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RESEARCH ARTICLE

Semantic variant primary progressive aphasia with *ANXA11* p.D40G

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Abstract

INTRODUCTION: Pathogenic variants of annexin A11 (*ANXA11*) have been identified in patients with amyotrophic lateral sclerosis (ALS) with or without frontotemporal dementia (FTD). We explored *ANXA11* pathogenic variants in a Korean FTD cohort to investigate the prevalence and the role of *ANXA11* variation in FTD.

METHODS: We used next-generation sequencing (NGS) to search for pathogenic variants in *ANXA11* in two nationwide FTD cohorts in Korea.

RESULTS: We identified a pathogenic variant in *ANXA11*, c.119A > G (p.D40G), in six patients with semantic variant primary progressive aphasia (svPPA), representing 5.5% of the svPPA cohort (6/109), and representing 2.3% of the FTD cohort overall (6/259). Only one patient later developed features suggestive of ALS.

DISCUSSION: This study links a rare variant in *ANXA11* to a sporadic clinical syndrome in which specific TAR DNA-binding protein-43 (TDP-43) forms an obligate co-fibril

Young-Eun Kim, So Young Moon, and Eun-Joo Kim contributed equally.

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with annexin A11. The variant, p.D40G, lies within the N-terminal portion of annexin A11's TDP-43 type C interacting domain, suggesting that genetic variation in that region may promote co-fibrillization.

KEYWORDS
annexin A11, ANXA11, clinical genetics, frontotemporal dementia (FTD), FTLD-TDP type C, semantic variant primary progressive aphasia (svPPA), TDP-43

Highlights

- The pathogenic variant of annexin A11 (*ANXA11I*) is linked to frontotemporal dementia (FTD) syndrome.
- *ANXA11* (p.D40G) may be one of the possible genetic causes of semantic variant primary progressive aphasia (svPPA).
- *ANXA11* (p.D40G) may enhance heteromeric amyloid filaments of annexin A11 and TDP-43, promoting frontotemporal lobar degeneration with TAR DNA-binding protein-43 (TDP-43) inclusions (FTLD-TDP) type C.

1 | BACKGROUND

Frontotemporal dementia (FTD) is highly inheritable, with 25%–30% of cases having known pathogenic variants, usually in microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), or chromosome 9 open reading frame 72 (C9orf72) (*C9orf72*).[1] FTD overlaps clinically and pathologically with amyotrophic lateral sclerosis (ALS), and many ALS-causing pathogenic variants can also manifest as FTD. Among the FTD syndromes, however, semantic variant primary progressive aphasia (svPPA) stands out for its sporadic nature. Few patients report a family history, and the most common underlying histopathology, frontotemporal lobar degeneration with TAR DNA-binding protein-43 (TDP-43) inclusions (FTLD-TDP) type C, has not been directly linked to genetic disease.

One ALS gene loosely tied to FTD is annexin A11 (*ANXA11*) on human chromosome 10q22-q23. *ANXA11* encodes a calcium-dependent phospholipid-binding annexin A11 protein, which is involved in cell division, calcium signaling, and apoptosis.[2] In neurons, annexin A11 provides a tether between RNA granules and lysosomes as they are transported down dendritic microtubules.[3] Pathogenic variants of *ANXA11* were first discovered in European ALS cases in 2017.[2] Subsequently, several European and Asian ALS cohorts have been screened for *ANXA11* mutations, uncovering multiple *ANXA11* variants in familial or sporadic ALS cases.[4–10] One study also identified an *ANXA11* mutation in a patient with ALS-FTD.[5]

Recently our group reported a patient with svPPA who carries an *ANXA11* pathogenic variant (p.D40G), and we suggested that this variant might represent a novel genetic cause primarily associated with svPPA or svPPA-ALS.[11] Since this report, FTLD-TDP, type C, and annexin A11 were reported to co-localize in post-mortem brain tissue[12] and to form a heteromeric co-fibril now resolved ultra–structurally using cryo-electron microscopy.[13]

To shed light on the potential link between *ANXA11* pathogenic variants and FTD, we performed next-generation sequencing (NGS) in Korean patients. We identified five more patients with svPPA harboring the same variant (p.D40G) reported previously, and we describe the clinical, demographic, and neuroimaging features of patients with this variant.

2 | METHODS

2.1 | Patients

We conducted genetic analysis on patients recruited through two nationwide FTD cohort studies in Korea. One is the FTD sub-cohort of the Longitudinal study of Early onset dementia And Family members (LEAF-FTD), a nationwide early-onset dementia cohort, whose first phase ran from 2021 to 2023 and second phase is ongoing from 2024.[14] The other was an FTD subset of the Clinical Research Center for Dementia of South Korea (CREDOS-FTD), the earlier Korean dementia cohort, which had been in operation from 2010 to 2018 and enrolled patients with FTD exclusively.[15,16] Overall, 80 patients from the first phase of LEAF-FTD and 179 patients from CREDOS-FTD who had undergone whole-exome sequencing (WES) were included in the study. All LEAF-FTD participants regardless of genetic status or family history were included, but there was no patient with known genetic mutation or strong family history. All CREDOS-FTD participants in this study were also included in previously published genetic screening studies by our group,[17–19] but *ANXA11* screening was not performed in those studies. Therefore, we investigated

pathogenic variants of *ANXA11* in the established CREDOS-FTD NGS database.

2.2 | Clinical and molecular methods

Detailed methods for patient enrollment and genetic analyses in each cohort have been described elsewhere.[14–19] In brief, all participants from LEAF-FTD met the diagnostic criteria for behavioral variant FTD (bvFTD),[20] svPPA, and nonfluent/agrammatic variant PPA (nfvPPA),[21] corticobasal syndrome (CBS),[22] and progressive supranuclear palsy-Richardson syndrome (PSP-RS).[23] Patients with clinical and electrophysiological evidence of ALS[24] were categorized as FTD-ALS, regardless of the clinical FTD subtype. All participants underwent a standardized clinical assessment, brain magnetic resonance imaging (MRI), and amyloid positron emission tomography (PET). Patients from CREDOS-FTD met the FTD criteria proposed by Knopman et al.[25] or the same consensus diagnostic criteria for each FTD subtype applied in LEAF-FTD, and they were evaluated using the CREDOS-FTD protocol.[15]

