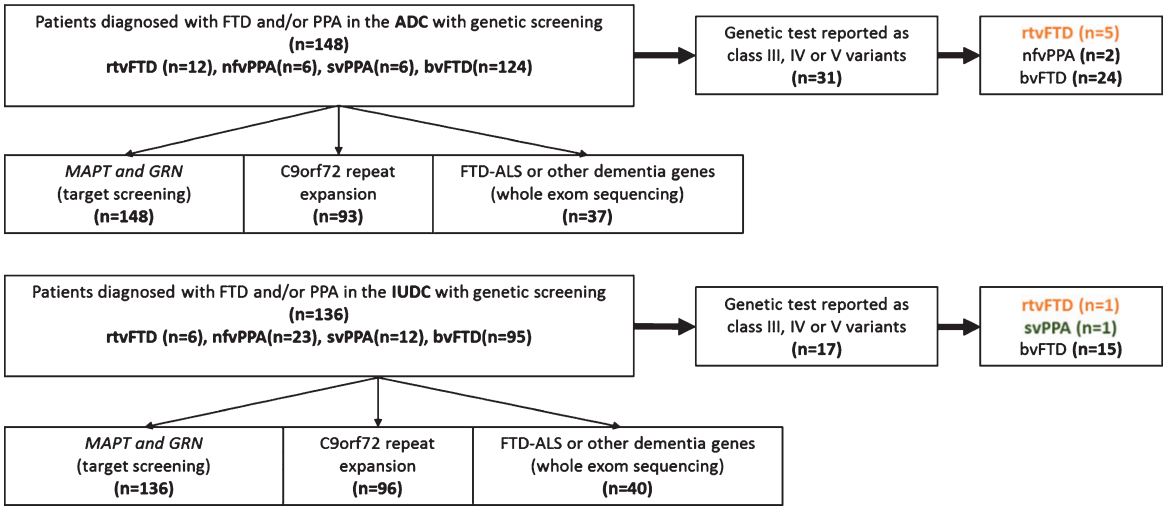

Fig. 1. Patient selection.

Summary of the cases

Case 1: A 59-year-old male presented with behavioral problems, memory deficit, depression, topographagnosia, and developed swallowing problems and mutism. The modified Goldman score [4] for family history was 2. We identified a heterozygous pathogenic variant in the *GRN* gene (NM 002087.3) c.388_391del, p.(Gln130Serfs*125).

Case 2: A 64-year-old female presented with prosopagnosia, behavioral changes, memory deficit, depression, and developed topographagnosia and motor restless. The modified Goldman score [4] for family history was 1. We identified a heterozygous likely pathogenic variant in the *MAPT* gene (NM 005910.5) c.914G>C, p.(Ser305Thr).

Case 3: A 58-year-old male presented with behavioral changes, depression, memory deficits, and developed prosopagnosia and atypical parkinsonism. The modified Goldman score [4] for family history was 4. We identified a heterozygous VUS in the *MAPT* gene (NM 005910.5) c.1055C>T, p.(*Ser 352Leu*). In addition, extensive 3R and 4R tauopathy was reported in his autopsy which is suggestive for a pathogenic mutation in the *MAPT* gene [18] (Fig. 2).

Case 4: A 53-year-old female presented with memory deficits, depression, apathy, and developed anomia and several behavioral problems. The modified Goldman score [4] for family history was 1. We identified a heterozygous pathogenic variant in the *MAPT* gene, (NM 005910.5) c.1216C>T, p.(*Arg406 Trp*).

