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Relationship Between Sporadic Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders: A Study in Families

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ABSTRACT

Background: Because the behavioral variant of frontotemporal dementia (bvFTD) shows major clinical overlap with primary psychiatric disorders (PPD) that affect similar neuroanatomical circuits, a common genetic vulnerability between FTD and PPD was hypothesized.

Aims: We studied whether PPD are more prevalent in families of patients with sporadic frontotemporal dementia compared with healthy controls (HC), subjects with Alzheimer's disease (AD), and individuals with bipolar disorder (BD).

Methods: In this case-control study performed between January 2013 and February 2019, we investigated the first-degree family history concerning depression, psychosis (including schizophrenia), BD, and autism spectrum disorder for 73 bvFTD patients, 153 patients with BD, 108 patients with AD, and 101 HC with a semistructured questionnaire (QFTD-NL 1.0) according to *DSM-IV*, *DSM-5*, or *ICD-10* criteria.

Results: Patients with bvFTD had a 2.58-fold higher odds of having a first-degree family member with depression compared to HC ($P = .04$). Furthermore, they showed 3.26-fold higher odds of having a first-degree relative with psychosis compared to HC ($P = .09$).

Conclusions: Our results implicate a link between dementia, including sporadic bvFTD, and depression. Further study into the genetic overlap between bvFTD and PPD might provide clues to targeting common disease mechanisms.

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Frontotemporal dementia (FTD) is a common cause of early-onset dementia.[1] The behavioral variant of FTD (bvFTD) is the most common variant of FTD and is characterized by personality and behavior changes in combination with executive dysfunction and disturbances of social cognition.[2] Clinically, bvFTD shows similarities with various primary psychiatric disorders (PPD).[1] Several case reports have described the diagnostic difficulty due to symptomatic overlap between bvFTD and PPD.[1] It is therefore not surprising that around 50% of bvFTD patients receive a PPD diagnosis prior to their bvFTD diagnosis.[1,3] bvFTD shares social withdrawal and lack of initiative with major depression and schizophrenia. Although relatively less frequent, psychotic symptoms such as delusions and hallucinations may occur in bvFTD.[1,4] Disinhibition and elated mood may be similar to mania, whereas the repetitive and ritualistic behavior in bvFTD may be reminiscent of obsessive-compulsive disorder.[1] Profound deficits in social cognition, including facial emotion recognition, theory of mind, and empathy, are a core feature of bvFTD.[5,6] Likewise, social cognitive deficits have also been shown to be present in autism, major depression, bipolar disorder (BD), and schizophrenia.[7–9]

Whereas research in FTD has traditionally been placed in the neurodegenerative field, we would like to shift the focus toward a shared vulnerability hypothesis between bvFTD and PPD. An intriguing question remains as to whether bvFTD shares pathophysiologic elements with the major PPD that resemble bvFTD. It is conceivable that, due to a shared vulnerability of neuroanatomical circuitries related to the frontotemporal brain areas, bvFTD and PPD are associated and therefore tend to co-occur more often. Indeed, the occurrence of PPD has been associated with circuits similar to those that are involved in bvFTD, such as the prefrontal cortex, temporal lobe, amygdala, insula, anterior cingulate cortex, and white matter connections.[10–15] Interestingly,

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Clinical Points

- Distinguishing between the behavioral variant of frontotemporal dementia (bvFTD) and primary psychiatric disorders (PPD) is challenging due to overlapping clinical symptoms.
- Depression occurs more often in families of patients with Alzheimer's disease and sporadic bvFTD. bvFTD, Alzheimer's disease, and depression might share genetic and environmental risk factors.
- Further studies need to elucidate the relationship between PPD and bvFTD. Clinicians are advised to take a psychiatric and neurologic family history.

among these major psychiatric disorders, a shared polygenic risk has already been found.[16]

bvFTD is autosomal dominant in up to 27% of cases with the main mutations being the hexanucleotide repeat expansion in the *C9orf72* gene and pathological variants in the microtubule-associated protein tau gene (*MAPT*) and the progranulin gene (*GRN*).[1,17] It has become clear that psychiatric presentations are relatively frequent in *C9orf72* repeat expansion carriers, as these patients often show symptoms like psychosis (21%–65%), late-onset depression, and/or mania.[1,18,19] In autosomal dominant bvFTD due to variants in *MAPT* and *GRN,* psychiatric presentations may occur as well, though less frequently.[1,20,21] At present, as far as the authors are aware, only for *C9orf72* mutation carriers has it been established that their family history is enriched for schizophrenia, suicide, and autism spectrum disorder (ASD).[9] This finding suggests that the *C9orf72* mutation, maybe in combination with genetic modifiers, exerts a pleiotropic effect and can be associated with a primary psychiatric phenotype.[9] Enrichment of family history for PPD has not been studied in genetically sporadic bvFTD.

