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ANXA11 Mutations in the FTD Spectrum: A Novel Finding in a Patient With Semantic Variant Primary Progressive Aphasia

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Keywords: *ANXA11* gene | D40G mutation | frontotemporal lobar degeneration | right temporal variant frontotemporal dementia | semantic variant primary progressive aphasia

ABSTRACT

Background: Semantic variant primary progressive aphasia (svPPA) is typically a sporadic disorder, and few cases have been linked to *ANXA11* mutations. Comprehensive analyses of genetic mutations in svPPA are limited. Furthermore, the clinical and genetic distinctions between typical svPPA and right temporal variant frontotemporal dementia (rtvFTD) are poorly understood.

Methods: A 68-year-old patient with svPPA carrying a heterozygous *ANXA11* c.119A>G (p.D40G) mutation underwent comprehensive neuropsychological, neuroimaging, and genetic assessments at baseline and at the one-year follow-up timepoint. Additionally, systematic reviews were conducted to identify reported cases of *ANXA11* mutations in the FTD spectrum and the genetic mutations associated with svPPA. Clinical-genetic profiles of typical svPPA and rtvFTD were compared based on data from the literature.

Results: Thirty-two patients with *ANXA11* mutations were identified, including 11 with pure FTD phenotypes and the majority exhibiting FTD-amyotrophic lateral sclerosis (ALS). Among 167 svPPA-related cases, *MAPT*, *GRN*, and *C9ORF72* mutations were most frequently implicated; *ANXA11* mutations were primarily identified in East Asian patients. Comparative analysis revealed overlapping age at onset, disease duration, sex distribution, and *APOE* ε4 allele frequencies between typical svPPA and rtvFTD but differing clinical presentations.

Conclusions: This study reports a case of typical svPPA in China associated with the *ANXA11* p.D40G mutation without ALS-related features. Our findings highlight the importance of *ANXA11* mutations in FTD pathogenesis.

Abbreviations: ABC, Aphasia Battery of Chinese; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant FTD; EEG, electroencephalography; EMG, electromyography; FTD, frontotemporal dementia; MRI, magnetic resonance imaging; nfvPPA, nonfluent variant primary progressive aphasia; NGS, next-generation sequencing; NPI, Neuropsychiatric Inventory; rtvFTD, right temporal variant frontotemporal dementia; SD, semantic dementia; svPPA, semantic variant primary progressive aphasia; WES, whole-exome sequencing.

Yaping Meng and Wenping Li contributed equally to this work.

1 | Background

Frontotemporal dementia (FTD) is the third most prevalent type of dementia across all age groups, after Alzheimer's disease (AD) and dementia with Lewy bodies [1]. FTD represents a clinically and genetically heterogeneous group of neurodegenerative disorders characterized by frontal and anterior temporal lobes atrophy and corresponding behavioral changes and/or impairment of executive function and language at early stages, mainly including three phenotypes of behavioral variant FTD (bvFTD) [2], semantic variant primary progressive aphasia (svPPA), and nonfluent variant primary progressive aphasia (nfvPPA) [3].

Genetic factors play a significant role in FTD, which are most frequently associated with mutations in genes such as *MAPT*, *GRN*, and *C9ORF72* [4]. However, the role of less common mutations, such as those in *ANXA11*, remains poorly understood. The *ANXA11* gene, located on human chromosome 10q22.3, was first proposed to be associated with amyotrophic lateral sclerosis (ALS) in 2017 and gradually became known as a causative gene for typical ALS. ALS is a progressive neurodegenerative disease that affects both upper and lower motor neurons and is characterized by progressive muscle atrophy and weakness, medullary palsy, pyramidal signs [5], and potential cognitive and behavioral changes during the disease course [6, 7]. Current evidence suggests a close relationship between FTD and ALS in terms of clinical features, genetic background, and neuropathology as a disease spectrum [8].

However, reports of *ANXA11* mutations associated with FTD, particularly svPPA, are limited. To date, four main *ANXA11* mutations associated with the FTD-ALS spectrum have been identified: p.P36R, p.G38R, p.D40Y, and p.D40G [9, 10]. Among these, the p.D40G mutation was first reported in a patient diagnosed with a right-sided variant of svPPA, notably without any ALS-related manifestations [11]. Here, we present a case of typical svPPA linked to the same p.D40G mutation. Comprehensive neuropsychological, neuroimaging, and genetic assessments were performed, and the results were compared with those reported in the literature. To contextualize this case, we systematically reviewed the mutation spectrum of *ANXA11* and its associated clinical manifestations in FTD.

Among the FTD spectrum disorders, svPPA is often regarded as a sporadic condition. Typical svPPA manifests predominantly as language deficits, including impaired naming and single-word comprehension, whereas its right-sided variant, often termed right temporal variant FTD (rtvFTD), presents with early behavioral abnormalities, prosopagnosia, and episodic memory impairment due to predominant right temporal lobe atrophy [12]. Recent studies indicate a greater prevalence of genetic mutations in rtvFTD than in the left-sided variant [13], emphasizing the importance of detailed genetic investigations. Interestingly, some studies suggest that the frequency of svPPA-associated genetic variants is greater than previously reported [10]. Moreover, a single-centre study highlights the need for molecular analysis of dementia-related genes in all patients with typical svPPA and rtvFTD [14]. In this study, we performed a comprehensive analysis of the genetic and clinical characteristics of typical svPPA and rtvFTD, highlighting their similarities and differences. By summarizing and comparing the clinical-genetic profiles of these two syndromes, this study aims to provide deeper insights into their pathogenesis and heterogeneity.