The methods of WES performed on the two cohorts were as follows. Genomic DNA was extracted from peripheral blood leukocytes using a Wizard Genomic DNA purification kit according to the manufacturer's instructions (Promega, Madison, WI, USA). A total of 107 genes that are related to FTD, ALS, or other dementias in LEAF-FTD cohort (Table 1) and variants in *ANXA11* in the CREDOS-FTD NGS database were screened. Sequencing libraries were prepared according to the manufacturer's instructions using either a TruSightTM One Sequencing Panel (Illumina Inc., San Diego, CA, USA) or an Agilent SureSelect all Exon kit 50Mb (Agilent, Santa Clara, CA, USA). The flow cell was loaded on either a NextSeq 500 or a NovaSeq 6000 sequencing system (Illumina) for sequencing with 2 × 100 bp read lengths. Reads were mapped to the GRCh37/hg19 build using the Burrows-Wheeler Aligner (BWA), and variants were detected using GATK software. Variants with allele frequencies >0.001 were filtered out based on public databases, including the Genome Aggregation Database (http://gnomad.broadinstitute.org/) and 1722 ethnically matched controls from the Korean Reference Genome Database (KRGDB).[26] The variants were classified according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines.[27] All amino acid variants were confirmed using Sanger sequencing or DeepVariant (https://github.com/google/deepvariant, version 1.2.0). Hexanucleotide repeat expansion of chromosome 9 open reading frame 72 (*C9orf72*) was tested for all participants using the triplet repeat-primed polymerase chain reaction, as described previously.[28]

2.3 | Data analysis

Data analysis was conducted using SPSS version 21.0 (SPSS, Chicago, IL, USA), with results including the mean, median, standard deviation (SD), and range for quantitative variables, as well as absolute or relative frequencies for categorical variables.

RESEARCH IN CONTEXT

1. **Systematic review**: Pathogenic variants in annexin A11 (*ANXA11*) have been identified in amyotrophic lateral sclerosis (ALS), but their prevalence in frontotemporal dementia (FTD) syndrome remains uncertain. We identified a pathogenic variant in *ANXA11*,c.119A > G(p.D40G) in a patient with semantic variant primary progressive aphasia (svPPA), the FTD syndrome associated with a specific TAR DNA-binding protein 43 (TDP-43) fold, type C, which forms as a heteromeric fibril in concert with annexin A11. Thus we performed genetic screening of *ANXA11* to investigate its prevalence and role in Korean patients with FTD.
2. **Interpretation**: In this study, a pathogenic variant in *ANXA11* (p.D40G) was identified in six svPPA patients, accounting for 5.5% (6/109) of the svPPA and 2.3% (6/259) of the overall FTD cohort. Our findings suggest that a pathogenic variant in *ANXA11* (p.D40G) may enhance heteromeric amyloid filaments of annexin A11 and TDP-43 type C linked to a specific FTD syndrome, svPPA.
3. **Future directions**: Further studies on *ANXA11* variants in FTD syndrome are needed to confirm our conjecture.

3 | RESULTS

3.1 | Demographic and clinical characteristics

The 80 LEAF-FTD participants including 37 patients with bvFTD, 32 with svPPA, and 11 with nfvPPA, and the 179 CREDOS-FTD patients including 74 bvFTD, 77 svPPA, 23 nfvPPA, and 5 FTD-ALS were recruited, with a final cohort of 259 patients with FTD (111 bvFTD, 109 svPPA, 34 nfvPPA and 5 FTD-ALS). Participants were balanced between men and women, 22.8% had a family history of dementia or psychiatric disease in first-degree relatives, and all showed moderate overall clinical impairment. The detailed demographic and clinical data of the entire cohort are summarized in Table 2, and those for each FTD cohort in Table 3.

3.2 | Detection of the pathogenic variant of the *ANXA11* gene

Except for one patient with bvFTD carrying a cytochrome P450 Family 27 Subfamily 1 (*CYP27A1*) mutation in LEAF-FTD reported

TABLE 1 List of frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and other dementia-related genes.

Gene symbol	RefSeq	Gene description	Chromosomal location
AARS2	NM_020745.4	Alanyl-tRNA synthetase 2, mitochondrial	6p21.1
ABCD1	NM_000033.4	ATP-binding cassette subfamily D member 1	Xq28
AGRN	NM_198576.4	Agrin	1p36.33
ALS2	NM_020919.3	Amyotrophic lateral sclerosis 2	2q33.1
ANG	NM_001145.4	Angiogenin, ribonuclease, RNase A family, 5	14q11.1-q11.2
ANXA11	NM_145869.1	Annexin A11	10q22.3
APEX1	NM_001244249.1	Apurinic/apyrimidinic endodeoxyribonuclease 1	14q11.2
APP	NM_000484.4	Amyloid beta precursor protein	21q21.3
ARHGEF28	NM_001080479.2	Rho guanine nucleotide exchange factor 28	5q13.2
ARSA	NM_000487.6	Arylsulfatase A	22q13.33
CAMTA1	NM_015215.2	Calmodulin-binding transcription activator 1	1p36.31-p36.23
CCNF	NM_001761.3	Cyclin F	16p13.3
CFAP410	NM_004928.3	Cilia and flagella associated protein 410	21q22.3
CHCHD10	NM_213720.3	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10	22q11.23
CHCHD2	NM_016139.2	Coiled-coil-helix-coiled-coil-helix domain containing 2	7p11.2
CHMP2B	NM_014043.3	Chromatin-modifying protein 2B	3p11.2
CHRNA4	NM_000744.6	Acetylcholine receptor, neuronal nicotinic, alpha-4 subunit	20q13.2-q13.3
CSF1R	NM_001288705.3	Colony-stimulating factor 1 receptor	5q32
CYLD	NM_001378743.1	CYLD lysine 63 deubiquitinase	16q12.1
DAO	NM_001917.4	D-amino-acid oxidase	12q24
DARS2	NM_018122.5	Aspartyl-tRNA synthetase 2, mitochondrial	1q25.1
DCTN1	NM_004082.4	Dynactin 1	2p13
DNAJC7	NM_003315.3	DnaJ heat shock protein family (Hsp40) member C7	17q21.2
DNMT1	NM_001130823.3	DNA methyltransferase 1	19p13.2
DPP6	NM_130797.4	Dipeptidyl peptidase like 6	7q36.2
EIF2B1	NM_001414.4	Eukaryotic translation initiation factor 2B subunit alpha	12q24.31
EIF2B2	NM_014239.4	Eukaryotic translation initiation factor 2B subunit beta	14q24.3
EIF2B3	NM_020365.5	Eukaryotic translation initiation factor 2B subunit gamma	1p34.1
EIF2B4	NM_001034116.2	Eukaryotic translation initiation factor 2B subunit delta	2p23.3
EIF2B5	NM_003907.3	Eukaryotic translation initiation factor 2B subunit epsilon	3q27.1
ELP3	NM_018091.5	Elongator acetyltransferase complex subunit 3	8p21.1
ERBB4	NM_005235.2	Erb-b2 receptor tyrosine kinase 4	2q34
EWSR1	NM_005243.4	EWS RNA binding protein 1	22q12.2
FIG4	NM_014845.5	FIG4 phosphoinositide 5-phosphatase	6q21
FHIP2A	NM_02940.4	FHF complex subunit HOOK interacting protein 2A	10q25.3
FUS	NM_004960.3	FUS RNA binding protein	16p11.2
GALC	NM_000153.4	Galactosylceramidase	14q31.3
GBA1	NM_000157.4	Glucosylceramidase beta 1	1q22
GGNBP2	NM_024835.4	Gametogenetin binding protein 2	17q12
GLA	NM_000169.3	Galactosidase alpha	Xq22.1
GLE1	NM_001003722.1	GLE1 RNA export mediator	9q34.11
GLT8D1	NM_001278280.1	Glycosyltransferase 8 domain containing 1	3p21.1
GRN	NM_002087.2	Granulin	17q21.32
HAVCR2	NM_032782.5	Hepatitis A virus cellular receptor 2	5q33.3

