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Genetic screen in a large series of patients with primary progressive aphasia

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Abstract

Introduction—Primary progressive aphasia (PPA) is a neurological syndrome, associated with both frontotemporal dementia and Alzheimer's disease, in which progressive language impairment emerges as the most salient clinical feature during the initial stages of disease.

Methods—We screened the main genes associated with Alzheimer's disease and frontotemporal dementia for pathogenic and risk variants in a cohort of 403 PPA cases.

Results—In this case series study, 14 (3.5%) cases carried (likely) pathogenic variants: four *C9orf72* expansions, nine *GRN,* and one *TARDBP.* Rare risk variants, *TREM2* R47H and *MAPT*A152T, were associated with a three- to seven-fold increase in risk for PPA.

Discussion—Our results show that while pathogenic variants within the most common dementia genes were rarely associated with PPA, these were found almost exclusively in *GRN* and *C9orf72,* suggesting that PPA is more TDP43- than tau-related in our series. This is consistent with the finding that PPA frequency in dominantly inherited dementias is the highest in kindreds with *GRN* variants.

Keywords

Primary progressive aphasia; Genetics; *C9orf72*; *GRN*; *TARDBP*

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Supplementary data

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1. Introduction

Primary progressive aphasia (PPA) is a neurodegenerative syndrome characterized by prominent, relatively isolated language impairment that develops gradually, while other cognitive and behavioral domains are relatively preserved [1]. In the early stages of disease, activities of daily living (except those related to language) are maintained; however, some patients go on to develop more widespread symptoms of dementia or rto present behavioral deficits typical of the behavioral variant of frontotemporal dementia (FTD). In recent years, PPA has been divided into three main distinct variants: progressive nonfluent agrammatic, semantic, and logopenic [2].

Nonfluent variant PPA (nfvPPA), also known as progressive nonfluent aphasia or PPA-agrammatic, is mainly characterized by disrupted language production (short, simple phrase structure and omission of grammatical morphemes) and slow, labored speech. Apraxia of speech is common, but single-word comprehension is preserved. Many patients with nfvPPA will eventually progress to a syndrome with generalized motor problems, such as corticobasal syndrome or progressive supranuclear palsy [3,4]. One of the most distinctive features of nfvPPA is atrophy within the left inferior frontal gyrus, where Broca's area is located [5]. Nonfluent cases with agrammatism or motor speech disturbance will most often show frontotemporal lobar degeneration (FTLD) with tau or, less often, FTLD with TDP-43, usually of type A, pathologies.

Semantic variant PPA (svPPA), also known as semantic dementia, is mainly characterized by profound impairment in object naming and single-word comprehension deficits, especially for low-frequency items. Other features include surface dyslexia (reading that is literally phonetic) and dysgraphia, whereas articulation, grammar, and repetition are spared. These patients often show a very distinct pattern of atrophy in the ventral and lateral portions of the anterior temporal lobes, sometimes predominantly left-sided, but often bilateral [6]. This variant has been associated with FTLD with TDP-43 pathology, usually of type C [7].

In the logopenic variant PPA (lvPPA), patients have halting anomic speech, with single-word retrieval deficits, and often show inability to repeat phrases and sentences, while grammatical processing, word comprehension, and motor speech are relatively preserved. These patients show abnormalities in the posterior (temporoparietal) part of the language network [5], with Alzheimer's disease (AD) being the most common underlying pathology [8,9].

Although most PPA cases are sporadic, there have been reports of familial PPA cases with disease-causing variants in the three most common FTD genes, *MAPT, GRN*, and *C9orf72,* and also in the AD gene *PSEN1.* However, the overall genetic contribution to each PPA variant, and its underlying processes, is not clear. Based on underlying pathology mostly associated with the distinct PPA variants, it would be expected to observe mostly *MAPT* and perhaps some *GRN* variants in nfvPPA cases, *GRN/TARDBP* in svPPA cases, and *PSEN1*/*PSEN2*/*APP* variants in lvPPA. To test this hypothesis and to determine the relative frequency of pathogenic variants in the various PPA subgroups, we screened the main

causative and risk-associated genes for AD and FTD in the largest cohort of PPA cases to date.