2 | Case Presentation

A 68-year-old right-handed man with a master's degree visited our memory clinic and presented with a progressive naming difficulty that had lasted for 3 years. His initial symptoms included difficulty naming low-frequency objects and poor single-word comprehension, occasionally accompanied by forgetfulness of recent events. Despite these challenges, his speech remained fluent and grammatically correct, and he showed no impairment in recognizing familiar people or objects. No signs of lower motor neuron disease, such as tongue atrophy, fasciculations, muscle weakness, dysphagia, or dysarthria, were observed. His medical history included depression at age 30 years, which was treated successfully with paroxetine for 1 year, after which he remained medication-free for more than three decades. He denied a family history of dementia, depression, and other related neurological or mental disorders. His parents died of natural causes in their 90s, and no significant medical history was reported among his first-degree relatives. He is a retired teacher who has lived in the city for a long time, with no history of unique chemical exposure.

No localized neurological signs other than language and cognitive function were observed via physical examination. Neuropsychological assessments revealed mild general cognitive impairment and worse performance in delayed recall and naming abilities. For neuropsychiatric symptoms, the Neuropsychiatric Inventory (NPI) score was 0. The results of the neuropsychological tests from the initial visit are summarized in Tables 1 and 2.

The complete blood count, B-vitamin level, and thyroid function test results were within normal ranges. The results of serological tests for syphilis and human immunodeficiency virus (HIV) were negative. Apolipoprotein E (APOE) genotyping revealed an ε2/ε3 genotype. Brain magnetic resonance imaging (MRI) revealed bilateral temporal atrophy, with the left side predominant, as shown in Figure 1. No clinically significant abnormalities were detected via electroencephalography (EEG). The patient did not cooperate with the electromyography (EMG) examination.

On the basis of this clinical information, neuropsychological test results, and neuroimaging features, the patient was clinically diagnosed with svPPA. Whole-exome sequencing (WES) was subsequently conducted using the MGISEQ-2000 platform (BGI-Tianjin Clinical Laboratories, Tianjin, China) and revealed a heterozygous c.119A>G (p.D40G) mutation in the *ANXA11* gene, which was further confirmed by Sanger sequencing (Figure 2).

3 | One-Year Follow-Up

At the one-year follow-up, the patient displayed behavioral changes, including suspicion of other people's motives, stubbornness, seriousness, anachronistic language and humor that others found unamusing. He also displayed social disinhibition,

TABLE 1 | Neuropsychological assessment of the patient.

Cognitive domain	Test and subtest	Initial visit	One-year follow-up
General cognition	MMSE(/30)	28	25
	MoCA(/30)	20	19
Episodic memory	AVLT total learning(/75)	22	26
	AVLT delay recall(/15)	0	0
	AVLT recognition(/15)	11	14
	BVMT-R total learning(/36)	15	11
	BVMT-R delay recall(/12)	6	4
	BVMT-R recognition(/12)	6	5
Processing speed	SDMT	26	35
	TMT-A	41	43
	SCWT-W	76	55
	SCWT-C	55	45
Executive function	SCWT-CW	32	25
	TMT-B	114	78
Language composite	AFT	20	13
	VFT	11	6
	BNT(/20)	13	14
Visuospatial function	JLO(/30)	28	22
Neuropsychiatric symptoms	NPI(/144)	0	7
	FBI(/72)	11	18

Note: Higher scores indicate better performance except for the TMT-A, TMT-B, NPI and FBI. The total score is noted for each scale if it has. Impairments were observed in the MoCA, AVLT, BVMT-R, SDMT, BNT and FBI at the initial visit. Further declines were observed in the MMSE, MoCA, SCWT, AFT, VFT, NPI and FBI at the one-year follow-up.

Abbreviations: AFT, Animal Fluency Test; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; BVMT-R, Brief Visuospatial Memory Test-Revised; FBI, Frontal Behavioral Inventory; JLO, Judgment of Line Orientation Test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; SCWT-CW, Stroop Color-Word Test (color-word condition); SCWT-W, and-C, Stroop Color-Word Test (word reading and color naming); SDMT, Symbol Digit Modalities Test; TMT-A, Trail Making Test-A; TMT-B, Trail Making Test-B; VFT, Vegetable Fluency Test.

such as engaging in conversations with strangers and suddenly singing during interactions, but still maintained fluency and correct grammar. Neuropsychological assessments revealed a further decline in general cognition and naming abilities, with slight worsening in visual, reaction and enumeration naming skills according to the Aphasia Battery of Chinese (ABC). Additionally, comprehension, processing speed, and executive function were also impaired at the follow-up compared with the initial visit. Notably, the patient's NPI score increased from 0 to 7, reflecting mild symptoms of aggression, hyperexcitability, and behavioral disinhibition (Tables 1 and 2). There were no significant changes in other clinical manifestations or imaging features.