Due to symptomatic overlap between bvFTD and PPD and neuroanatomical circuitries,[1,22,23] we hypothesize that the family history of patients with sporadic bvFTD is more often positive for primary psychiatric disorders compared to that of healthy control subjects. In this study, we examined positive family history of psychiatric disorders in patients with sporadic bvFTD compared to healthy control subjects (HC), patients with Alzheimer's disease (AD), and individuals with bipolar disorder (BD).

METHODS

This case-control study was performed between January 2013 and February 2019 at the Alzheimer Center Amsterdam in collaboration with the Erasmus Medical Center of Rotterdam and the department of Old Age Psychiatry of GGZInGeest, Amsterdam, The Netherlands.

Participants

Patients were included consecutively from the Amsterdam Dementia Cohort (bvFTD: n = 123, AD: n = 108), the Dutch Older Bipolar Cohort of GGZInGeest (BD: n = 153), and the Erasmus Medical Center (bvFTD: n = 12).[24,25] HC (n = 101) were selected from a healthy control subjects database of the Alzheimer Center Amsterdam or recruited at the outpatient department of neurology and neurosurgery, mostly being healthy spouses of neurologic patients. All patients and control subjects had to be able to speak and understand Dutch or English to be included in this study; they also had to know their first-degree relatives (no adopted study participants). Patients with bvFTD were included when diagnosed with probable or definite bvFTD according to the international consensus criteria.[2] HC were included if they were cognitively healthy and had no first-degree family member with a clinical diagnosis of any subform of FTD. They were excluded when they had a lifetime psychiatric disorder according to *DSM-IV*, *DSM-5*, or *ICD-10* criteria (except for burnout), subjective memory complaints, any neurologic movement disorder, or any form of dementia. From these cohorts, patients were included if the participants and/or their caregivers had knowledge of the medical history of their biological first-degree family members. Patients with AD served as a second control group. They were diagnosed according to the criteria of McKhann et al[26] and were excluded in the case of a clinical presentation of a frontal lobe syndrome. As the family history for psychiatric disorders in BD is generally positive for PPD, BD served as a positive control group. BD was diagnosed based on *DSM-IV-TR* criteria,[27] applying the same inclusion and exclusion criteria as in the previous (2014) study of Dols et al.[24]

All patients and control subjects or their legal representatives gave consent to participation in this study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Medical Ethical Committee of the VU University Medical Centre (VUMC), Amsterdam (approval number: 2014.574).

Genetic Screening

All bvFTD patients were reviewed for a positive family history of bvFTD. In case of a positive family history for FTD, genetic counseling was offered to test for a causative genetic mutation (eg, *MAPT*, *GRN*, or *C9orf72*). Patients with an unknown genetic testing result or an identified (probable) causal variant were excluded (Amsterdam Dementia Cohort: n = 15, Erasmus Medical Center: n = 1). Because *C9orf72* repeat expansions may be present in bvFTD patients with a seemingly negative family history,[28] we screened all available blood samples of bvFTD patients that had been taken and stored in our biobank for the presence of this mutation. The *C9orf72* repeat length was determined using the AmplideX PCR/CE *C9orf72* Kit (Asuragen), whereby < 25 repeats were considered as normal, between 25 and 29 repeats as intermediate, and > 29 repeats as pathological.[29] All bvFTD patients (also with negative family history for FTD) whose *C9orf72* mutation status was positive or unknown were

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excluded. This led to the exclusion of 46 participants with bvFTD (Amsterdam Dementia Cohort: n = 37, Erasmus Medical Center: n = 9). The final bvFTD cohort therefore consisted of 73 cases.

Participants with AD have undergone biomarker affirmation of amyloid pathology and it is therefore considered very unlikely that they carried a *C9orf72* expansion. Additionally, the prevalence of *C9orf72* repeat expansions in psychiatric cohorts is very low, which warrants the lack of available *C9orf72* testing in this group.[19,30,31] Statistical analysis was performed on 73 patients with sporadic bvFTD, 108 patients with AD, 153 patients with BD, and 101 HC.

Measurements

Family history information was obtained from a questionnaire designed in 2013 (QFTD-NL 1.0; see Supplementary Appendix 1). This questionnaire is adapted from the validated Questionnaire for Bipolar Disorders (QBP-NL), which is used in the Netherlands and the United States for research involving patients with bipolar disorder.[32] Questionnaire QFTD-NL 1.0 was used by the interviewer to investigate family history in first-degree family members (parents, children and siblings) for 4 mental disorders: depression, psychosis (past history of episodes with delusions or hallucinations), BD, and ASD. The response options were 1 (no), 2 (possible), 3 (certainly: diagnosed and/or treated), 4 (unknown), or 5 (inapplicable). A specific psychiatric disorder was scored as "present in family" only when "certainly" was answered. If one of the first-degree family members had a positive family history for the specific PPD, the family history was scored as positive. The QFTD-NL 1.0 was administered either by telephone or at the VUMC outpatient department by a research assistant to the patients' caregivers in case of bvFTD and AD, or to the subjects themselves in case of BD and the healthy control subjects.

