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Differences in Sex Distribution Between Genetic and Sporadic Frontotemporal Dementia

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Abstract.
Background: Reported sex distributions differ between frontotemporal dementia (FTD) cohorts. Possible explanations are the evolving clinical criteria of FTD and its subtypes and the discovery of FTD causal genetic mutations that has resulted in varying demographics.
Objective: Our aim was to determine the sex distribution of sporadic and genetic FTD cases and its subtypes in an international cohort.
Methods: We included 910 patients with behavioral variant frontotemporal dementia (bvFTD; $n = 654$), non-fluent variant primary progressive aphasia (nfvPPA; $n = 99$), semantic variant primary progressive aphasia (svPPA; $n = 117$), and right temporal variant frontotemporal dementia (rtvFTD; $n = 40$). We compared sex distribution between genetic and sporadic FTD using χ^2-tests.
Results: The genetic FTD group consisted of 51.2% males, which did not differ from sporadic FTD (57.8% male, $p = 0.08$). In the sporadic bvFTD subgroup, males were predominant in contrast to genetic bvFTD (61.6% versus 52.9% males, $p = 0.04$). In the other clinical FTD subgroups, genetic cases were underrepresented and within the sporadic cases the sex distribution was somewhat equal.

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Conclusion: The higher male prevalence in sporadic bvFTD may provide important clues for its differential pathogenesis and warrants further research.

Keywords: Behavioral variant frontotemporal dementia, genetic, non-fluent variant primary progressive aphasia, right temporal variant frontotemporal dementia, semantic variant primary progressive aphasia, sex differences, sex distribution, sporadic

INTRODUCTION

Frontotemporal dementia (FTD) is an umbrella clinical term encompassing a group of neurodegenerative syndromes characterized by progressive deficits in behavior, executive function, or language [1]. The behavioral variant of FTD (bvFTD) [2], primary progressive aphasia (PPA), which can be further subdivided into the semantic variant (svPPA) and non-fluent variant of primary progressive aphasia (nfvPPA) [3], and a right temporal variant of FTD (rtvFTD) [4–6] are clinical subtypes of FTD. In addition, FTD has been associated with amyotrophic lateral sclerosis (ALS) [7] since 5–10% of FTD cases has concomitant motor neuron disease symptoms, whereas 40–50% of ALS cases demonstrate FTD symptoms [8]. Moreover, the tauopathies corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) show clinical, genetic, and pathological overlap with FTD [7, 9, 10]. Currently, we know that 20–30% of the FTD cases have a genetic cause [11], mostly accounted for by heterozygous mutations in the genes microtubule associated protein tau (*MAPT*), progranulin (*GRN*), and the repeat expansion in the chromosome 9 open reading frame 72 (*C9orf72*) [12, 13], or rare mutations in genes, such as *TARDBP*, *FUS*, *VCP*, *CHMP2B*, *TBK1*, *PSEN1*, and *OPTN* [1, 11]. Non-genetic FTD cases are generally referred to as "sporadic FTD", meaning that no pathogenic gene mutation has been identified in the context of a negative family history for FTD [14].

Over the years, epidemiological studies on FTD differ with respect to inclusion of clinical subtypes as well as the inclusion of genetic versus sporadic FTD cases. Thus far, no uniform data have been reported regarding sex distribution in FTD and its related syndromes in the last two decades [15–28]. FTD studies that have reported the sex distribution of their cohorts could not report this separately for the genetic and sporadic FTD group since most epidemiological FTD studies were conducted before the discovery of the *C9orf72* hexanucleotide repeat expansion in 2011 [16–18, 20–22]. Also, these older studies are further limited by the use of outdated diagnostic criteria for FTD and inadequate sample sizes to calculate sex ratios for clinical FTD subtypes separately.

A recent paper of Heuer et al. [14] did compare the sporadic and genetic variant of the subtype bvFTD as part of the "Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL)" and the "Longitudinal Evaluation of Familial Frontotemporal Lobar Degeneration (LEFFTDS)" consortia (also known as ALLFTD). This North American study did not focus on the unbalanced sex distribution between these two FTD variants in their demographics and did not include the other clinical FTD subtypes [14]. Another recent retrospective study described an overall equal sex distribution in genetic FTD, with a male predominance in the *C9Orf72* group, an equal sex distribution in the *MAPT* group and a female predominance in the *GRN* group [13]. Yet again, the latter study did not report the sex distributions for sporadic FTD or the clinical FTD subtypes.

The lack and inconsistency of reporting sex distribution separately for the subtypes of FTD in its genetic or sporadic form, may have withheld crucial knowledge to further understand the pathogenesis of FTD. Therefore, in this retrospective international study, we aimed to clarify the previously reported inconsistent sex distribution in sporadic and genetic FTD and its clinical subtypes bvFTD, nfvPPA, svPPA, and rtvFTD.