(Continues)

TABLE 1 (Continued)

Gene symbol	RefSeq	Gene description	Chromosomal location
HFE	NM_000410.3	Homeostatic iron regulator	6p22.2
HNRNPA1	NM_031157.2	Heterogeneous nuclear ribonucleoprotein A1	12q13.1
HNRNPA1P10	–	Heterogeneous nuclear ribonucleoprotein A1 pseudogene 10	19p13.2
HNRNPA2B1	NM_031243.2	Heterogeneous nuclear ribonucleoprotein A2/B1	7p15
HNRNPH2	NM_019597.5	Heterogeneous nuclear ribonucleoprotein H2	Xq22.1
HTRA1	NM_002775.5	HtrA serine peptidase 1	10q26.13
ITM2B	NM_021999.5	Integral membrane protein 2B	13q14.2
ITPR2	NM_002223.2	Inositol 1,4,5-trisphosphate receptor type 2	12p11.23
KIAA1217	NM_019590.3	KIAA1217	10p12.2-p12.1
KIF5A	NM_004984.2	Kinesin family member 5A	12q13.3
KIFAP3	NM_014970.3	Kinesin associated protein 3	1q24.2
LILRB2	NM_001080978.4	Leukocyte immunoglobulin like receptor B2	19q13.42
LRRK2	NM_198578.4	Leucine rich repeat kinase 2	12q12
MAPT	NM_005910.5	Microtubule-associated protein tau	17q21.1
MATR3	NM_199189.2	Matrin3	5q31.2
MOBP	NM_182935.3	Myelin associated oligodendrocyte basic protein	3p22.1
NEFH	NM_021076.3	Neurofilament heavy chain	22q12.2
NEK1	NM_001199397.1	NIMA related kinase 1	4q33
NOTCH3	NM_000435.3	Notch receptor 3	19p13.12
NT5C3B	NM_052935.5	5′-nucleotidase, cytosolic IIIB	17q21.2
NTN5	NM_145807.4	Netrin 5	19q13.33
OPTN	NM_021980.4	Optineurin	10p13
PFN1	NM_005022.3	Profilin 1	17p13.2
PINK1	NM_032409.3	PTEN-induced kinase 1	1p36.12
PLCD1	NM_001130964.1	Phospholipase C delta 1	3p22.2
PON1	NM_000446.5	Paraoxonase 1	7q21.3
PON2	NM_000305.3	Paraoxonase 2	7q21.3
PON3	NM_000940.2	Paraoxonase 3	7q21.3
PRKN	NM_004562.3	Parkin RBR E3 ubiquitin protein ligase	6q26
PRNP	NM_000311.3	Prion protein	20p13
PRPH	NM_006262.3	Peripherin	12q13.12
PSEN1	NM_000021.4	Presenilin 1	14q24.2
PSEN2	NM_000447.3	Presenilin 2	1q42.13
SCFD1	NM_016106.3	Sec1 family domain containing 1	14q12
SERPINI1	NM_001122752.2	Serpin family I member 1	3q26.1
SETX	NM_015046.5	Senataxin	9q34.13
SIGMAR1	NM_005866.2	Sigma non-opioid intracellular receptor 1	9p13.3
SNCA	NM_000345.4	Synuclein alpha	4q22.1
SNCB	NM_003085.5	Synuclein beta	5q35.2
SOD1	NM_000454.4	Superoxide dismutase 1	21q22.11
SORL1	NM_003105.6	Sortilin related receptor 1	11q24.1
SPG11	NM_025137.3	SPG11, spatacsin vesicle trafficking associated	15q14
SPTLC1	NM_006415.3	Serine palmitoyltransferase long chain base subunit 1	9q22.31
SQSTM1	NM_003900.4	Sequestosome 1	5q35.3

(Continues)

TABLE 1 (Continued)

Gene symbol	RefSeq	Gene description	Chromosomal location
SRCAP	NM_006662.2	Snf2 related CREBBP activator protein	16p11.2
SS18L1	NM_198935.1	SS18L1 subunit of BAF chromatin remodeling complex	20q13.33
TAF15	NM_139215.2	TATA-box binding protein associated factor 15	17q11.1-q11.2
TARDBP	NM_007375.3	TAR DNA binding protein	1p36.22
TBK1	NM_013254.3	Tank-binding kinase 1	12q14.2
TET2	NM_001127208.3	Tet methylcytosine dioxygenase 2	4q24
TIA1	NM_022173.4	TIA1 cytotoxic granule-associated RNA-binding protein	2p13.3
TMEM106B	NM_001134232.2	Transmembrane protein 106B	7p21.3
TNIP1	NM_006058.5	TNFAIP3 interacting protein 1	5q33.1
TREM2	NM_018965.2	Triggering receptor expressed on myeloid cells 2	6p21.1
TRPM2	NM_003307.3	Transient receptor potential cation channel subfamily M member 2	21q22.3
TUBA4A	NM_006000.2	Tubulin alpha 4a	2q35
TYROBP	NM_003332.4	Transmembrane immune signaling adaptor TYROBP	19q13.12
UBQLN2	NM_013444.3	Ubiquilin 2	Xp11.21
UNC13A	NM_001080421.2	Unc-13 homolog A	19p13.11
VAPB	NM_004738.4	VAMP (vesicle-associated membrane protein)-associated protein B and C	20q13.33
VCP	NM_007126.3	Valosin-containing protein	9p13.3
VEGFA	NM_003376.6	Vascular endothelial growth factor A	6p21.1
ZNHIT3	NM_004773.3	Zinc finger HIT-type containing 3	17q12

Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; *GRN*, progranulin; *MAPT*, microtubule-associated protein Tau; RefSeq, reference sequence.

TABLE 2 Demographic and clinical characteristics of the entire cohort of LEAF-FTD and CREDOS-FTD cohorts combined.