4 | Methods

4.1 | Search Strategy

First, we conducted a systematic literature search of the PubMed and China Knowledge Network Infrastructure (CNKI) databases up to April 2025. The search was performed using the following keywords: ("annexin A11" OR "ANXA11") AND (("frontotemporal dementia" OR "FTD") OR ("amyotrophic lateral sclerosis-frontotemporal dementia" OR "ALS-FTD")). We subsequently searched the above databases with the following keywords: ("semantic variant primary progressive aphasia" OR "semantic dementia" OR "right temporal variant FTD") AND ("gene" OR "genetics") from 2003 to April 2025. Given the variability in naming conventions for rtvFTD, additional searches were performed to capture studies using synonymous terms, including "right temporal variant semantic dementia", "right temporal variant svPPA", "right predominant semantic dementia", "bvFTD presenting with right temporal atrophy", "right temporal variant bvFTD", and "FTD patient with right temporal atrophy". Finally, we extracted and summarized the clinical and genetic characteristics of each case from the literature.

4.2 | Patient Selection

Through detailed screening, on the one hand, we identified 13 FTD-relevant cases with *ANXA11* mutations, including our case, and the phenotypes of each case are listed in Table 3. Furthermore, additional data, such as sex, age at onset, age at death, disease duration (from age at onset to age at death or age at the last follow-up), family history, clinical onset, EMG, CT/MRI findings (predominant temporal atrophy distribution), and APOE genotype, were collected. On the other hand, we included patients with genetic mutations who were diagnosed with semantic dementia (SD) or svPPA according to the 1998 or 2011 diagnostic criteria [3, 24]. For rtvFTD, we followed the proposed clinical and neuroimaging framework [12], and all of the participants presented at least two of the following symptoms: prosopagnosia, episodic memory impairment, and behavioral changes. Clinical, neuroimaging, and genetic data from the references were sourced and compared between typical svPPA and rtvFTD patients (Table S1 and Table 4).

4.3 | Statistical Analyses

Qualitative and quantitative variables are presented as proportions (%) and means (standard deviations [SDs]), respectively. Differences in continuous variables and categorical variables between typical svPPA patients and rtvFTD patients were analyzed using two-sample t tests and chi-square tests, respectively. The analyses were performed using the Statistical Package of the Social Sciences (SPSS) Statistics Version 26.0 (IBM), and the level of significance was established at $P = 0.05$.

TABLE 2 | The ABC testing of the patient.

Language domain	Test and subtest	Initial visit	One-year follow-up
Spontaneous speech (/100)	Information content	100	83
	Fluency	100	100
	Repetition	100	100
Comprehension (/100)	Yes/no questions	100	83
	Auditory word/picture matching	100	100
	Following directions	100	100
Naming (/100)	Visual naming	100	83
	Reaction naming	100	80
	Enumeration naming[a]	20	13
Reading (/100)	Oral reading	100	100
	Auditory word and print matching	100	100
	Reading and following written directions	100	100
	Reading and filling in the blanks	100	75
Writing (/100)	Spontaneous writing	100	100
	Writing name and address	100	100
	Written naming of pictures	100	100
	Writing from dictation	100	83
	Copying	100	100

Note: Declines were observed in information content, yes/no questions, visual naming, reaction naming, enumeration naming, reading and filling in the blanks, and writing from dictation at the one-year follow-up.
Abbreviation: ABC, Aphasia Battery of Chinese.
[a]The score of enumeration naming refers to numbers of animal naming per minute.

5 | Results

5.1 | Data Extraction

A total of 13 papers encompassing case reports and clinical studies featuring individuals afflicted with FTD and ALS-FTD caused by *ANXA11* mutations were included, comprising a collective total of 32 patients. Additionally, 68 cohort studies, including ours, were eligible for the systematic review, and 167 results were closely related to the genes involved in typical SD/svPPA or rtvFTD. The summarized findings are detailed in Table 3 and Table S1.

5.2 | Review of FTD or FTD-ALS Patients With *ANXA11* Mutations

As depicted in Table 3 and Figure 4, seven distinct *ANXA11* variants were identified among the 32 patients, with p.P36R being the most common mutation (40.63%, 13/32), followed by p.D40G (37.50%, 12/32). A significant proportion of patients originated in China (43.75%, 14/32), followed by Korea (40.63%, 13/32), France (12.50%, 4/32), and the USA (3.13%, 1/32). The age at onset ranged from 49 to 79 years. Most patients (65.63%, 21/32) exhibited symptoms of FTD-ALS and presented with bulbar symptoms or limb weakness along with personality and behavioral changes or language impairments. The remaining 34.38% (11/32) were diagnosed with FTD without ALS-related symptoms, including 4 patients with bvFTD, 4 patients with typical svPPA, and 3 patients with rtvFTD. Most pure FTD patients with *ANXA11* mutations (72.73%, 8/11) did not have a positive family history. While follow-up data were limited, two patients were reported to have survived beyond 10 years. Neuroimaging findings, including temporal lobe atrophy patterns on CT/MRI, EMG, and Mini-Mental State Examination (MMSE) scores, are also summarized in Table 3.