METHODS

Patient selection

In this international retrospective cohort study, data was collected from multiple international FTD databanks: the Amsterdam Dementia Cohort [29], the Montreal Neurological Institute Cohort (clinical cohort), cohorts from the University of Ulm and Technical University of Munich (as part of the prospective

Table 1
Demographics per clinical FTD subtype and of the total sample

Group	**Total sample**	*bvFTD*	*nfvPPA*	*svPPA*	*rtvFTD*
n	**910**	654	99	117	40
Genetic (%)	**215** (23.6)	191 (29.2)	11 (11.1)	6 (5.1)	7 (17.5)
Sex, male (%)	**398** (56.3)	386 (59.0)	43 (43.4)	62 (53.0)	21 (52.5)
Median EAAO (min-max)	**61** (21–83)[a]	61 (21–83)[b]	64 (45–83)[c]	61 (45–80)[d]	56.5 (42–70)[e]

bvFTD, behavioral variant of frontotemporal dementia; nfvPPA, non fluent variant of primary progressive aphasia; svPPA, semantic variant of primary progressive aphasia; rtvFTD, right temporal variant of frontotemporal dementia; EAAO, estimated age at symptom onset. [a]n = 82 missing EAAO data in total; [b]n = 58 missing EAAO data; [c]n = 12 missing EAAO data; [d]n = 10 missing EAAO data; [e]n = 2 missing EAAO data.

study of the German Consortium of Frontotemporal Lobar Degeneration [30]), the Policlinico Milan Cohort [31, 32], and the Sydney FRONTIER cohort [33], see Supplementary Table 1 for the number of cases per country. All participating sites collected data from dedicated FTD clinics. Sites selected cases who met clinical diagnostic criteria for *probable* or *definite* bvFTD or PPA [2, 3]. rtvFTD cases were selected based on the presence of predominant right temporal atrophy in the presence of a FTD clinical profile. *Possible* bvFTD cases were not included for this study to avoid inclusion of primary psychiatric disease misdiagnosed as FTD [34].

Data collected from each site included diagnosis, sex, genetic status, type of genetic tests being performed, type of genetic mutation (for participants with a genetic variant of FTD) and the estimated age at symptom onset (as reported by the patient or caregiver).

The genetic testing package performed at each site covered at least the most prevalent pathogenic genetic abnormalities for FTD in the genes *C9orf72*, *MAPT*, and *GRN*, except for the Policlinico Milan Cohort that did not include the *MAPT* mutation screening due to its low frequency in Italy [13]. Cases were defined as sporadic FTD if genetic testing was negative and as genetic FTD when a pathogenic mutation was present (see Supplementary Table 2 for an overview of the genetic mutations in our cohort).

In total, 1,089 patients with a clinical diagnosis within the FTD spectrum of either bvFTD, rtvFTD, svPPA, or nfvPPA, were selected. Cases were excluded if either the FTD subtype was unknown ($n = 26$, 64% male), the genetic status was unknown ($n = 141$, 60% male) or sex was unknown ($n = 12$). This led to the final inclusion of 910 FTD cases.

In addition, we combined our bvFTD sex prevalence data with those from the ALLFTD cohort, retrieved from Heuer et al. (2020) [14] to enlarge the North-American inclusions in this study.

Data analysis and statistics

All analyses were conducted using SPSS, version 26.0 (IBM). We first compared the sex distribution between the genetic and sporadic FTD group. Then we calculated the sex distribution for each FTD subtype. We compared the estimated age at symptom onset between females and males for both the genetic and the sporadic FTD groups. Differences in sex ratio in the genetic and sporadic group in the cohort and in each clinical subtype were assessed by performing a chi-square analysis. Cramer's V scores are reported as effect size measurement of the chi-square analyses. Continuous variables were tested for normality followed by either an independent sample *T*-test or Mann Whitney U test accordingly.

RESULTS

The demographic data of the 910 FTD patients included in the study are shown in Table 1.

The male/female distribution in the genetic FTD group (51.2% male) did not significantly differ from that of the sporadic FTD group (57.8% male; Pearson χ^2, $p = 0.08$, Cramer's V = 0.06).