	Total	bvFTD	svPPA	nfvPPA	FTD-ALS	p.D40G
Number	259	111	109	34	5 6	
Age, years	65.9 ± 8.8	64.6 ± 9.3	66.4 ± 7.8	69.3 ± 8.7	61.7 ± 11.4	70.3 ± 7.6
Onset age, years	61.6 ± 8.8	60.1 ± 9.5	62.0 ± 7.7	65.7 ± 8.9	60.2 ± 11.9	62.5 ± 7.5
Sex (M:F)	122:137	60:51	43:66	17:17	2:3	0:6
FTD-CDR (SB)	9.0 ± 6.1	9.9 ± 6.1	9.0 ± 6.5	6.7 ± 4.8	5.0 ± 2.2	1.6 ± 1.1
MMSE	16.3 ± 9.2	17.1 ± 8.2	15.0 ± 10.2	17.1 ± 8.7	19.8 ± 6.9	26.3 ± 2.7
Familial history*	22.8% (59/259)	21.6% (24/111)	28.4% (31/109)	11.8% (4/34)	0% (0/5)	50% (3/6)

Note: Data are mean ± SD unless otherwise indicated.
Abbreviations: ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; CREDOS, Clinical Research Center for Dementia of South Korea; F, female; FTD, frontotemporal dementia; LEAF, Longitudinal study of Early onset dementia And Family members; M, male; MMSE, Mini-Mental State Examination; nfvPPA, non-fluent variant primary progressive aphasia; SB, Sum of Boxes; svPPA, semantic variant primary progressive aphasia.
*Family history of dementia or neuropsychiatric disease in first-degree relatives.

elsewhere,[29] no known FTD/ALS-related pathogenic variants were detected outside of *ANXA11*. None of the patients had abnormal repeat expansions of *C9orf72*. A single pathogenic variant (c.119A > G; p.Asp40Gly [p.D40G]) in *ANXA11* was detected in six patients (five from the LEAF-FTD [Case 1 to Case 5] and one from the CREDOS-FTD [Case 6]), all of whom were women clinically diagnosed with possible or probable svPPA. One patient (Case 2) also harbored a variant in prion protein gene (*PRNP*) (p.Val180Ile).[30] One of the six patients was reported previously (Case 1).[11] Other than the p.D40G variant, no other *ANXA11* variant was found in the current cohort, and p.D40G

TABLE 3 Demographic and clinical characteristics of patients by LEAF-FTD and CREDOS-FTD cohorts.

	LEAF-FTD				CREDOS-FTD				
	Total	bvFTD	svPPA	nfvPPA	Total	bvFTD	svPPA	nfvPPA	FTD-ALS
Number	80	37	32	11	179	74	77	23	5
Age, years	64.6 ± 7.5	63.8 ± 7.56	64.7 ± 7.6	67.1 ± 6.3	66.5 ± 9.3	65.0 ± 10.1	67.1 ± 7.8	70.4 ± 9.6	61.7 ± 11.4
Onset age, years	60.3 ± 7.3	59.9 ± 7.38	59.7 ± 6.8	63.8 ± 7.0	62.2 ± 9.5	60.2 ± 10.4	62.9 ± 7.8	66.6 ± 9.7	60.2 ± 11.9
Sex (M:F)	30:50	16:21	9:23	5:6	92:87	44:30	34:43	12:11	2:3
FTD-CDR (SB)	7.9 ± 5.7	9.5 ± 6.1	6.8 ± 5.2	5.4 ± 3.8	9.5 ± 6.3	10.1 ± 6.1	9.9 ± 6.7	7.4 ± 5.2	5.0 ± 2.2
MMSE	17.8+ ± 8.4	17.6 ± 7.5	17.9 ± 8.9	16.6 ± 8.1	15.6+ ± 9.4	16.9 ± 8.6	13.9 ± 10.4	16.6 ± 8.1	19.8 ± 6.9
Familial history*	30.0% (24/80)	24.3% (9/37)	43.8% (14/32)	9.1% (1/11)	17.3% (31/179)	18.9% (14/74)	18.2% (14/77)	13.0% (3/23)	0% (0/5)

Note: Data are mean ± SD unless otherwise indicated.

Abbreviations: ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; CREDOS, Clinical Research Center for Dementia of South Korea; F, female; FTD, frontotemporal dementia; LEAF, Longitudinal study of Early onset dementia And Family members; M, male; MMSE, Mini-Mental State Examination; nfvPPA, non-fluent variant primary progressive aphasia; SB, Sum of Boxes; svPPA, semantic variant primary progressive aphasia.

*Family history of dementia or neuropsychiatric disease in first-degree relatives.

was found in no other FTD syndrome. The six patients represent 5.5% (6/109) of the svPPA cohort and 2.3% (6/259) of the FTD cohort overall.

3.3 | Description of patients carrying the *ANXA11* p.D40G variant

Key characteristics of the six patients carrying *ANXA11* p.D40G are provided in Table 4.

3.3.1 | Case 1

Case 1 was a 70-year-old right-handed woman who developed trouble recognizing familiar people, word-finding difficulties, and memory problems at age 64. There was no other neurological deficit and no electrophysiological evidence of ALS. She is the second of four children, consisting of two sons and two daughters. The older brother, who is 2 years older, does not seem to have a good memory, but he has never been diagnosed with dementia or neurodegenerative diseases, and her younger sister and younger brother are both healthy. The father died of cardiovascular disease in his forties, and the mother died in her seventies, but she did not have dementia. At the time of diagnosis, at age 65, she had a Mini-Mental State Examination (MMSE) score of 25, Clinical Dementia Rating (CDR) score of 0.5, and Global Deterioration Scale (GDS) score of 3. Confrontation naming was specifically impaired from early on. She showed normal language function in the Korean version of the Western Aphasia Battery (K-WAB).[31] Her brain MRI showed focal atrophy of the right anterior temporal lobe (Figure 1). The F-18-fluorodeoxyglucose (^{18}F-FDG)-PET revealed focal decreased glucose metabolism in the bilateral anterior temporal areas, predominantly on the right and in the right ventromedial frontal area (Figure 2). ^{18}F-Flutemetamol PET (amyloid PET) was negative. This patient was clinically diagnosed with right predominant svPPA. Six years after onset, she continued to carry out activities of daily living (ADLs) well with only prosopagnosia, naming, and verbal memory difficulties.

3.3.2 | Case 2

Case 2 was a 64-year-old right-handed woman with 8 years of object naming and face recognition difficulties. She had a family history of dementia, with her mother, older sister, and aunt having developed cognitive deficits in their early and mid-sixties. The patient showed mild functional impairment at the time of diagnosis with an MMSE score of 30, CDR of 0.5, and GDS of 3. Delayed word recall and confrontation naming were impaired. The results of K-WAB were normal. Atrophy of both anterior temporal lobes, slightly worse on the right, was observed on brain MRI at age 55 (Figure 1). ^{18}F-Flutemetamol PET was negative, and the patient was diagnosed with svPPA. Although she refused further electrophysiologic evaluations such as electromyography (EMG), she had no findings suggestive of ALS by age 64. Of interest, p.Val180Ile

TABLE 4 Summary of demographic and clinical data of affected individuals with the *ANXA11* p.D40G variant.