5.3 | Genetic Analysis of Typical SD/svPPA and rtvFTD Patients

As demonstrated in Table S1 and in Figures 3 and 4, 167 patients diagnosed with SD/svPPA were enrolled in the study, which included 128 individuals with typical svPPA (76.65%), 19 with rtvFTD (11.38%), and 12 with svPPA-ALS (7.19%), while the remaining patients had other related diseases. Mutations in *MAPT* were the most frequently identified genetic contributors (25.15%, 42/167), followed by mutations in *GRN* (13.17%, 22/167), *C9ORF72* (11.38%, 19/167), *TARDBP* (11.38%, 19/167), and *TBK1* (7.19%, 12/167). Mutations in genes such as *CHCHD10*, *ANXA11*,

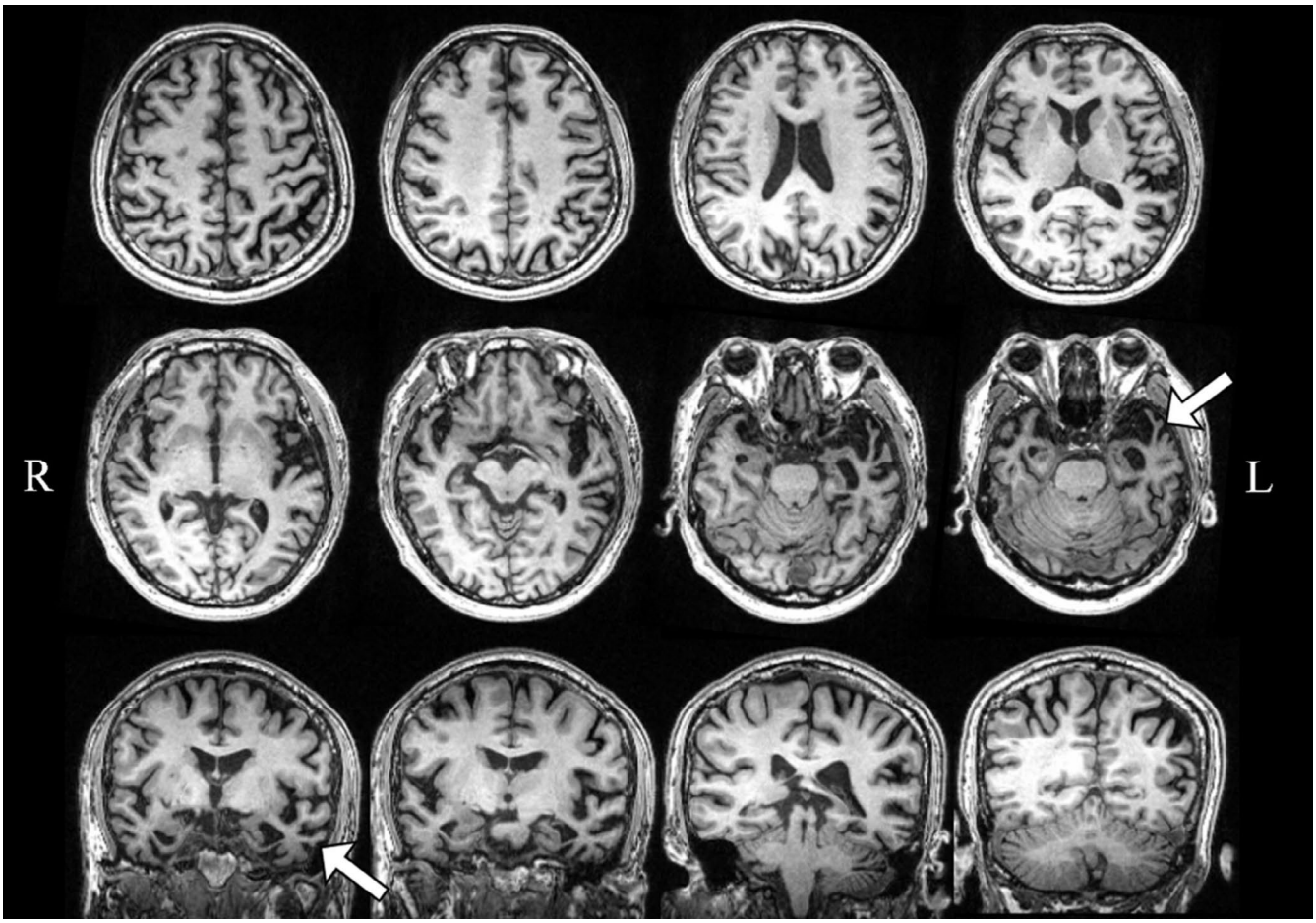

FIGURE 1 | Brain MRI of the patient with *ANXA11* mutation at the initial visit. Axial (upper two rows) and coronal (lower row) T1-weighted images show prominent atrophy in the bilateral anterior temporal lobes with left-predominant (arrow) and mild atrophy in the left frontal, parietal, and insular compared with the right side. *R* = right; L = left.

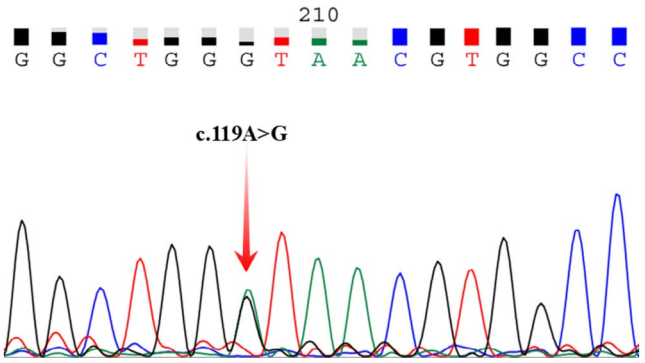

FIGURE 2 | Sanger sequencing shows the *ANXA11* c.119A>G (p.D40G) mutation.