Within the genetic FTD group, the estimated age at symptom onset did not differ significantly between males (median 58.0 years) and females (median 59.0 years; Mann-Whitney U test $p = 0.62$, r = –0.03). In the sporadic FTD group, however, the estimated age at symptom onset was significantly higher in females (median = 63.5 years) compared to males (median = 61.0 years) with a median difference of 2.5 years (Mann Whitney U test, $p = 0.04$, r = –0.08). The two clinical subgroups bvFTD and nfvPPA, seemed to have driven this observation, as results lost significance when one of these clinical subtypes were excluded from the latter analysis (Supplementary Table 3). Albeit not significant, sporadic bvFTD, nfvPPA and svPPA showed a higher estimated age

Table 2
Sex distribution in genetic and sporadic FTD (per subtype)

	Genetic	Sporadic	*p*
bvFTD $n = 654$			
Male	101 (52.9%)	285 (61.6%)	
Female	90 (47.1%)	178 (38.4%)	0.04[a]
nfvPPA $n = 99$			
Male	3 (27.3%)	40 (45.5%)	
Female	8 (72.7%)	48 (54.5%)	0.34[b]
svPPA $n = 117$			
Male	3 (50%)	59 (53.2%)	
Female	3 (50%)	52 (46.8%)	1.00[b]
rtvFTD $n = 40$			
Male	3 (42.9%)	18 (54.5%)	
Female	4 (57.1%)	15 (45.5%)	0.69[b]

bvFTD, behavioral variant of frontotemporal dementia; nfvPPA, non fluent variant of primary progressive aphasia; svPPA, semantic variant of primary progressive aphasia; rtvFTD, right temporal variant of frontotemporal dementia. [a]Pearson χ^2; [b]Fisher – exact test.

at symptom onset in females than in males. Within sporadic rtvFTD, females had a lower reported estimated age at symptom onset than the males, with a non-significant median difference of 3 years (Supplementary Table 4).

Table 2 shows the sex distribution of genetic and sporadic FTD for each of the FTD subtypes. We observed a significant difference in sex distribution between genetic and sporadic bvFTD (Pearson χ^2, $p = 0.04$, Cramer's V = 0.08), showing a higher number of males in the sporadic group while sex distribution was equal in the genetic group. No sex distribution differences were found for the other three FTD subtypes, nfvPPA, svPPA, and rtvFTD ($p = 0.34$, $p = 1.0$, $p = 0.69$ and Cramer's V 0.012, 0.01, 0.09 respectively); however, the number of genetic cases was notably small in these subgroups and the sex distribution in the sporadic cases was somewhat equal (Table 2).

Combination of genetic and sporadic bvFTD with data from the ALLFTD study

We combined the bvFTD sex prevalence data from our study with the data from the ALLFTD cohort, retrieved from Heuer et al. [14], which confirmed the differential sex distribution between genetic and sporadic bvFTD (Pearson χ^2, $p = 0.004$, Cramer's V 0.10, Table 3).

Table 3
Combination of genetic and sporadic bvFTD with data from the ALLFTD study

	Genetic bvFTD	Sporadic bvFTD	*p*
Male	154 (53.1%)	384 (63.1%)	
Female	136 (46.9%)	225 (36.9%)	0.004[a]

Combination of genetic and sporadic bvFTD cases from ALLFTD, retrieved from [14] and sporadic and genetic bvFTD cases from our study. bvFTD, behavioral variant of frontotemporal dementia. [a]Pearson χ^2.

DISCUSSION

Here, we report the sex distribution in genetic and sporadic FTD and its clinical subtypes by combining cases from 5 international sites to clarify the inconsistent sex ratio's being previously reported. This study demonstrated an unequal sex distribution in the sporadic bvFTD group with a significant male predominance (61.6% males) compared to the genetic bvFTD group (52.9% males). In contrast, this significant sex imbalance was obscured when combining all subtypes together; with a balanced sex distribution in the genetic FTD group (51.2% male), whilst showing an unequal sex distribution in the sporadic FTD group (57.8% males), although not significant.

Our results are consistent with the recent findings of Moore et al., describing an equal sex distribution in genetic FTD [13] and the recent study of Heuer et al. of the ALLFTD cohort showing a male predominance in the sporadic bvFTD group as opposed to an equal sex distribution in the genetic group [14]. By combining the genetic and sporadic bvFTD cases from our study with those of the ALLFTD study, we confirmed our findings in a large international retrospective cohort. Previous other studies may have been underpowered to detect differences in sex distribution between genetic and sporadic bvFTD. Indeed, we calculated that a sample size of 785 bvFTD cases would be required to have 80% power at 0.05 type I error probability.

In the other clinical FTD subgroups, sex ratios were similar in the sporadic groups and the number of genetic cases were notably small. However, there was a trend toward a female predominance in the nfvPPA subgroup which has been reported before in a pathologically confirmed PPA cohort [35].