Confounders

On the basis of previous studies and empirical evidence, we identified age and education level as confounding variables.[33–35] Gender of the study participants themselves was not considered a confounding variable, as we see no clinically relevant relationship between gender of the participant and PPD in family members. Also, number of first-degree family members was not considered a relevant confounder, as we see no clinically relevant relationship between study groups (bvFTD, HC, AD, and BD) and number of first-degree family members. Additionally, in our cohort, the number of first-degree family members did not differ between groups ($P = .22$).

Statistical Analysis

Descriptive statistics were performed to observe differences between the different study groups (bvFTD, HC, AD, and BD), using χ^2 tests for categorical variables and 1-way analysis of variance (ANOVA) test on log-transformed data for continuous variables. Next, prevalence of a positive family history for the 4 PPD (depression, psychosis, BD, and ASD) for each study group was determined. To study the associations between bvFTD and a positive family history for PPD versus that of the study groups (HC, AD, and BD) and a positive family history for PPD, separate logistic regression analyses were performed with the different study groups as independent variable (whereby bvFTD is the reference category) and a positive family history for PPD as dependent variable. Unadjusted models are presented first, and then adjusted models with correction for confounding variables (age and education) are presented. An effect was considered significant at a P value $< .05$. All statistical analyses were conducted using IBM SPSS Statistics 22 (SPSS Inc; Chicago, IL).

Table 1. Demographic and Family Characteristics of the Study Groups

Characteristic	bvFTD (n = 73)	HC (n = 101)	AD (n = 108)	BD (n = 153)	*P* Value
Age, mean ± SD, y[a]	64.9 ± 9.1	63.8 ± 7.9	66.2 ± 7.6	68.3 ± 7.4	< .01
Male, %[b]	63	39	49	48	.02
Education, %[b]					< .01
Low	24	9	31	21	
Average	37	16	31	33	
High	39	75	38	46	
No. of first-degree family members, mean ± SD[a]	7.3 ± 2.5	7.0 ± 2.6	7.4 ± 2.2	7.7 ± 2.6	.22

[a]Data are not normally distributed. One-way ANOVA test has been used on log-transformed data to compare properties of the study groups.
[b]χ^2 test has been used to compare properties among the study groups.
Abbreviations: AD = Alzheimer's disease, ANOVA = analysis of variance, BD = bipolar disorder, bvFTD = behavioral variant of frontotemporal dementia, HC = healthy controls.

Data Availability Statement

Anonymized data will be shared by request from any qualified investigator.

RESULTS

Baseline Characteristics

Demographic and family characteristics of the study groups are summarized in Table 1. bvFTD patients had a mean ± SD age of 64.9 ± 9.1 years. BD patients were significantly older compared to bvFTD patients. The other groups did not differ significantly in age (separate *t* tests not shown). HC were significantly higher educated (75%) compared to bvFTD patients, with education level considered as a relevant confounding factor.[33–35] AD and BD subjects did not differ significantly in education level compared to bvFTD patients. The number of first-degree family members did not differ significantly between groups.

The prevalence of a positive family history of each of the 4 PPD is displayed in Figure 1 and in Supplementary Table 1. Results of logistic regression analyses are displayed in Table 2 and Supplementary Table 2. Compared to HC, sporadic patients with sporadic bvFTD had a 2.58 times higher odds of having a first-degree family member with depression (95% CI, 1.03–6.46; $P = .04$). We also found that AD and

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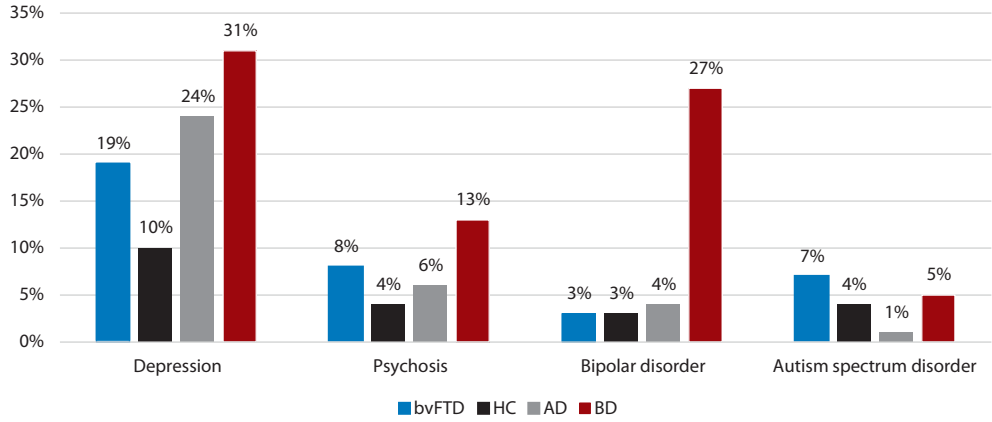
Figure 1. Prevalence of Occurrence of PPD in First-Degree Family Members of Patients With bvFTD, HC, Patients With AD, and Patients With BD



Abbreviations: AD = Alzheimer's disease, BD = bipolar disorder, bvFTD = behavioral variant of frontotemporal dementia, HC = healthy controls, PPD = primary psychiatric disorders.