2. Methods

2.1. Cohort description

We screened 403 patients diagnosed with PPA recruited from two collaborating centers: University of California San Francisco Memory and Aging Center (UCSF series: 238 individuals) and Northwestern University (Northwestern series: 165 individuals). Application of consensus criteria for PPA (as described in [2,10] for the UCSF and Northwestern series, respectively) categorized patients into 125 nonfluent, 122 semantic, 89 logopenic, and five mixed PPA cases (Fig. 1A). The remaining cases were either unclassifiable (18 with too severe, mild, or other symptoms) or uncharacterized (44) at the time of inclusion. Two hundred nineteen cases (54.3%) were female, and most (at least 91.8%, no available information for 13 cases) were of European descent. All participants signed informed consent for genetic analyses.

2.2. Targeted sequencing

Samples were screened using targeted sequencing of a panel of genes previously implicated in neurodegenerative disorders, including the most common causative genes for Mendelian forms of AD and FTD, and eight genes previously implicated in language and reading deficits (Supplementary Material). Exons and flanking intronic regions for these genes were captured using a custom-designed library (SeqCap EZ Choice Library, NimbleGen) and sequenced on an Illumina HiSeq2500 instrument at the UCLA Neuroscience Genomics Core (http://www.semel.ucla.edu/ungc). Sequence reads were mapped to the GRCh37/hg19 reference genome, and variants were joint-called using the GATK software [11]. The joint variant calling file was annotated using ANNOVAR [12].

2.3. Dementia genes screening

The exonic regions of the seven most common AD and FTD genes (APP *TARDBP, FUS, GRN, MAPT, PSEN1,* and *PSEN2)* were screened for known (AD&FTD Mutation Database: http://www.molgen.ua.ac.be/ADMutations) or novel pathogenic variants (according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) published guidelines [13]). The transcripts NM_001136129 (APP), NM_001170634 *(FUS),* NM_002087 *(GRN),* NM_001123066 *(MAPT),* NM_000021 *(PSEN1),* NM_000447 *(PSEN2),* and NM_007375 (*TARDBP*) were used as reference. Known and novel (likely) pathogenic variants were confirmed by Sanger sequencing. The presence of a pathological hexanucleotide repeat expansion in *C9orf72* was detected using both fluorescent and repeat-primed PCR, as previously described [14]. Genotypes for *MAPT* A152T (rs143624519), *TREM2* R47H (rs75932628), and *APOE* (rs429358 and rs7412) risk alleles, and the 17q.21.31 (rs1560310) haplotype, were obtained using TaqMan® SNP assays and/or extracted from the targeted sequencing data. Statistical analysis was performed in R (version 3.1.3, http://www.r-project.org).

3. Results

3.1. Dominant FTD variants in a subset of PPA cases

Overall, we identified a total of 13 PPA cases that carried a pathogenic variant in the known AD- and FTD-associated genes: four with an expanded *C9orf72* repeat and nine with *GRN* loss-of-function variants (Table 1). We also identified one case harboring a likely pathogenic variant in *TARDBP*, corresponding to a total frequency of 3.5% (14 of 403) carriers of causative variants in this PPA series. Most of these carriers (9 of 14) had a positive family history (i.e., first- or second-degree relatives with a clinical diagnosis of dementia), and their ages at onset ranged from 49 to 69 years. When stratified by PPA variant, we identified seven carriers of pathogenic variants among the 125 nfvPPA cases, corresponding to a frequency of 5.6% (Fig. 1B). Three of the nfvPPA cases carried a *C9orf72* repeat expansion, whereas the other four had different pathogenic variants in the *GRN* gene. By contrast, within the 122 individuals diagnosed with svPPA, we identified one case with a *C9orf72* repeat expansion and one with a likely pathogenic *TARDBP* variant (1.6%, Fig. 1B), whereas among the 89 lvPPA cases, we found only one carrier of a pathogenic *GRN* variant (1.1%, Fig. 1B).

Most of the *GRN* variants identified in this series—frameshift deletions Gln130SerfsTer125, Ser226TrpfsTer28, Trp304CysfsTer58, and Thr382SerfsTer30, splice variants c.264+2T>C and c.709–2A>G, and stop gain variant Arg493Ter—were already reported in the literature in association with FTD cases (first described [15–19]). We also identified one novel *GRN* loss-of-function variant: frameshift deletion Ile422GlufsTer72 (absent from the population database gnomAD, http://gnomad.broadinstitute.org/). In addition to these pathogenic variants, we also identified a known, likely pathogenic variant in the *TARDBP* gene, Ile383Val. This variant was first described as pathogenic in familial amyotrophic lateral sclerosis patients [20] and is associated with a substantial increase in TDP-43 truncation products in vitro [21]; however, it has also been reported in 5/128,243 individuals (minor allele frequency, MAF = 1.949E-05) in the gnomAD population database and is predicted to be tolerated by both SIFT and Polyphen, therefore we are considering it likely pathogenic. None of the rare, deleterious variants identified in the eight genes previously associated with language or reading deficits (Supplementary Material) had sufficient evidence to be classified as disease causing or risk associated.