VCP, *TREM2*, *OPTN*, *SQSTM1*, and *LRRK2* were less common. Geographically, most patients were from China (32.34%, 54/167) and Italy (11.98%, 20/167). *ANXA11* mutations were more prevalent in East Asia, whereas *C9ORF72* mutations have not been reported in Chinese patients. Table S1 provides additional information regarding the ages at onset and death, disease duration, onset of clinical symptoms, temporal lobe atrophy, family history, and *APOE* gene reported for each patient.

5.4 | Comparison of Demographic Characteristics Between svPPA Patients and rtvFTD Patients

A comparative analysis was conducted between typical svPPA patients and rtvFTD patients with age ranges of 34–78 years and 46–67 years, respectively, and mean ages at disease onset of 57.17 ± 8.53 and 57.53 ± 6.34 years, respectively. A positive family history was present in 64.80% of svPPA patients and 68.40% of rtvFTD patients who carried gene mutations. No statistically significant differences were observed between the two groups with respect to age at onset, disease duration, sex distribution, family history, or APOE ε4 allele frequency ($P > 0.05$, Table 4).

6 | Discussion

This study highlights the complex genetic and clinical landscape of FTD, with a specific focus on the implications of *ANXA11* mutations in disease pathogenesis and phenotypic variability. By reviewing and integrating clinical data and genetic findings, several critical points emerged that contribute to our understanding of the molecular underpinnings and clinical heterogeneity of svPPA.

TABLE 3 | Summary of *ANXA11* mutations related to FTD-ALS spectrum reported previously.

Reference	Pub-year	Country	Number	Mutant gene	Mutation sites	Phenotype	Sex	AO(Y)	AD(Y)	DD	Clinical onset	FHD	Temporal atrophy	EMG	MMSE
Zhang et al. [10]	2018	China	1	*ANXA11*	c.107C>G/p.P36R	ALS-bvFTD	M	70	Alive	3Y	Bulbar	UR	Bil	+	20
Ma et al. [15]	2020	China	1	*ANXA11*	c.107C>G/p.P36R	bvFTD	F	65	Alive	1Y	Personality	–	*R*>L	–	19
Teyssou et al. [9]	2021	France	2	*ANXA11*	c.112G>A/p.G38R	ALS-FTD	UR	68	Alive	20 M	UL	+	UR	UR	UR
							UR	61	Alive	46 M	UL	–	UR	UR	UR
			2	*ANXA11*	c.118G>T/p.D40Y	ALS-FTD	UR	56	Alive	67 M	LL	+	UR	UR	UR
							UR	59	Alive	49 M	Bulbar	+	UR	UR	UR
Wang et al. [16]	2022	China	1	*ANXA11*	c.119A>G/p.D40G	bvFTD-ALS	F	66	Alive	18 M	Behavior	+	Bil	+	25
Yang et al. [17]	2022	China	1	*ANXA11*	c.107C>G/p.P36R	ALS-bvFTD	M	70	Alive	About 3Y	Bulbar	UR	Bil	+	20
			1	*ANXA11*	c.107C>G/p.P36R	ALS-FTD	UR	UR	UR	UR	Muscle, cognition	UR	UR	UR	UR
Ma et al. [18]	2022	China	1	*ANXA11*	c.119A>G/p.D40G	ALS-FTD	F	54	Alive	6 M	Bulbar, language, memory	–	L>*R*	UK	7
Kim et al. [11]	2022	Korea	1	*ANXA11*	c.119A>G/p.D40G	rtvFTD	F	64	Alive	6Y	Prosopagnosia, language, memory	–	*R*>L	–	25
Sung et al. [19]	2022	Korea	1	*ANXA11*	c.107C>G/p.P36R	ALS-svPPA	F	79	Alive	5Y	Bulbar	UR	UR	UR	UR
			1	*ANXA11*	c.107C>G/p.P36R	ALS-nfvPPA	M	71	75	45 M	L	UR	UR	UR	UR
			1	*ANXA11*	c.107C>G/p.P36R	ALS-nfvPPA	M	76	78	27 M	Bulbar	UR	UR	UR	UR
			1	*ANXA11*	c.107C>G/p.P36R	ALS-bvFTD	M	65	Alive	22 M	Bulbar	UR	UR	UR	UR
			1	*ANXA11*	c.107C>G/p.P36R	ALS-bvFTD	F	64	Alive	16 M	L	UR	UR	UR	UR
			1	*ANXA11*	c.119A>G/p.D40G	ALS-bvFTD	F	54	55	19 M	Bulbar	UR	UR	UR	UR
			1	*ANXA11*	c.119A>G/p.D40G	ALS-svPPA	M	68	72	49 M	Bulbar	UR	UR	UR	UR
Nan et al. [20]	2024	China	1	*ANXA11*	c.119A>G/p.D40G	bvFTD	F	49	51	2Y	UR	–	Bil	UR	19

(Continues)

TABLE 3 | (Continued)