Patient	1	2	3	4	5	6
Sex	Female	Female	Female	Female	Female	Female
Age at onset	64	55	71	60	54	71
Age at the first evaluation	65	55	77	69	55	72
Current age	70	64	82	70	61	75**
Initial symptoms	Prosopagnosia, word-finding difficulty	Prosopagnosia, impaired object naming	Impaired object naming, Word meaning loss, Prosopagnosia	Prosopagnosia	Behavioral change, memory decline	Impaired object naming
Family history	–	Dementia	Psychiatric disorders	–	–	Dementia
Neuropsychological test results	Severe impairment of confrontation naming	Severe impairment of confrontation naming and verbal memory	Severe impairment of confrontation naming and verbal memory	Nomal cognition	Severe impairment of confrontation naming and verbal/visual memory Mild impairment of generative naming	Severe impairment of confrontation naming and verbal memory Mild impairment of visuospatial function and generative naming
K-WAB	AQ 97.4, LQ 95.7	AQ 95.8, LQ 94.7	AQ 90.2, LQ 92.7	AQ 97.8, LQ 91.1	–	–
CGA-NPI	2	0	16	1	11	4
MMSE	25	30	26	28	27	22
CDR	0.5	0.5	0.5	0.5	0.5	0.5
FTD-CDR (SB)	1	2.5	0.5	1	–	3
Brain MRI findings	Right-side dominant, bilateral anterior temporal pole atrophy	Right-side dominant, Bilateral anterior temporal pole atrophy	Left-side dominant anterior temporal pole atrophy	Right-side dominant, Bilateral anterior temporal pole atrophy	Bilateral anterior temporal atrophy	Right-side dominant, bilateral anterior temporal pole atrophy
Molecular brain imaging study findings	• ^{18}F-Flutemetamol PET: Negative • ^{18}F-FDG-PET: Focal decreased glucose metabolism in the bilateral anterior temporal areas, predominantly on the right side and in the right ventromedial frontal area	• ^{18}F-Flutemetamol PET: Negative	• ^{18}F-Florbetaben PET: Positive • ^{18}F-FDG-PET: Decreased glucose metabolism in the bilateral anterior temporal area, worse on the left side	• ^{18}F-Flutemetamol PET: Negative • ^{18}F-FDG-PET: Focal decreased glucose metabolism in the bilateral anterior temporal areas, predominantly on the right side	• ^{18}F-Flutemetamol PET: Negative	• ^{18}F-FDG-PET: Glucose hypometabolism in the bilateral anterior temporal areas, slightly worse on the right side • ^{18}F-FP-CIT PET: Normal
Genetic findings	*ANXA11* c.119A > G (p.D40G) Apo E 3,3	*ANXA11* c.119A > G (p.D40G), *PRNP* c.538G > A (p.Val180Ile) Apo E 4,4	*ANXA11* c.119A > G (p.D40G) Apo E 3,3	*ANXA11* c.119A > G (p.D40G) Apo E 3, 3	*ANXA11* c.119A > G (p.D40G) Apo E 3,3	*ANXA11* c.119A > G (p.D40G) Apo E 3,3
Initial diagnosis*	svPPA, Right	svPPA, Right	svPPA, Left	svPPA, Right	svPPA*	svPPA, Right

Abbreviations: ^{18}F-FDG-PET, F-18-fluorodeoxyglucose positron emission tomography; ^{18}F-FP-CIT PET, N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane positron emission tomography; *ANXA11*, annexin A11; *ApoE*, Apolipoprotein E; AQ, Aphasia Quotient; CDR, Clinical Dementia Rating; CGA-NPI, Caregiver-Administered Neuropsychiatric Inventory; FTD, frontotemporal dementia; K-WAB, Korean version of Western Aphasia Battery; LQ, language quotient; MMSE, Mini-Mental State Examination; SB, Sum of Boxes; svPPA, semantic variant primary progressive aphasia.

*Imaging supported.