3.2. MAPT A152T and TREM2 R47H rare variants increase risk for PPA

MAPT variant A152T, shown to reduce tau binding to microtubules while increasing tau oligomer formation, was identified as a genetic risk factor for both FTLD-spectrum disorders and AD [22,23]. In our PPA series, we identified a total of seven (1.74%) *MAPT* A152T carriers (three nonfluent, two logopenic, one semantic, and one mixed PPA cases). In our controls, recruited worldwide across collaborating centers, we identified only 10/4351 (0.23%) A152T carriers [23], consistent with the frequency reported in gnomAD (0.29%, with two homozygous carriers). A combined analysis performed on the 403 patients placed the estimated odds ratio (OR) for PPA in an individual carrying *MAPT* A152 T at 7.67 (CI: 2.462–22.45, Fisher's *P*-value = .00027).

Another rare variant that has been, mostly, associated with AD risk is the R47H variant in the *TREM2* gene [24,25]. We identified a total of six (1.49%) carriers of this variant (one logopenic, two nonfluent, and three uncharacterized/unclassifiable cases). In a subset of the National Institute of Mental Health controls, we identified 17/3855 (0.44%) carriers, a frequency similar to that reported in the gnomAD database (0.49%, with two homozygous carriers). A combined analysis placed the estimated OR for PPA in an individual carrying *TREM2* R47H at 3.41 (CI: 1.09–9.13, Fisher's *P*-value = .01735).

The APOE ε4 allele is the most prevalent genetic risk factor for sporadic AD, with a two- to three-fold increase in risk in people with one APOE ε4 allele and about 12-fold increase in those with two alleles (reviewed in [26]). We identified 114 carriers of at least one ε4 allele, of which 14 were ε4-ε4 (also six e2-ε4, and 94 ε3-ε4).

The 17q.21.31 haplotype, also commonly referred as MAPT/tau haplotype, has been linked to many neurological diseases, with H1 haplotype being consistently associated with progressive supranuclear palsy. In this series, most samples (273, 67.7%) had a H1-H1 tau haplotype, whereas 114 (28.3%) and 16 (4%) had a H1-H2 and H2-H2 haplotype, respectively.

4. Discussion

We report the largest genetic study of PPA to date, where we identified a total of 14 out of 403 cases with causative variants. We found mostly *GRN* pathogenic variant carriers, as well as four *C9orf72* expansion and one likely pathogenic *TARDBP* variant carriers, while no pathogenic variants were identified in either *MAPT* or in the AD-associated genes, suggesting that PPA is more TDP43- than tau-related in our series. The frequency of disease-causing variants was higher within the nfvPPA cases (7 of 125, 5.6%), when compared to the semantic (2 of 122, 1.6%) and logopenic cases (1 of 89, 1.1%). Importantly, nfvPPA cases only carried *GRN/C9orf72* variants and not *MAPT* mutations, as it would be expected based on the multiple reports of predominant tau pathology in nfvPPA.

Although disease-associated variants in the three most common FTD genes, *MAPT, GRN,* and *C9orf72,* and also a few in the AD genes, *PSEN1* and *TREM2,* have been reported in the literature, these were mostly single PPA case reports (summarized in Table 2). Within this group, most nfvPPA cases were reported to carry either *GRN* or *MAPT* pathogenic variants, while *PSEN1* variants and *C9orf72* expansions were also reported. The number of case reports with disease-causing variants in svPPA is far scarcer, with *MAPT* and *GRN* causative variants associated with familial cases, while a protein-truncating variant in *TREM2* has been reported in two sporadic svPPA cases, and a *C9orf72* expansion in a few sporadic and familial cases. On the other hand, the few logopenic cases reported in the literature with causative variants have been primarily associated with *GRN* variants, and—in one case—with a *C9orf72* expansion (Table 2).