Reference	Pub-year	Country	Number	Mutant gene	Mutation sites	Phenotype	Sex	AO(Y)	AD(Y)	DD	Clinical onset	FHD	Temporal atrophy	EMG	MMSE
			1	*ANXA11*	c.107C>G/p.P36R	bvFTD	M	69	73	4Y	UR	−	Bil	UR	23
			1	*ANXA11*	c.107C>G/p.P36R	FTD-ALS	F	69	75	6Y	UR	−	L>*R*	UR	21
			1	*ANXA11*	c.463C>T/p.Q155*	svPPA	M	52	56	4Y	UR	−	Bil	UR	18
Shen et al. [21]	2024	China	2	*ANXA11*	UR/p.P36R	ALS-FTD	UR	UR	UR	UR	UR	UR	UR	UR	UR
			1	*ANXA11*	UR/p.A367V	ALS-FTD	UR	UR	UR	UR	UR	UR	UR	UR	UR
Snyder et al. [22]	2024	USA	1	*ANXA11*	UR/p.S55L	bvFTD	UR	UR	UR	UR	UR	+	UR	UR	UR
Lee et al. [23]	2025	Korea	5	*ANXA11*	c.119A>G/p.D40G	rtvFTD	F	55	Alive	9Y	Prosopagnosia	+	*R*>L	UR	30
						svPPA	F	71	Alive	11Y	Language, prosopagnosia	+	L>*R*	UR	26
						rtvFTD	F	60	Alive	10Y	Prosopagnosia	−	*R*>L	UR	28
						svPPA	F	54	Alive	7Y	Memory, behavior	−	Bil	UR	27
						rtvFTD-ALS[a]	F	71	Alive	4Y	Memory, behavior	+	*R*>L	UR	22
Current study		China	1	*ANXA11*	c.119A>G/p.D40G	svPPA	M	65	Alive	4Y	Language	−	L>*R*	UK	28

Abbreviations: AD, age at death; ALS, amyotrophic lateral sclerosis; AO, age at onset; bvFTD, behavioral variant FTD; DD, disease duration; EMG, electromyography; F, female; FHD, family history of dementia; FTD, frontotemporal dementia; L, limb; LL, lower limb; M, male; M, month; MMSE, Mini-Mental State Examination; rtvFTD, right temporal variant FTD; svPPA, semantic variant primary progressive aphasia (L, left; R, right; Bil, bilateral); UK, unknown; UL, upper limb; UR, not reported; Y, year.

[a]The patient later developed features suggestive of ALS at age 73.

TABLE 4 | Demographic and genetic characteristics of svPPA patients.

	Typical SD/ svPPA ($n=128$)	Actual n (typical SD/svPPA)	rtvFTD ($n=19$)	Actual n (rtvFTD)	P
Age at onset, years	57.17 (8.53)	115	57.53 (6.34)	19	0.864
Age range, years	34–78	115	46–67	19	—
Disease duration, years	5.51 (3.58)	70	7.32 (5.42)	19	0.184
Sex, male, (%)	50 (44.20%)	113	8 (42.10%)	19	0.862
Family history, n (%)	57 (64.80%)	88	13 (68.40%)	19	0.762
APOE ε4 allele frequency	7 (18.40%)	38	3 (37.50%)	8	0.473

Note: Data are presented as the mean (SD) or n (%) as indicated. N reflects the number of participants with available data for each variable. Continuous variables and categorical variables were analyzed by using two-sample t tests and chi-square tests, respectively.
Abbreviations: rtvFTD, right temporal variant frontotemporal dementia; SD, semantic dementia; svPPA, semantic variant primary progressive aphasia.

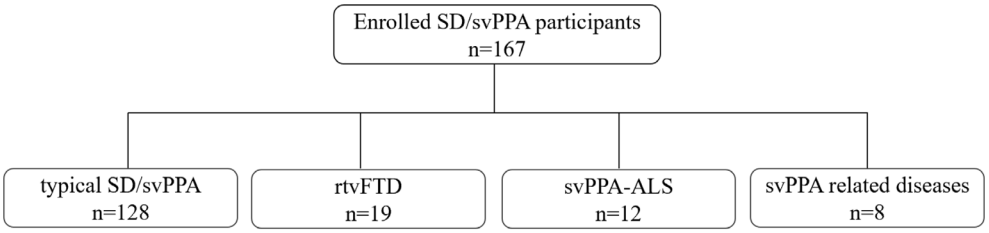

FIGURE 3 | Flow chart of the classification of enrolled svPPA participants. A total of 167 participants diagnosed with SD/svPPA were classified into four subtypes: Typical SD/svPPA ($n=128$), rtvFTD ($n=19$), svPPA-ALS ($n=12$), and svPPA-related diseases ($n=8$). SD, semantic dementia; svPPA, semantic variant of PPA; rtvFTD, right temporal variant FTD; ALS, amyotrophic lateral sclerosis.