Table 2. Odds Ratios (OR), 95% Confidence Intervals (95% CIs), Nagelkerke Pseudo R^2, and *P* Values for the Association Between bvFTD and PPD in First-Degree Family Members Versus That for Study Groups and PPD in First-Degree Family Members[a]

	Unadjusted Model				Adjusted Model			
Study Group	OR	95% CI	R^2	*P* Value	OR	95% CI	R^2	*P* Value
Depression								
HC	2.20	0.92–5.27	0.033	.08	2.58	1.03–6.46	0.045	**.04**
AD	0.76	0.37–1.58	0.005	.47	0.79	0.38–1.66	0.005	.53
BD	0.55	0.27–1.10	0.022	.09	0.59	0.29–1.19	0.024	.14
Psychosis								
HC	2.17	0.59–7.99	0.022	.24	3.26	0.84–12.56	0.086	.09
AD	1.51	0.47–4.87	0.007	.49	1.39	0.42–4.59	0.034	.59
BD	0.59	0.22–1.59	0.012	.30	0.60	0.21–1.68	0.121	.33
Bipolar Disorders								
HC	0.93	0.15–5.73	<0.001	.94	1.62	0.26–10.20	0.124	.61
AD	0.74	0.13–4.13	0.003	.73	0.77	0.14–4.44	0.007	.77
BD	0.08	0.02–0.34	0.177	**<.01**	0.08	0.02–0.34	0.177	**<.01**
Autism Spectrum Disorders								
HC	1.78	0.46–6.88	0.012	.40	1.41	0.34–5.90	0.080	.64
AD	7.79	0.89–68.16	0.104	.06	11.11	1.15–107.01	0.302	**.04**
BD	1.54	0.29–8.32	0.006	.61	1.07	0.18–6.38	0.137	.94

[a]Unadjusted models without correction for confounders and adjusted models corrected for age and education level are displayed. Statistically significant effects are shown in bold.
Abbreviations: AD = Alzheimer's disease, BD = bipolar disorder, bvFTD = behavioral variant of frontotemporal dementia, HC = healthy controls, PPD = primary psychiatric disorders.

BD subjects had a higher odds of having a first-degree family member with depression. Furthermore, bvFTD patients showed higher odds of having a family member with psychosis (including schizophrenia; odds ratio [OR] = 3.26; 95% CI, 0.84–12.56; *P* = .09) compared to HC. Families of bvFTD subjects more often had a family history of ASD compared to AD subjects (95% CI, 1.15–107.01; *P* = .04), but not significantly more often compared to HC. As expected, depression, psychosis, and bipolar disorder occured the most in families of BD patients (*P* < .01).

DISCUSSION

In this study, we examined whether depression, psychosis, BD, and ASD are more prevalent in first-degree family members of patients with sporadic bvFTD compared to healthy control subjects and subjects with AD and BD. Compared to healthy control subjects, all patient groups showed a more positive family history for depression. Moreover, there was an insignificant finding of higher prevalence of psychosis in bvFTD.

In the early stage of bvFTD, the clinical presentation can be confused with that of late-onset depression.[6] Our study shows a relationship between dementia and depression. Depression is frequently seen in patients with several types of dementia. A recent study[36] showed that the prevalence of depression during the disease in bvFTD almost doubles that of AD (38% versus 20%; 13% in HC). It is known that a history of premorbid depression significantly increases the risk of developing AD. A good explanation for this

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association is lacking. Next to the possibility that depression is a symptom of an already degenerating brain, theories about shared inflammatory mechanisms and accelerated aging have been postulated.[37] The relationship between sporadic bvFTD and depression has been poorly studied and could have various causes, which might be partly similar to those involved in the relationship between depression and AD, especially since inflammatory processes have also been identified in the pathophysiology of FTD.[38] Yet another possible hypothesis is that sporadic bvFTD and depression might have a (yet unknown) shared polygenic architecture. Moreover, common genetic polymorphisms have been found in both depression and bvFTD.[39] Further studies are needed to investigate a possible genetic relationship between bvFTD and depression.