Genetic screens of the three causative FTD genes in smaller PPA cohorts (32 and 100 cases) identified a few causative variants in *GRN,* as well as *C9orf72* expansion carriers (Table 2) [30,49]. Although in one study (including 32 patients) all causative variants were identified

in nfvPPA cases (two in *GRN* and two *C9orf72* repeat expansions), in the larger study (including 100 patients), three logopenic cases carried *GRN* variants, while one semantic and one unclassified PPA had *C9orf72* expansions. Although in these smaller genetic studies FTD causative genes by themselves accounted for about 5%–12.5%, in our large cohort, the frequency of PPA cases with causative variants in the eight most common dementia genes was only 3.5%. Low frequencies of familial PPA have been previously reported [56], and disease-causing variants in *MAPT, GRN,* and *C9orf72* are mostly associated with familial cases. This could provide a possible explanation for such low frequency of carriers, as well as the fact that most FTD cases with these causative genes seem to be associated with the behavioral variant of FTD, not language variants.

Besides AD and FTD causative variants, we also screened our series for rare neurodegeneration risk variants: *MAPT* A152 T, associated with FTD and progressive supranuclear palsy [23], and *TREM2* R47H, associated with AD [24,25]. We identified seven (1.74%) *MAPT* A152T carriers among the 403 PPA patients compared to 10/4351 (0.23%) in our controls, corresponding to a 7.7-fold increase in risk for PPA. The risk for PPA is not as high as that reported for progressive supranuclear palsy (OR = 8.13) but is considerably higher than the risk for FTD (OR = 3.35) [23]. Four of the seven *MAPT* A152T carriers in our series fall under the general heading of FTD (nfvPPA and svPPA), which could reflect a contribution of PPA cases to the effect observed in FTD [23]. On the other hand, many patients with nfvPPA eventually progress to progressive supranuclear palsy [3,4], suggesting that the *MAPT* A152T effect we observed in this series could also be driven by progressive supranuclear palsy cases initially manifesting as PPA.

We also observed a higher frequency of the rare *TREM2* R47H variant (1.49%) in PPA patients compared to a subset of our controls (0.44%), suggesting that this variant also increase the risk for PPA (3.4-fold increase). This might be explained by the fact that (1) we included in our series a smaller subset of logopenic cases, for which AD is reported to be the most common underlying pathology [8,9]; (2) while we identified one logopenic case with the *TREM2* R47H variant, the other carriers were mostly uncharacterized/unclassifiable PPA cases, so it remains possible that the *TREM2* effect we observed in our series is driven by the lvPPA cases.

The *APOE* ε4 allele is by far the strongest genetic risk factor for AD, as over 40% of cases are ε4 carriers. In our series, 28.3% of PPA cases carried at least one APOE ε4 allele, while 3.5% carried two e4 alleles. These frequencies are quite similar to those reported in over 74,000 individuals from a prospective study in the Danish general population (30% ε4 and 2.8% ε4-ε4 carriers) [57]. Previous studies have also looked at the frequency of e4 carriers in PPA subjects, where frequencies ranged from 20% (in the FTLD-tau group) to 30% (in the AD group), similar to what was observed in their set of 190 control subjects (26% ε4 carriers) [7,58]. However, the rate of APOE ε4 positives in our series was higher, and closer to reported AD frequencies, among lvPPA patients (36.0% ε4 and 7.9% ε4-ε4 carriers vs. 21.6% and 1.6% in nfvPPA vs. 26.2% and 1.6% in svPPA), consistent with the reported association between lvPPA and AD pathology [8,9].

The H1 MAPT/tau haplotype has been consistently associated with progressive supranuclear palsy [59]. Most of our PPA cases were carriers of the H1-H1 haplotype, 67.8%, a frequency slightly higher than that reported in population databases, such as the 1000 Genomes and Wellderly projects (58%–64% for European populations) [60,61]. When categorized by each subset of PPA variants, the frequency of H1-H1 carriers in our series was higher among nfvPPA cases (72.0% vs. 64.0% in lvPPAvs. 65.6% in svPPA), which is consistent with the fact that nfvPPA cases are mostly associated with FTLD-tau pathology.