Several hypotheses may explain the difference in sex distribution in sporadic bvFTD. First, there may be a, so-far undiscovered, sex-linked genetic cause of FTD. The balanced sex distribution in the genetic group results from FTD autosomal mutations and thus equally affect both sexes. However, the sex chromosomes have not been included in genome wide association studies of FTD [36, 37], thus pos-

sibly withholding sex-linked genetic risk factors. Nevertheless, sporadic FTD is considered to be a strongly polygenic disease and in turn phenotypic expression of genetic FTD and ALS might be partially moderated by sex-related risk factors as unbalanced sex ratios have been reported in *GRN* mutation and in *C9orf72* expansion carrier groups [13, 38, 39].

Second, the male predominance in the sporadic bvFTD group reported here may be explained by environmental risk factors. For instance, head trauma has been associated in one study with a three-fold increased risk of sporadic bvFTD [40]; in general, males have a higher incidence rate of traumatic brain injury (TBI) [41]. Likewise, men seem to have an overall higher risk of developing amyotrophic lateral sclerosis (ALS) [28], with the exception of bulbar ALS, that seems to be more frequent in postmenopausal women [24]. Head trauma, which is more frequent in men, is also pointed out as possible risk factor. Which in turn might be a possible explanation for the reported higher ALS incidence in men [42, 43]. It should be noted that significant head trauma was an exclusion criterion in the Sydney FRONTIER cohort [33]. However, subclinical events (e.g., concussions) were not consistently reported and are likely to also be more frequent in males due to their higher participation in contact sports. As such, the prevalence of TBI or subclinical events were unknown in this cohort and the possible associations between TBI and sporadic FTD could not therefore be tested.

Third, it is possible that females were underrepresented in our cohort. A potential referral bias to tertiary centers could play a role. It may be conceivable that female FTD patients are being referred in a later stage due to sociological factors, such as less impact of behavioral changes in women than in men due to their diverging social roles while the existence of a positive family history in the genetic group prevents this referral bias from occurring. An alternative explanation could also be a higher frequency of psychiatric misdiagnosis in females [44] resulting in a lower prevalence of females in memory clinics and possibly a diagnosis of FTD in a later disease stage. This hypothesis is supported by our finding of a later reported estimated age at symptom onset in female sporadic FTD cases.

Lastly, we hypothesize a possible biological explanation related to social cognitive skills which are crucially involved in FTD, namely that females have a higher cognitive social reserve leading to a later age at symptom onset (as shown in our results). Both the higher male ratio in autism spectrum disorders [45], a disorder known to affect social skills, and a small postmortem study showing the higher density of Von Economo neurons (known to be involved with social cognition) in females [46] provide support for this possible female advantage in social cognition. Moreover, a recent study found that women with bvFTD show greater atrophy burden in brain regions known to be affected by FTD compared to the atrophy burden in men whilst showing similar clinical characteristics [47]. Along these lines, female partners may recognize social cognitive deficits in male patients earlier than vice versa. Interestingly, the large overrepresentation of male persons in the benign bvFTD phenocopy syndrome supports this idea [48, 49] but is highly unlikely to explain a male overrepresentation in our bvFTD group since we excluded *possible* bvFTD cases.

As far as we are aware, we were able to perform the largest study on sex distribution in FTD in both the genetic and sporadic variant and its clinical subtypes by combining data from five international research sites. This study, however, has a few limitations. First, the retrospective design of our study prevented a complete collection of the family history. Heuer et al. [14] for example, defined their sporadic cases as "no autosomal dominant family history of an FTLD syndrome and no evidence of an underlying frontal lobe degeneration disease associated genetic mutation" whereas we only divided the cases into genetic and sporadic cases based on local genetic testing. Even though local genetic testing policies slightly differ between sites, genetic testing was offered in cases with a positive family history. In addition, the genetic testing at least had to include the gene mutations mostly accounted for heritable FTD at site of origin, thus minimizing the chance of a familial/genetic FTD case being included in the sporadic group. Secondly, the estimated age of symptom onset reported by the patient or caregiver is subjective and might be influenced by the informant or by the informant's social role as mentioned above. Furthermore, the sample size of svPPA, nfvPPA, and rtvFTD was relatively small compared to the bvFTD group. Moreover, logopenic variant of PPA cases with underlying Alzheimer's disease pathology are often mistakenly included as nfvPPA and svPPA which, together with the smaller sample size, may have precluded the identification of significant differences in sex distributions in these subgroups. Lastly, the absence of pathological data, cognitive testing and cases diagnosed with

CBD, PSP, or FTD-ALS, limited the examination of the proposed hypotheses for the complete FTD disease spectrum.

In conclusion, the male predominance in sporadic behavioral variant of FTD found in this study indicates the possible existence of sex differences in the pathogenesis of FTD. Our findings urge further research into sex diversity in sporadic FTD, from both social and biological perspectives.

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SUPPLEMENTARY MATERIAL

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