We did not find a significant relationship between bvFTD and psychosis (including schizophrenia), which is possibly due to the relatively small sample size of sporadic bvFTD cases. We would recommend a replication study in a larger sample group. The potential interrelatedness between frontotemporal dementia and schizophrenia has already been suggested by others, based on observational evidence.[40–42] A shared etiology has also been found in a study by Schoder et al,[43] who compared the risk of schizophrenia in first-degree family members of patients with bvFTD with first-degree family members of patients with AD. They found that schizophrenia occurs more often in family members of patients with FTD compared to those of patients with AD. It is important to note however that bvFTD patients in the respective study have not been screened for *C9orf72* repeat expansions, and therefore a major effect of this mutation cannot be ruled out in the previous study. Despite the low lifetime prevalence of psychosis of approximately 4.6 per 1,000 people worldwide,[44] we found that bvFTD subjects had a 3.26-fold higher odds of having psychosis (including schizophrenia) running in first degree family members compared to HC subjects ($P = .09$). Future studies including larger sample sizes and including genetic research should further investigate overlapping genetic factors between these disorders.

Our results do not show an enriched family history for ASD in bvFTD patients. bvFTD and ASD have strikingly overlapping symptoms in the social cognitive and executive domain.[2,27] Moreover, compulsive behavior can be a feature of both.[2] Autism spectrum disorders have a prevalence of 10–15 per 1,000 in the general population.[45] A larger sample size is probably needed to show significant associations. On the other hand, the genetic architecture of ASD has been shown to be less polygenic than that of schizophrenia or BD.[46] It is noteworthy that a remarkably low percentage of familial autism in AD was found. This finding might be in line with the finding of autism as a protective factor for AD and warrants further study.[47]

We observed that BD occurs more often in families of BD patients compared to families of bvFTD patients. From the literature, we already know that first-degree family members of BD subjects have an excess risk of the disorder.[48] We have not observed a difference between bvFTD patients and the AD and HC groups. As described before, it can be a diagnostic challenge to distinguish BD from bvFTD. In the literature, the clinical syndrome of mania or BD has been described to mimic bvFTD.[49,50] Worldwide prevalence of bipolar spectrum disorders is 24 per 1,000 people.[51] Previous case reports have described a co-occurrence of BD and bvFTD in patients with an underlying *GRN* or *C9orf72* mutation.[50,52] In this study, we did not routinely test the patients with bvFTD on mutations in the *GRN* gene; however, occurrence of mutations in this gene is exceptional in patients with a negative family history for FTD.[53,54] A recent study[50] also described a co-occurrence of sporadic bvFTD and BD. Common inflammatory pathways involved in bvFTD and BD have been found, which might give rise to co-occurrence of these disorders within families.[52] This hypothesis was not confirmed by our results.

To our knowledge, our study is the first to systematically investigate the familial prevalence of 4 major psychiatric disorders in sporadic bvFTD. Our results are in line with those of a recent clinical-pathological study in FTD, in which it was found that the family history of FTD brain donors was enriched for both psychiatric medical history and psychiatric family history, in particular in patients who had underlying TAR-DNA binding protein 43 (TDP-43) pathology.[55] As mentioned before, our QFTD-NL 1.0 questionnaire is based on the QBP-NL, a validated questionnaire. A strength of the study is that this questionnaire enables the collection of family historical information from a relatively large cohort in a time- and cost-effective way. Another main strength is that we tested all bvFTD patients on a *C9orf72* repeat expansion and excluded patients with known genetic mutations, as these would likely have influenced the results. Although *MAPT* and *GRN* mutations cannot be excluded, their presence is very unlikely with a negative family history.[53,54] One more strength was the inclusion of BD patients as the positive control group for the outcome measure BD among first-degree family members of bvFTD patients, showing a high prevalence as expected.

Our study has some methodological limitations. Like all case-control studies, we have to deal with recall bias. We do not expect significant effects between groups on the effect of recall bias. Although we are aware of the fact that some participants have answered the questions themselves, whereas other participants let caregivers answer the questionnaire, we included only caregivers who were well aware of the patient's first-degree family history. This could also have introduced a selection bias. Another limitation is the lack of available psychiatric history of all included patients, because this could have been a relevant confounding factor. Additionally, pathological verification of the clinical diagnosis is lacking in our cohort, which hypothetically could imply misdiagnosis in a minority of cases. A main limitation is the relatively low patient numbers, especially of bvFTD patients, that are inherent to the relatively low prevalence of sporadic bvFTD. Apart from prospective systematic collection of psychiatric family

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history in bvFTD, a future approach could be the creation of collaborative epidemiologic databases. The last limitation is that we investigated information only of first-degree family members. Potentially, including healthy spouses of patients as controls could have introduced a bias toward a stronger psychiatric background in the spouses of psychiatric patients, which could have weakened the contrast between the disease groups and controls. As this bias concerns only a small effect in small subgroups, we consider it highly unlikely that this potential bias has affected our results. Potentially, information on second- or third-degree relatives could have contributed to a more complete genetic picture of families. However, that information is prone to recall bias. Our results implicate a relationship between dementia including sporadic bvFTD and depression and possibly also a specific relationship between bvFTD and psychosis (including schizophrenia), which could be explained by genetic factors, environmental factors, or both. Further study into the genetic overlap between bvFTD and PPD might provide clues to targeting common disease mechanisms.