The present series suggested that there was no genetic feature that can reliably distinguish among the different PPA variants. For example, based on literature reports, we had hypothesized that nfvPPA cases would be mostly associated with *MAPT* mutations; however, we only observed *C9orf72* and *GRN* mutations in this PPA subgroup. In addition, mutations in the same gene, for example, *GRN*, were associated with both nfvPPA and lvPPA syndromes, suggesting that the causal mechanism may be complex, with other risk alleles in different genes, possibly interacting with nongenetic factors and producing variation in clinical presentation. We studied four such candidates, rare variants in *MAPT* and *TREM2,* and common variants at the *APOE* and 17q21.31 loci, and found them to be overrepresented in PPA, sometimes in PPA subgroups, raising the possibility that rare and common variants may contribute to clinical presentation across PPA subgroups.

Like most genetic screens in clinically diagnosed syndromes, our study has a number of limitations: first, cases were recruited at two different US tertiary referral centers, which could lead to some ascertainment bias; second, although we applied uniform methods of disease phenotyping and genetic analysis, slight differences in the application of diagnostic criteria across these centers could also lead to measurement errors. Third, symptoms observed in PPA cases do not always clearly allow classification in one of the three variants, as shown by the 18 unclassifiable and 44 uncharacterized cases in our cohort.

In conclusion, our genetic screen of AD- and FTD-associated genes in the largest PPA cohort reported to date showed that both causative and risk-associated variants are rarely associated with PPA. Distinct clinical syndromes are not specifically associated with one pathology or one type of mutation, pointing to a complex etiology, possibly including rare and common risk-associated variants, and nongenetic factors. Further studies with even larger sample sizes will be needed to clarify this complex etiology and the genetic basis of the various clinical syndromes in PPA. Specifically, (1) pathological examination in all cases will reduce the inevitable measurement error associated with clinical diagnosis across multiple clinical centers and will provide valuable information about the relationship between asymmetry of degeneration, clinical presentation, and risk-associated genetic variants; (2) genome-wide sequence analysis will identify additional rare and common risk-associated variants; (3) calculation of polygenic risk scores [62] will contribute to estimating the genome-wide contribution of common variation to these phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. Systematic review: Disease-causing variants in the frontotemporal dementia genes *MAPT, GRN,* and *C9orf72,* and also a few in the Alzheimer's disease genes *PSEN1* and *TREM2,* have been reported in the literature for patients diagnosed with primary progressive aphasia (PPA). However, these were mostly single case reports while large cohorts have not been studied in depth.
2. Interpretation: Our findings show that causative variants within the main dementia genes are rarely associated with PPA, accounting for only 3.5% of cases in our series, while known rare risk variants for Alzheimer's disease and frontotemporal dementia also increase the risk for PPA.
3. Future directions: This study suggests that these language variants have a complex etiology and genetic basis, possibly including rare and common risk-associated variants, and nongenetic factors. Future studies with even larger sample sizes, including genome-wide sequence analysis and calculation of polygenic risk scores, will be needed to elucidate the genetic architecture of PPA.

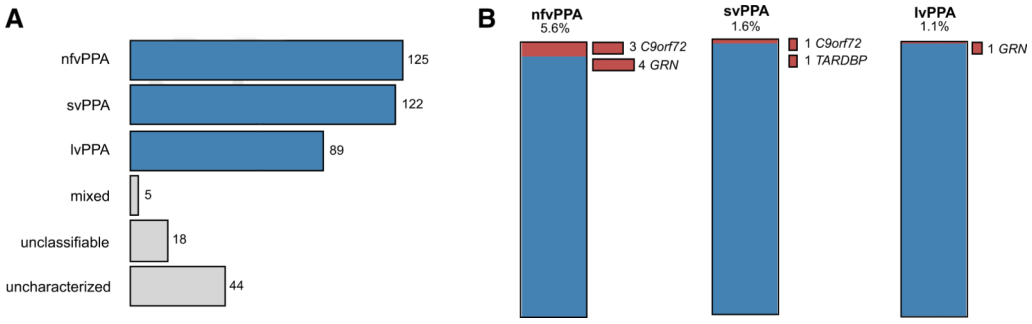

Fig. 1.

Clinical and genetic characteristics of the PPA cohort. (A) Clinical categorization of the 403 PPA patients included in this study, following the consensus criteria for PPA. (B) Carriers of (likely) pathogenic variants in the main AD and FTD genes (red) among the three PPA variants. Abbreviations: PPA, logopenic variant primary progressive aphasia; nfvPPA, nonfluent variant PPA; svPPA, semantic variant PPA.