**Age at last follow-up.

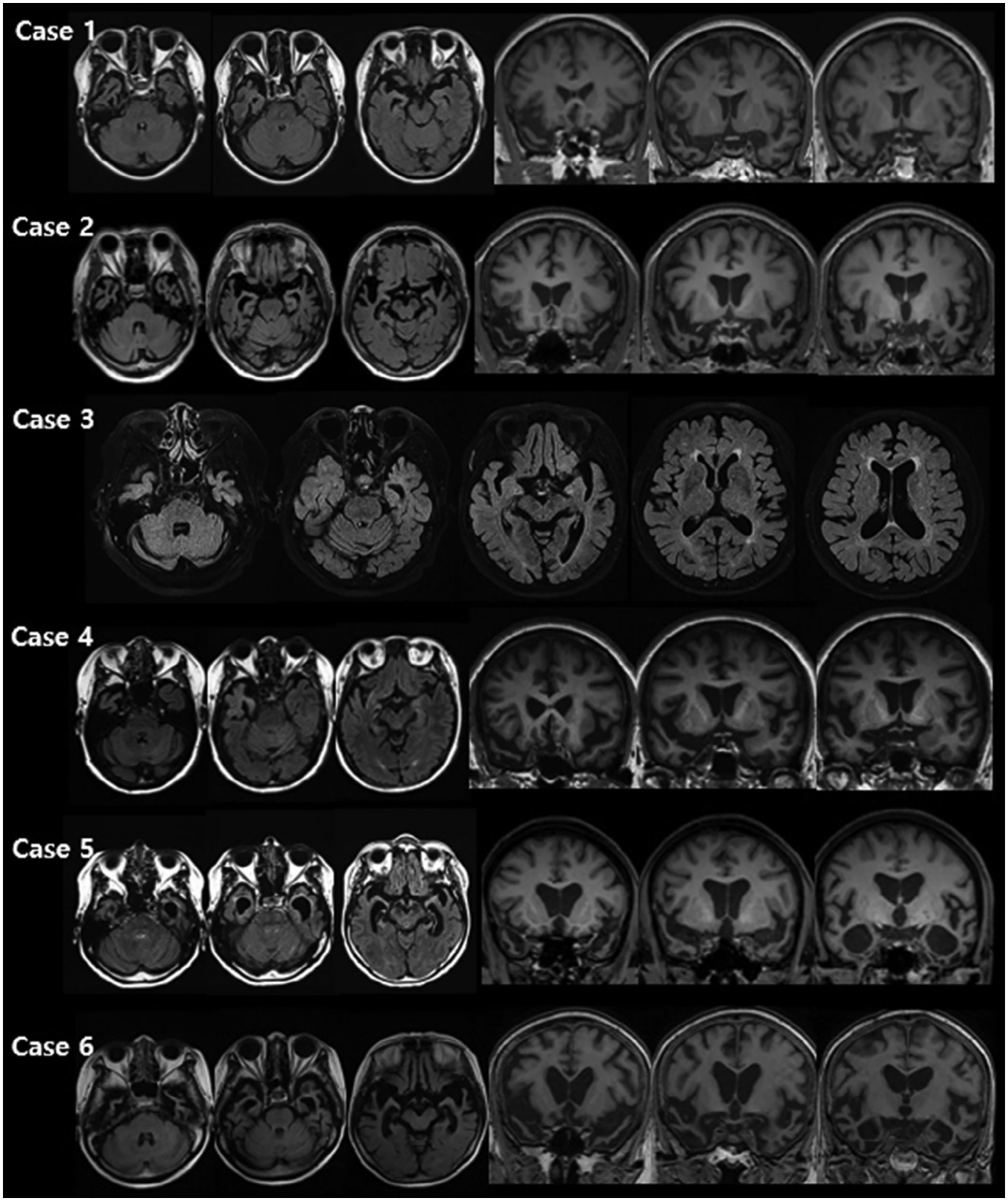

FIGURE 1 Brain MRI images of cases with D40G of *ANXA11*. FLAIR axial and T1-weighted coronal brain MR images of each patient showed bilateral anterior temporal atrophy (case 5), worse on the right (case 1, 2, 4, 6) or left (case 3). FLAIR, Fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

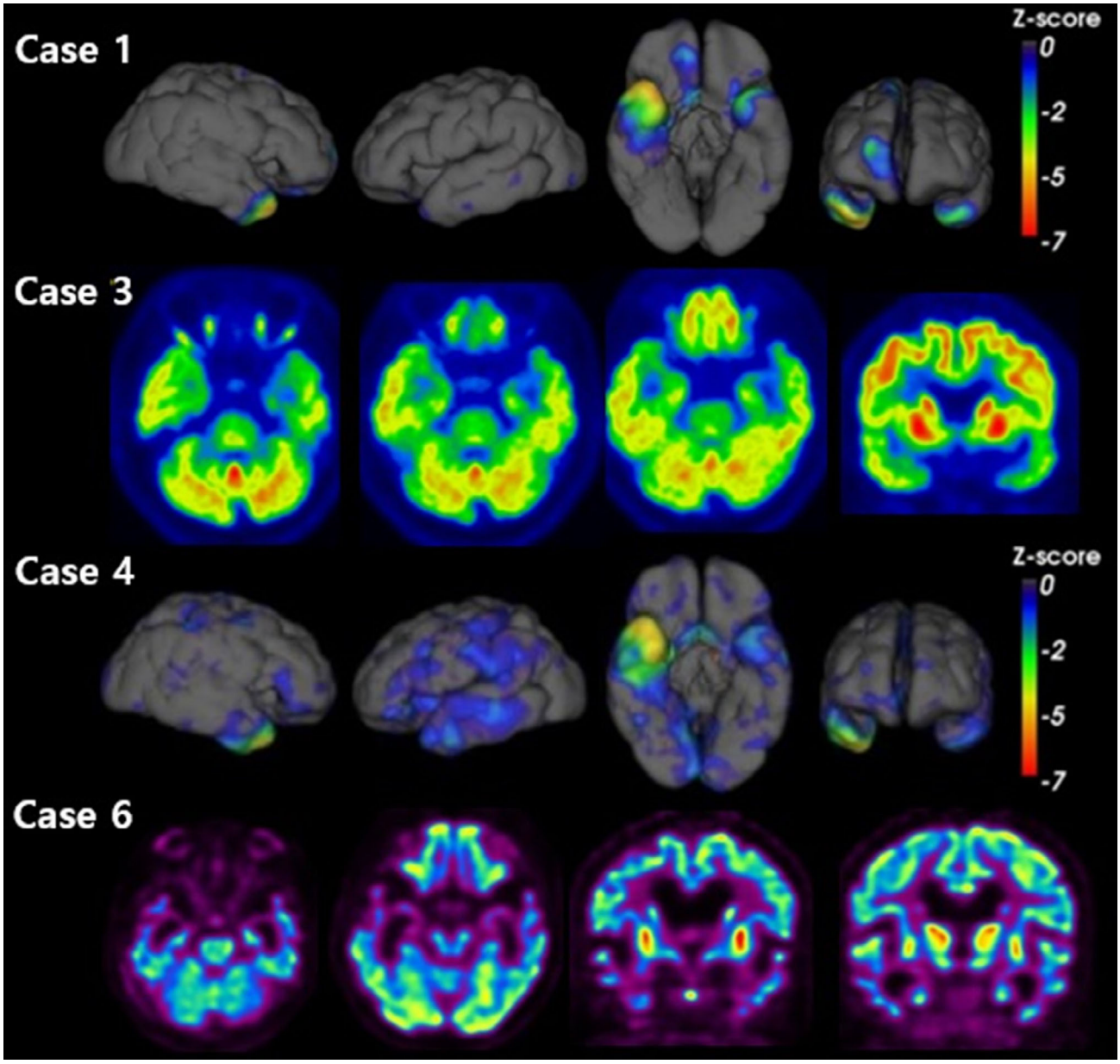

FIGURE 2 ^{18}F-FDG-PET images. ^{18}F-FDG-PET images revealed decreased glucose metabolism in the bilateral anterior temporal areas, worse on the right side (case 1, 4, 6) or the left side (case 3). The images of Case 1 and Case 4 were obtained from the Australian e-Health Research Centre (https://aehrc.csiro.au/wileyonlinelibrary.com]). The images were quantified and correlated with a 3D surface image using CapAIBL (https://milxcloud.csiro.au/wileyonlinelibrary.com]). To quantify uptake in PET images, focal uptake values were divided by those of the cerebellum (reference region). After quantification, a *z*-score map was created on the 3D surface image. The images of Case 1 were reprinted with permission from the European Journal of Neurology 2022;29:3124-3126.[11] 18F-FDG-PET, [18F]-fluoro-2-deoxy-D-glucose positron emission tomography; 3D, three-dimensional; PET, positron emission tomography.

of *PRNP*, a pathogenic variant that causes familial Creutzfeldt–Jakob disease (CJD),[30] was found along with the *ANXA11* variant, but until now there was no clinical or neuroimaging evidence to support CJD.

3.3.3 | Case 3

Case 3 was an 82-year-old right-handed woman whose chief complaint was impaired object naming for 11 years. One year after symptom onset, she had difficulty recognizing faces or words corresponding to her favorite foods. She had a family history of psychiatric disorders in her brother and daughter, with unknown mental illness and schizophrenia, respectively. At the time of diagnosis at age 77, total score of MMSE was 26, CDR 0.5, GDS 3, and confrontation naming and verbal memory were severely impaired. Naming difficulties were frequently observed in daily life, but the patient showed a normal Aphasia Quotient (90.2) and Language Quotient (92.7) on the K-WAB test. Brain MRI showed focal atrophy in the left anterior

temporal lobe combined with mild atrophy throughout the cerebral cortex (Figure 1). ^{18}F-FDG-PET demonstrated decreased glucose metabolism in the bilateral anterior temporal areas, worse on the left side (Figure 2). Her ^{18}F-florbetaben PET scan was positive. Based on the clinical and imaging findings, her clinical syndromic diagnosis was svPPA.