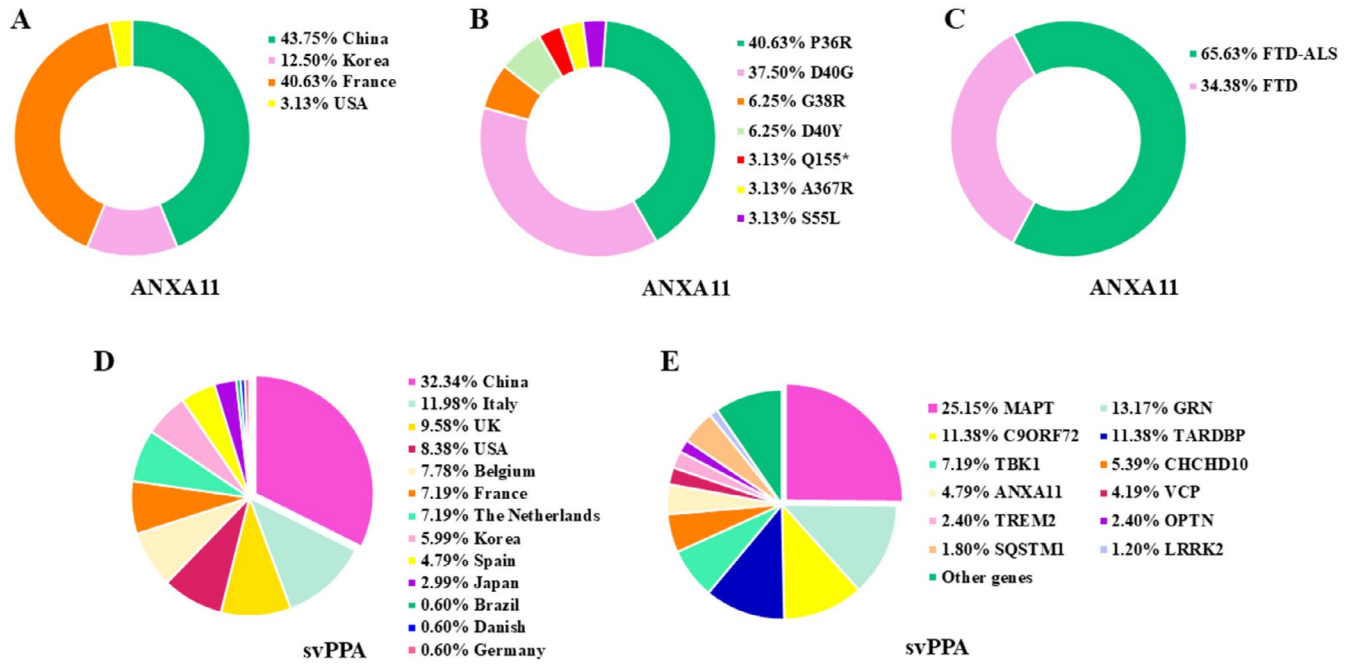

FIGURE 4 | Genetic analysis of the FTD-ALS spectrum with *ANXA11* mutations ($n=32$) and the genetic spectrum of the SD/svPPA patients ($n=167$). (A) Geographical distribution of *ANXA11* variants related to FTD-ALS spectrum patients previously reported. (B) Proportions of specific *ANXA11* variants identified. (C) Proportions of clinical subtypes of *ANXA11*-related cases categorized as FTD-ALS and FTD. (D) Geographical distribution of reported svPPA cases. (E) Genetic mutations identified in svPPA patients.

The *ANXA11* gene encodes annexin A11, which is a phospholipid-binding protein that forms phospholipid vesicles in vitro in a calcium-dependent manner [25]. This protein may be involved in various cellular processes, such as vesicle trafficking, apoptosis, cytokinesis, and cytoplasmic division [26]. Notably, a repeat sequence near the C-terminus of the protein is associated with lysosomal function, whereas the N-terminus contains a calcium cyclin-binding site, a specialized structural domain that

mediates the ubiquitination and proteasomal degradation of target proteins [27]. Recent studies have revealed a pathophysiological association between annexin A11 and TDP-43, particularly in FTLD-TDP type C. Under physiological conditions, both proteins are involved in the transport and metabolism of neuronal RNA, and thus they play essential roles in maintaining cellular homeostasis. Hydrophobic interactions between their low-complexity domains (LCDs) were shown to facilitate the formation of heterotypic amyloid filaments, which has redefined the histopathology of FTLD-TDP type C [28]. The p.D40G mutation in *ANXA11*, located near the calcyclin-binding region within the LCD, disrupts annexin A11 binding to calcyclin, leading to protein conformational changes and abnormal aggregation [29, 30]. These aggregates may alter the intracellular localization and function of TDP-43, disrupt RNA processing, and ultimately contribute to neuronal degeneration and death [31–33].

In our study, a svPPA patient without ALS caused by the p.D40G mutation in the *ANXA11* gene is presented. The first svPPA patient with the same mutation, described by Eun-Joo Kim et al. in 2022, was a 64-year-old female with difficulty recognizing familiar individuals and bilateral anterior temporal lobe atrophy, predominantly on the right side [11]. In contrast, our patient had predominantly left-sided atrophy and presented naming difficulties and reduced single-word comprehension, characteristics of typical svPPA. Patients with an identical mutation site manifested distinct clinical phenotypes. The diverse clinical manifestations of *ANXA11* mutations may be attributed to the specific regions of the central nervous system involved, e.g., annexin A11-positive aggregates were found in motor neurons of the spinal cord in postmortem tissue from an ALS patient carrying the p.D40G mutation [9, 26]. Additionally, other risk genes related to cognitive impairment or neurodegeneration may affect clinical progression. For instance, it has been observed that APOE interacts with C9ORF72 and influences cognitive features in patients with ALS [34].

While most *ANXA11* mutations manifest as FTD-ALS, the significant phenotypic variability among patients emphasizes the broad spectrum of disorders. These findings emphasize the need for targeted genetic screening for *ANXA11* mutations, particularly in FTD patients with overlapping motor and cognitive symptoms. A more precise genotype–phenotype correlation may be elucidated by investigating the regional, genetic, and phenotypic variability of *ANXA11* mutations.