Table 1

Pathogenic variants identified within the main AD and FTD genes

Patient	PPA variant	Gender	Age at onset	Family history*	Gene	Variant	gnomAD frequency (allele count)
1	svPPA	M	51	Yes	*TARDBP*	c.A1147G:p.Ile383Val	1.949E-05 (5)
2	svPPA	M	49	No	*C9orf72*	Repeat expansion	-
3	nfvPPA	F	65	Yes	*C9orf72*	Repeat expansion	-
4	nfvPPA	M	62	N/A	*C9orf72*	Repeat expansion	-
5	nfvPPA	F	49	Yes	*C9orf72*	Repeat expansion	-
6	nfvPPA	F	63	No	*GRN*	c.264+2T>C	-
7	Uncharacterized	M	57	Yes	*GRN*	c.388_391delCAGT:p.Gln130SerfsTer125	7.217E-06 (2)
8	Uncharacterized	F	56	No	*GRN*	c.675_676delCA:p.Ser226TrpfsTer28	-
9	Uncharacterized	M	53	Yes	*GRN*	c.709–2A>G	-
10	nfvPPA	F	50	Yes	*GRN*	c.910_911dupTG:p.Trp304CysfsTer58	4.064E-06 (1)
11	nfvPPA	M	69	Yes	*GRN*	c.1145delC:p.Thr382SerfsTer30	4.081E-06 (1)
12	nfvPPA	F	64	Yes	*GRN*	c.1256_1263dupGAAGCGAG:p.Ile422GlufsTer72	-
13	lvPPA	F	60	Yes	*GRN*	c.C1477 T:p.Arg493Ter	4.065E-06 (1)
14	Mixed	F	67	No	*GRN*	c.C1477 T:p.Arg493Ter	4.065E-06 (1)

Abbreviations: AD, Alzheimer's disease; FTD, frontotemporal dementia; lvPPA, logopenic variant primary progressive aphasia (PPA); nfvPPA, nonfluent variant PPA; svPPA, semantic variant PPA.

*Patients were considered to have family history if any of their first or second degree relatives had a clinical diagnosis of dementia.

Table 2

Summary of pathogenic variants in PPA cases reported in the literature

PPA variant	Gene	Variant	Number of cases	References
nfvPPA	*GRN*	p.Cys31LeufsTer34	1 familial	[27]
		p.Gly35GlufsTer19	1 familial	[28]
		IVS3 –2delA	1 familial	[29]
		p.Gln130SerfsTer124	1 familial	[27]
		p.Cys139Arg	1 sporadic	[30]
		p.Cys157LysfsTer97	1 familial and 1 sporadic	[31–33]
		p.Arg161GlyfsTer36	1 sporadic	[34]
		IVS7+ 1delTGAG	1 familial	[35]
		IVS7–1G > A	5 familial	[36]
		p.Gln257ProfsTer27	1 familial	[37]
		p.Thr272SerfsTer10	6 familial and 1 sporadic	[38,39]
		p.Gln300Ter	1 familial	[37]
		p.Cys366fsTer1	1 familial	[30]
		p.Gln415Ter	1 sporadic	[27]
		p.Val452TrpfsTer38	1 familial	[27]
		p.Arg493Ter	1 familial	[27]
		p.Cys521Tyr	1 familial	[40]
	MAPT	p.Gly639Ser	1 familial	[41]
		p.Val698Ile	1 familial	[42]
		p.Gly724Arg	1 sporadic	[43]
	C9orf72	repeat expansion	3 familial	[30,44]
			1 sporadic	
	PSEN1	p.Thr147Ile	1 familial	[45]
		p.Pro264Leu	1 familial	[46]
svPPA	*GRN*	p.Thr409Met	1 familial	[47]
	MAPT	p.Pro636Leu	1 familial	[48]
		IVS10+ 16C>T	13 familial	[27]
	C9orf72	Repeat expansion	1 familial and 2 sporadic	[44,49–51]
			3 not specified	
	TREM2	p.Gln33Ter	2 sporadic	[52]
lvPPA	*GRN*	p.M1?	1 familial	[53]
		Not specified	5 familial	[49,54]
			1 sporadic	
	C9orf72	Repeat expansion	1 not specified	[55]

Abbreviations: lvPPA, logopenic variant primary progressive aphasia (PPA); nfvPPA, nonfluent variant PPA; svPPA, semantic variant PPA.