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Supplementary Material

Article Title: Relationship Between Sporadic Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders: A Study in Families

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List of Supplementary Material for the article

1. Appendix 1 — Questionnaire QFTD-NL 1.0
2. Table 1 — Prevalence of occurrence of PPD in first-degree family members of bvFTD, HC, AD and BD
3. Table 2 — Odds ratios (OR), 95% confidence interval (95%CI), Nagelkerke pseudo R square and p-values for the association between study groups compared to healthy control subjects and PPD in first-degree family members

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Appendix 1. Questionnaire QFTD-NL 1.0

Instruction manual QFTD-NL 1.0

Questionnaire QFTD-NL 1.0 – Drawn up December 2012, supplemented January 2015, translated in English October 2019

- Interviewer should at least have a Bachelor's degree in Medicine or a related field
- Interviewer received a short practical instruction of carrying out questionnaire QFTD-NL 1.0 by a psychiatrist
- Interviewer has read the general instruction manual of the *M.I.N.I. Plus International Neuropsychiatric Interview Dutch version 5.0.0. (2000)* including questionnaires for the following disorders: depression, bipolar disorder, psychotic disorders, ADHD, alcohol, drug and substance use
- Questionnaire QFTD-NL 1.0 can be carried out real-life or by phone. In case of a cognitive stable participant questions can be asked to the participant directly. In case of a cognitive unhealthy participant questions should be asked to a relative who knows the medical and family history of the participant. Answers to the questions should be write down by the interviewer on a form.
- Part C should not be filled out in the case a participant scores negative on part B; or in the case of a cognitive healthy subject also positive on part A.
- In the case part C is filled out, a family tree should always be drawn or be described for all questioned disorders

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Screening questionnaire healthy control subject PART A

Code number _____
Name participant: _____ 0 Male 0 Female
Date of birth __ __ /__ __ /__ __ __ __ Date of interview __ __ / __ __ / __ __ __ _
Name researcher: _____

1. **Have you ever been treated by a psychologist or psychiatrist, and if so, why?**

_____

_____

_____

2. **Have you ever visited your general practitioner with complaints of mental illness, and if so, why?**

_____

_____

_____

3. Are you or were you addicted to a substance use or action. And if so, did you or your environment experience a negative influence of this use/action? Please explain.

_____

_____

_____

4. **Have you ever been treated by a neurologist, and if so, why?**

_____

_____

_____

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5. **Does your environment notice that your behavior changed recently? If so, please explain**

_____

_____

_____

6. **Mapping subjective complaints**
   - Do you experience memory complaints? yes/no
   - If so, which complaints do you experience?

   _____

   _____

   - Is your memory deteriorated compared to the past? yes/no
   - If so, how do you notice it?

   _____

   _____

   - Is your memory worse than your peers? yes/no
   - Do you worry about your memory? yes/no

7. **Do you know all your (biological) first-degree family members? If not, please specify.**

_____

_____

8. **Is a close family member possibly diagnosed with frontotemporal dementia? If so, how are you related to him/her?**

_____

_____

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QUESTIONNAIRE bvFTD (QFTD-NL 1.0) PART B

(to be filled out by researcher)

Code number _____

Name participant: _____ 0 Male 0 Female

Date of birth __ __ /__ __ /__ __ __ __ Date of interview __ __ / __ __ / __ __ __ _

Name researcher: _____

---

1. Participant agreed to use encoded data, obtained by this questionnaire, for scientific research

0 Yes 0 No

2. To which patient group does the participant belong?

0 1. Behavioral variant Frontotemporal Dementia

0 2. Alzheimer's disease

0 3. Healthy control subjects

0 4. Bipolar disorder

3. Participant meets inclusion criteria for respective patient group as can be read in the article of Icho et al. (2019)

0 Yes 0 No

4. Participant does not meet one or more of the exclusion criteria for respective patient group as can be read in the article of Icho et al. (2019)

0 Yes 0 No

5. Questionnaire was answered by (a well-known of) the participant, depending on the patient group

0 Yes 0 No

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QUESTIONNAIRE bvFTD (QFTD-NL 1.0) PART C

(to be filled out by researcher)

Code number _____

Name participant: _____ 0 Male 0 Female

Date of birth __ __ /__ __ /__ __ __ __ Date of interview __ __ / __ __ / __ __ __ _