Wang et al. [16] described a patient carrying the p.D40G variant who initially presented with bvFTD and subsequently developed bulbar and upper limb weakness within a few months. In a Korean cohort, Lee et al. [23] identified the same mutation in six patients diagnosed with svPPA. One of these patients developed ALS symptoms during the second year after disease onset at the age of 73, while the remaining five cases did not exhibit any clinical signs of ALS at follow-up over the course of the disease, which ranged from 6 to 11 years. Our patient has now been followed up for 1 year (the fourth year since symptom onset) and has still shown no significant ALS-related symptoms. Nevertheless, continuous follow-up and EMG are important to monitor disease progression and to find subclinical evidence in the future.

Most reported cases of FTD or ALS associated with *ANXA11* mutations are sporadic and lack a clear positive family history, which suggests that the mutation may have incomplete penetrance, that it may be a de novo mutation, or that the mutation may have variable expressivity. No clear conclusion has been established on the penetrance of the *ANXA11* p.D40G mutation in FTD cohorts, which is mainly due to the lack of large-scale family studies or population data. In a French cohort study, Teyssou et al. [9] found that *ANXA11* mutations, including p.D40G, may have incomplete penetrance and that some family members carrying the mutation did not exhibit clinical symptoms during follow-up. In 2025, Lee et al. [23] recruited 259 Korean patients with FTD and performed next-generation sequencing (NGS) to investigate the genetic contribution of *ANXA11* and concluded that the D40G mutation accounted for a mutation frequency of 2.3% in the FTD cohort overall (6/259), and of these patients, 3 had a positive family history.

The p.D40G mutation has previously been reported in European patients with ALS and has a common European founder [29]. In contrast, our systematic review highlights the predominance of *ANXA11* mutations in East Asian populations, which suggests potential regional or ethnic susceptibility. Although the variant had a very low frequency (< 0.0005%) in both European and East Asian populations based on the gnomAD database, we observed that *ANXA11* mutations associated with svPPA have been reported almost exclusively in East Asia. This relatively high detection rate may be explained by several factors: (1) the variant is extremely rare and may be missed in control populations with limited sample sizes; (2) it may represent an East Asian-specific or founder mutation; (3) incomplete penetrance could result in asymptomatic carriers; and (4) regional enrichment or sampling bias in patient cohorts cannot be excluded.

Our study provides valuable insights into the genetic landscape of svPPA. As highlighted in a recent review by Olszewska et al., 20%–50% of FTD cases are familial, with mutations in *MAPT*, *GRN*, and *C9ORF72* accounting for 60% of these cases. Among these, *C9ORF72* mutations are the most prevalent, contributing to approximately 25% of familial FTD cases [35]. We previously reported several variants in sporadic svPPA patients via genetic screening of a Chinese FTD and AD cohort [36]; these variants were identified in *GRN*, *MAPT*, *TARDBP*, *SPTBN2*, *EEF2*, *ABCA7*, *SORL1*, *NOS3*, and *ANXA11*, as identified in the present case. Interestingly, *C9ORF72* mutations are more common in Scandinavian and Northern European populations [37], whereas no mutations have been identified in Chinese svPPA patients to date. Moreover, another recent genetic screening study in a Chinese FTD cohort revealed *TBK1* and *OPTN* mutations as potentially common causative genes in svPPA patients [20]. Globally, the mutation rate for *TBK1* is high; however, *OPTN* mutations appear to be less prevalent in the current literature. These findings suggest that a broad spectrum of gene variants may contribute to the pathogenesis of svPPA with regional or ethnic differences, highlighting the importance of genetic analysis across populations.

The rtvFTD, a rarer clinical phenotype of FTD, which was originally considered the right-sided variant of svPPA, has distinct clinical features from typical svPPA and predominantly involves the right hemisphere. Although this study revealed demographic features similar to those of typical svPPA, rtvFTD patients had a slightly higher prevalence of positive family history, suggesting

a stronger genetic contribution. A study that analyzed 284 patients diagnosed with FTD or PPA identified genetic variants in 33% of rtvFTD patients ($n = 6$) [13]. Further research into the molecular differences between rtvFTD and svPPA may offer valuable insights for improving diagnostic accuracy and refining subtype-specific classification.

7 | Conclusion

This study reports a typical svPPA case associated with the c.119A>G (p.D40G) mutation in the *ANXA11* gene without concurrent ALS symptoms after 4 years of onset. Taken together with previous studies, these findings highlight the crucial role of *ANXA11* gene mutations in the development of FTD, including the svPPA phenotype, suggesting that ALS and FTD are on a spectrum based on a common genetic background. Further research is essential to elucidate the underlying mechanisms and develop targeted therapeutic approaches for *ANXA11* mutation-related FTD-ALS.

Author Contributions

Yaping Meng: conceptualization, methodology, writing – original draft, data curation, formal analysis, visualization, investigation, validation, software. **Wenping Li:** data curation, formal analysis. **Yanxin Zhang:** data curation, formal analysis. **Yaoru Li:** methodology. **Yong He:** data curation, formal analysis. **Nan Zhang:** funding acquisition, writing – review and editing, resources, supervision, conceptualization.

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Ethics Statement

This study was approved by the Ethics Committees of Tianjin Medical University General Hospital.

Consent

Informed consent was obtained from the patient and his guardian included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.