3.3.4 | Case 4

Case 4 was a 70-year-old right-handed woman who developed difficulties in recognizing familiar people and visuospatial dysfunction at age 60. She is the fourth of three sons and three daughters. The patient's first brother died of leukemia in his sixties, and her second sister is currently living a healthy life at the age of 80. The patient's second older brother, who is 4 years older, has memory impairment, and the patient thinks that her brother's symptom is similar to that of herself but he has never been diagnosed with dementia or neurodegenerative diseases. The patient's younger brother died in an accident in his late twenties or early thirties, and the youngest sister seems to have memory impairment, but she has not been diagnosed with dementia or neurodegenerative disease, either. The patient's father died in his early fifties, and the exact cause of death is unknown, and her mother died of old age at the age of 95 and had no dementia. At the time of diagnosis at age 69, the patient's MMSE score was 28, CDR 0.5, and GDS 3. Detailed neuropsychological tests and K-WAB showed no cognitive and language deficits. Focal atrophy in the right anterior temporal pole was seen on MRI (Figure 1). ^{18}F-FDG-PET disclosed focal glucose hypometabolism in the bilateral anterior temporal areas, predominantly on the right side (Figure 2).^{18}F-Flutemetamol PET was negative. She was clinically diagnosed with right predominant svPPA.

3.3.5 | Case 5

Case 5 was a 61-year-old right-handed woman who showed memory impairment and behavioral abnormalities since age at 55. Her memory decline began at age 51. She was diagnosed with amnestic mild cognitive impairment (MCI) at age 55, with an MMSE score of 27, CDR 0.5, and GDS 3. Around the time of the initial MCI diagnosis, her abnormal behaviors such as excessive affection for her husband without considering the surroundings and obsessively bringing home street trash developed. She had no family history of dementia. Neurological examinations were normal. Serial neuropsychological test results revealed severe impairment of verbal memory and confrontation naming. She progressed to the early stage of dementia at age 59. Brain MRI at age 60 showed severe cortical atrophy in bilateral temporal lobes including anterior temporal poles (Figure 1). Her ^{18}F-florbetaben PET was negative. She was not specifically evaluated for verbal or visual semantic knowledge, but imaging-supported svPPA was suspected based on the brain MRI findings.

3.3.6 | Case 6

Case 6 was a woman with a 1-year history of progressive cognitive deficits and behavioral changes, which started at age of 71. Her behavioral symptoms included disinhibition and inflexibility. Her sister had dementia, but more detailed family history was not obtained. Neurological examinations were unremarkable. Neuropsychological evaluation revealed severely impaired naming and verbal memory. MMSE score was 22, and CDR total score was 0.5. Brain MRI demonstrated prominent bilateral anterior temporal atrophy, which was slightly worse on the right side (Figure 1). A clinical syndromic diagnosis of svPPA was made. At that time, she participated in the CREDOS-FTD genetic screening study and did not show any pathogenic variants of known FTD, ALS, or other dementia genes (*ANXA11* was not included).[19] After the initial evaluations, her cognitive function continued to deteriorate, and her movement slowed. At age 73, dysarthria and weakness of the left extremities arose, but additional details were not available. Follow-up neuropsychological tests revealed severe impairment in all the cognitive domains. MMSE score was 19 and CDR was 1. MRI studies demonstrated severe progression of cortical atrophy in the bilateral anterior temporal areas. ^{18}F-FDG-PET demonstrated severe glucose hypometabolism in the bilateral anterior temporal areas, slightly worse on the right side (Figure 2). Dopamine transporter PET revealed normal striatal uptake. When she was transferred to a nursing hospital at age 75, she could not walk without assistance and had trouble speaking.

3.4 | Kinship analysis among six cases with p.D40G

To explore any evidence that six cases with p.D40G may be related to each other, we performed a kinship analysis of six individuals. Using the KING (KING_v2.3.0) toolset, we investigated the genotype data and calculated the kinship coefficient, which is defined as the probability that a pair of randomly selected homologous alleles is identical by descent. The results showed that all the estimated kinship coefficients were between −0.0544 and 0.0251, which is lower than the range of the third degree kinship (0.0442–0.884). These negative kinship coefficient estimates indicate that there is an unrelated relationship between the six individuals.

4 | DISCUSSION

In this study, we identified the same *ANXA11* p.D40G variant in six patients with svPPA, the FTD clinical syndrome linked to an underlying co-proteinopathy in which TDP-43 and annexin A11 form a heteromeric amyloid fibril, predominantly within distal dendrites.

Although variants of *ANXA11* were originally associated with autoimmune diseases, such as sarcoidosis and systemic lupus erythematosus, Smith et al. introduced six rare *ANXA11* variants in 13 ALS cases in 2017. This accounts for 0.8% of familial and 1.7% of

sporadic ALS in European populations.[2] Since then, several Asian ALS cohorts have presented inconsistent results for the frequency of *ANXA11* mutations; one reported no pathogenic variant in ALS patients of Han Chinese descent,[4,6] another reported frequencies similar to those of the European cohorts,[32] and the other reported variants in 5.6% of familial and 2.3% of sporadic ALS.[5] The latter study reported one novel variant (p.P36R), even in a patient with ALS-FTD, suggesting a pathogenic role of *ANXA11* mutation in ALS-FTD spectrum disorders.[5] Other *ANXA11* variants (p.G38R, p.D40Y, p.D40G) were subsequently identified in patients with ALS-FTD in French and Korean ALS cohorts.[9,33] However, the description of dementia features in previously reported ALS-FTD patients with *ANXA11* variants was insufficient to determine the nature of the FTD syndrome.[5,9,33]

To date, 139 single nucleotide variants in the *ANXA11* gene have been reported in ClinVar, including 5 likely pathogenic or pathogenic variants and 134 variants of uncertain significance (https://www.ncbi.nlm.nih.gov/clinvar; accessed on September 23, 2024). Although a clinically well-described right-predominant svPPA, also referred to as semantic behavioral variant FTD,[34] with a pathogenic variant in *ANXA11* was recently published by our group, the frequency of this variant in pure FTD syndromes or FTD-ALS was uncertain. To our knowledge, therefore, this is the first study to perform genetic screening for *ANXA11* in an FTD cohort.