Name researcher: _____

---

5. What is your cultural origin?

0 1. The Netherlands
0 2. Surinam or the Nederland's Antilles
0 3. Turkey
0 4. Morocco
0 5. Asia
0 6. Other: _____

6. What is your current marital status?

0 1. Married or cohabitants
0 2. Living apart together
0 3. Single
0 4. Divorced
0 5. Widow(er)

7. What is your highest <u>completed</u> education?

0 1. Less than primary school
0 2. Primary school completed
0 3. Primary school and further education less than 2 years
0 4. Less than general secondary education (MAVO), for example LTS, LEAO, LHNO
0 5. General secondary education, for example MULO/MAVO/MEAO
0 6. Higher secondary education, for example HAVO/VWO/HEAO/HBS/HBO
0 7. University degree

8. Do you smoke?

0 Yes 0 No 0 Ceased

0 Cigarettes 0 Cigars 0 Pipe

If yes/ceased: amount_____ /day, during _____ years = _____packyears

9. Do you drink alcohol?

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0 Yes 0 No 0 Ceased
If yes/ceased: amount _____ units/week, during _____ years

10. Have you ever used sleeping pills or anxiolytics?
(for example. benzodiazepines of barbiturates)
0 Yes 0 No

11. Have you ever used cannabis (marihuana or hasj)?
0 Yes 0 No

12. Have you ever used other recreational drugs?
Note: Multiple answer possibilities
0 Yes 0 No

0 1. Stimulants (for example Amphetamines, Ritalin®)
0 2. Opiates (for example Heroine, codeine, methadon)
0 3. Cocaine
0 4. Hallucinogens (for example LSD, mescaline, mushrooms)
0 5. Other (i.e.) _____

13. Have you ever been exposed to chemical substances (i.e. during work/recreational)
Including: asbestos, ammoniac, petroleum, acetone, paint, chlorin, radioactive substances
0 Yes 0 No
If yes: name_____ amount_____years
name _____amount_____years
name _____amount_____years

14. Do you experience thyroid problems?
0 Yes 0 No
If yes: hypothyroidism / hyperthyroidism *(score out what does not apply)*
Medication use: 0 Yes 0 No
If yes, name and dose _____

15. Are you familiar with cardiovascular disease?
Note: Multiple answers possible

1. Hypertension	0 Yes 0 No	
2. Diabetes mellitus	0 Yes 0 No	If yes: Type:
3. Hypercholesterolemia	0 Yes 0 No	
4. Myocardial infarction	0 Yes 0 No	

16. Have you ever had a head trauma in the past?
0 Yes 0 No

If yes:	Amnesia	0 Yes 0 No	0 Don't know
	Loss of consciousness	0 Yes 0 No	0 Don't know

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17. Have you ever performed a sport associated with head trauma?
Note: More possible answers
0 Yes 0 No

0 1. Boxing
0 2. Football
0 3. Else (namely) _____
Couple of years _____ , frequency _____ /week

NOTE: *The following questions should be answered for <u>each</u> family member, also in the case of no/don't know or not applicable*

In the case of possible/ certainly, please explain in the family tree, please also report age of origin and duration of disease (part D)

---

18. How many siblings do you have (including deceased ones)?
Brothers: _____
Sisters: _____

19. How many children do you have (including deceased ones)?
Children: _____

20. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>FRONTOTEMPORAL DEMENTIA</u>?

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	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

21. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of a <u>DEPRESSION</u>? *(no bipolar disorder, so no past history of a (hypo)mania; M.I.N.I. Plus p. 9-15)*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

22. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of a <u>BIPOLAR DISORDER?</u> *(so with a past history of a (hypo)mania combined with a depression; M.I.N.I. Plus p. 17-20)*

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	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

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23. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>PSYCHOSES?</u> *(so with a past history of episodes with delusions or hallucinations; M.I.N.I. Plus p. 41-47)*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

24. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>SUICIDE</u> and/or a <u>SEVERE SUIDIDE ATTEMPT?</u> *(medical help is needed in the last case)*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

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25. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of a <u>AUTISM SPECTRUM DISORDER?</u> *(autism, Asperger syndrome, PDD-NOS)*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

26. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>ADHD?</u> *(M.I.N.I. Plus p. 63-66)*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

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27. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>ALCOHOLISM?</u> *(M.I.N.I. Plus p. 33-36)*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

28. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>DRUG OR SUBSTANCE ABUSE?</u> *(M.I.N.I. Plus p. 37-39)*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

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29. Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>MOVEMENT DISORDERS?</u> *(Parkinson's disease, ALS, Corticobasaal degeneration (CBD), progressive supranuclear palsy (PSP))*

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

30. (Only for patients with bvFTD) Do you have a close family member (grandparents, parents, siblings or children) with a medical history of <u>Alzheimer's disease?</u>