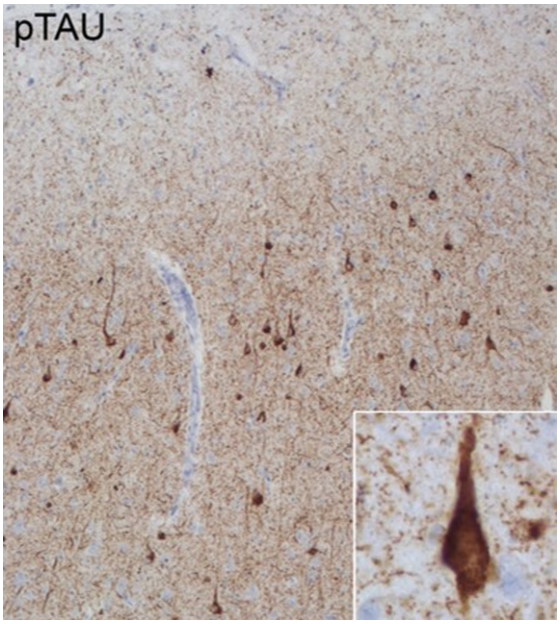

Fig. 2. Pathological features of Case 3. Anterior cingulate cortex stained with phospho-tau (p-tau) monoclonal antibody (AT8: Pierce Biotechnology, Rockford, IL, USA). Extensive 3R and 4R tauopathy which is characteristic for *MAPT* related frontotemporal lobar degeneration is observed in neurons across all layers.

Case 5: A 63-year-old male presented with behavioral changes, prosopagnosia, anomia, and single word comprehension deficit, and developed topographagnosia. The modified Goldman score [4] for family history was 1. We identified a heterozygous pathogenic variant in the *MAPT* gene (NM 005910.5) c.902C>T p.(*Pro301Leu*).

Case 6: A 58-year-old female presented with somatic and behavioral problems, memory deficit, and motor restless. The modified Goldman score [4] for family history was 3. We identified a heterozygous VUS in the *TARDBP* gene, (NM007375.3) c.1147A>G, p.(*Ile383Val*).

DISCUSSION

RtvFTD and svPPA are generally considered sporadic, non familial variants of FTD. In our combined cohorts, we can confirm that in svPPA rarely (∼5%) class III-V genetic variants in FTD related genes are found. However, 33% of rtvFTD patients that were screened for genetic mutations in FTD genes had a genetic variant. Moreover, these variants were in three different genes (*MAPT, GRN*, and *TARDBP*). This demonstrates that rtvFTD patients, unlike svPPA, are a heterogenous group that should be screened for genetic mutations.

The genetic diagnosis of four out of six rtvFTD cases was FTLD-*MAPT*. Previous clinico-radiological studies have shown that FTLD-*MAPT* links to bilateral anterior temporal atrophy [19], which might include rtvFTD. Moreover, the relationship between rtvFTD and *MAPT* mutations has been previously reported [11].

Besides the *MAPT* gene, the association between rtvFTD with variants in the *GRN* gene has been confirmed in separate case reports [20–23]. In many cases with a variant in the *GRN* gene, the asymmetric atrophy extends to the parietal lobe, which was not the case in our patient. Our finding underscores the observation that a pathogenic variant status in the *GRN* gene may be associated with an asymmetric atrophy pattern [24, 25], which can also involve uniquely the temporal lobe.

Although *TARDBP* gene mutations have been described in sporadic and familial amyotrophic lateral sclerosis (ALS) in early studies [26, 27], it has subsequently been associated with FTD without ALS [28–33]. Additionally, the heterozygous variant of Case 6 has been reported in subjects with temporal variant FTD without ALS [28–30].

In our study, four out of six patients had a strong family history for dementia. In the literature, a positive family history was reported in 37.5% (15 out of 40) of patients with rtvFTD [combined Chan et al. [34] and Josephs et al. [11]]. This percentage is quite high compared to svPPA in which a suggestive family history is identified in less than 5% of patients [6, 35].

Nonetheless, it is still unknown whether rtvFTD and svPPA share the same pathophysiology. A recent GWAS metadata analysis [36] has revealed that the svPPA gene network is uniquely associated with TAR DNA binding protein 43 metabolism. From this perspective, accompanying tauopathy in rtvFTD resembles the heterogeneous pathophysiology of bvFTD, rather than svPPA. On the other hand, although C9orf72 is the most common worldwide cause of genetic FTD [5], it should be noted that this variant was not found either in our study or other rtvFTD cohorts [11, 34]. Therefore, further research into the pathophysiological background of rtvFTD and how this relates to the other FTD subtypes is warranted.

In conclusion, currently, there is no consensus on whether rtvFTD is a mirror variant of svPPA or should be lumped with svPPA. Although reminiscent of svPPA, our findings show that rtvFTD, unlike svPPA, often has a genetic basis and the genetic variants are found in multiple genes. Therefore, genetic screening is essential in patients with rtvFTD.

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SUPPLEMENTARY MATERIAL

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