ANXA11 consists of a C-terminal core domain containing four calcium-binding annexin domains and an N-terminal domain holding low-complexity domains (LCDs) responsible for binding to other specific proteins associated with programmed cell death, such as calcyclin.[35] The p.D40G variant observed in this study is a founder mutation and located in proximity to the calcyclin binding region of the LCD, which interferes with the binding of calcyclin to annexin A11 and promotes accumulation of cytoplasmic annexin A11.[2] This region also sits at the N-terminal end of the annexin A11 amino acid sequence that forms a co-fibril with TDP-43 in FTLD-TDP type C, the predicted pathological substrate for all six of the patients reported here. Therefore, given the low prevalence of p.D40G in the general population (none among 42,048 individuals composing an East Asian cohort (gnomAD v.4.1.0 [https://gnomad.broadinstitute.org/variant/10-80170852-T-C?dataset=gnomad_r4]), our findings suggest that p.D40G may increase the risk of developing FTLD-TDP, type C, either by increasing cytoplasmic (especially dendritic) annexin A11 levels or by enhancing the stability or spreading potential of the heteromeric fibril.

The clinical phenotypes associated with the *ANXA11* p.D40G variant have been described primarily in the context of ALS cohorts and varied from typical ALS without dementia ($n = 7$)[2,5] to atypical ALS with PSP-like symptoms ($n = 1$)[10] to ALS-FTD, including bvFTD ($n = 1$) and svPPA ($n = 1$) syndromes.[33] Despite this phenotypic heterogeneity, it is striking that all patients with p.D40G in our FTD cohort presented with svPPA, which is known to have the lowest heritability of any FTD syndrome,[1] and when patients develop motor neuron disease it is usually a manifestation of isolated pyramidal tract degeneration.[36] Although only Case 6 had developed likely ALS symptoms at the end of the follow-up, the other patients were in early stages, such that ALS symptoms may still arise. Thus our group has previously suggested that *ANXA11* p.D40G may be one of the possible genetic causes of svPPA and svPPA-ALS.[11] Studying an ALS cohort, Sung et al. suggested an association between clinical phenotypes and domain-specific *ANXA11* variants (N-terminal LCDs vs C-terminal domains), especially the ALS-FTD phenotype, which was caused by N-terminal variants in 7 of 13 cases.[33] Therefore, the svPPA phenotype observed in our patients may be related to domain-specific *ANXA11* variants, which in turn implies that other FTD subtypes may emerge mainly from C-terminal variants. More reports on *ANXA11* variants in patients with FTD syndrome are needed to confirm this speculation.

As mentioned previously, svPPA is known to have a low heritability compared to other subtypes of FTD, but 50% (3/6) of our patients with svPPA harboring p.D40G had a family history of dementia or psychiatric disorder. However, none of them had a family history of FTD or ALS. Therefore, we cannot completely exclude the possibility of de novo mutation of p.D40G in our patients without family history. To date, however, de novo cases of p.D40G have not been reported, and there have been several families reported with a clear autosomal dominant pattern.[2] Thus, the p.D40G variant observed in our cases is more likely to be an autosomal dominantly inherited pathogenic variant with phenotypic heterogeneity and/or incomplete penetrance rather than a simple risk factor. Further studies are needed to address this question.

Although none of patients with p.D40G in this study had a history of autoimmune disease, the association of annexin 11 with autoimmune disorders[37] and a higher prevalence of autoimmune conditions in TDP-43-associated diseases (svPPA and progranulin mutation carriers)[38] have been reported. Therefore, although no patient in this study reported a history of autoimmunity, the possible links of *ANXA11* p.D40G and FTLD-TDP type C to immune function warrant further investigation.

Neuropathological findings related to *ANXA11* mutations have so far been reported in two patients with ALS (p.D40G, c.1086+1G > A)[2,39] and one with ALS-FTD/cognitive impairments (p.G38R).[9] Two former ALS cases showed ALS-TDP pathology, and the latter with ALS-FTD/cognitive impairments revealed ALS-TDP with FTLD-TDP type A. Annexin A11 aggregates were also found in neurons with or without co-localization with phospho-TDP-43. Recently, co-assembly of annexin A11 and TDP-43 in heteromeric amyloid filaments was unexpectedly discovered in FTLD-TDP type C. Although the patients studied lacked *ANXA11* variants, the authors suggested that pathogenic variants of *ANXA11* might enhance heteromeric amyloid filaments of annexin A11 and TDP-43.[13] Furthermore, one group identified annexin A11 aggregates with similar morphology, amount, and regional distribution of TDP-43 inclusions in FTLD-TDP type C pathology, whereas only a few annexin A11 aggregates were found in non-type C TDP pathologies such as limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), FTLD-TDP types A and B, and ALS-TDP.[12] Taken together, these observations may provide a pathophysiological basis for our previous and present findings strongly linking *ANXA11* p.D40G to svPPA. However, the phenotypic variation within the same p.D40G variant, which includes ALS, ALS-bvFTD, ALS-svPPA, bvFTD-ALS, and svPPA, raises the question

about whether this variant is associated with a single pathological substrate, FTLD-TDP, type C, with varied clinical manifestations or multiple pathological subtypes of FTLD-TDP.[2,5,11,33,40] In addition, since multisystem proteinopathies with concurrent diseases such as ALS, FTD, primary muscle diseases, and bone diseases, caused by the p.D40Y variant, which is a variant with only one amino acid change at the same location from p.D40G, has been reported,[41,42] further studies are needed to elucidate the role of *ANXA11* mutations not only in the central nervous system, but also in other systems, including the musculoskeletal system.

Lastly, Jiang et al. reported that ALS patients with *ANXA11* variants were more likely to be male than female, suggesting that this was because *ANXA11* was involved to some extent in the process of sexual differentiation.[32] Nevertheless, all six patients we identified with p.D40G of *ANXA11* were female in the current study, so it remains to be determined whether there are sex preferences of *ANXA11* mutations and, if so, what role *ANXA11* mutations play in biological sex differentiation.

The main limitation of this work is the lack of autopsy findings. Therefore, it is not yet clear whether the underlying neuropathology in our cases is FTLD-TDP type C with co-accumulation of annexin A11. Therefore, the mechanism through which p.D40G induces neurodegeneration remains uncertain. Further studies are needed to test our hypothesis that p.D40G leads, at least in some cases, to FTLD-TDP type C, as seen in sporadic cases.

In conclusion, the frequency of *ANXA11* mutations in our FTD cohort was 2.3%, all with the same variant of p.D40G and the clinical phenotype of svPPA. Because there were ethnic differences in the frequency and the types of variants of *ANXA11* mutations in the ALS cohorts, *ANXA11* mutations should be screened in Caucasian FTD cohorts to address its overall functions and potential role in neurodegeneration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

CONSENT STATEMENT

The institutional review board (IRB) approved the study (IRB No. 2021-233 and IRB No. 2012 12), and written informed consent was obtained from all participants. As informed consent did not include open access to the data used in the study, our data are not publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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