	NO	POSSIBLE	DIAGNOSED	UNKNOWN	INAPPLICABLE
a. Mother	☐	☐	☐	☐	
b. Grandmother maternal side	☐	☐	☐	☐	
c. Grandfather maternal side	☐	☐	☐	☐	
d. Father	☐	☐	☐	☐	
e. Grandmother paternal side	☐	☐	☐	☐	
f. Grandfather paternal side	☐	☐	☐	☐	
g. Siblings	☐	☐	☐	☐	☐
h. Children	☐	☐	☐	☐	☐

Thank you for taking part

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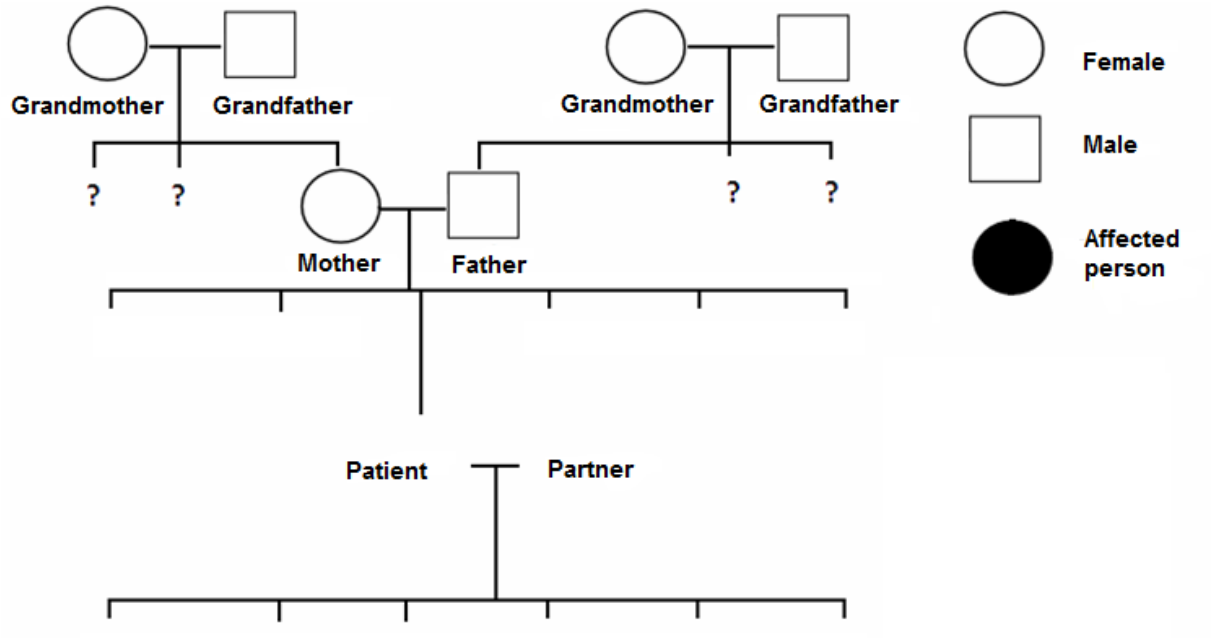
PART D: Family tree *



(Please register siblings and/or children if present)

NOTES:

FRONTOTEMPORAL DEMENTIA_____

_____

_____

DEPRESSION_____

_____

_____

BIPOLAR DISORDER_____

_____

_____

PSYCHOSES_____

_____

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SUICIDE OR SEVERE SUICIDE ATTEMPT_____

_____

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AUTISM SPECTRUM DISORDER_____

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_____

ADHD_____

_____

_____

ALCOHOLISM_____

_____

_____

DRUG OR SUBSTANCE ABUSE_____

_____

_____

MOVEMENT DISORDERS_____

_____

_____

OTHER REMARKS_____

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Supplementary table 1 Prevalence of occurrence of PPD in first-degree family members of bvFTD, HC, AD and BD.

	bvFTD	HC	AD	BD
Depression	14/72	10/101	26/108	38/124
Psychosis	6/73	4/101	6/107	16/122
Bipolar disorder	2/72	3/101	4/107	33/124
Autism spectrum disorder	5/73	4/101	1/107	2/44

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Supplementary table 2 Odds ratios (OR), 95% confidence interval (95%CI), Nagelkerke pseudo R square and p-values for the association between study groups compared to healthy control subjects and PPD in first-degree family members. Unadjusted models without correction for confounders and adjusted models corrected for age and education level are displayed. Significant effects are bold displayed.

	Unadjusted model				*Adjusted model*			
	Odds Ratio	**95%CI**	**R^2**	**p-value**	**Odds Ratio**	**95%CI**	**R^2**	**p-value**
Depression								
bvFTD	2.20	[0.92-5.27]	0.033	0.08	2.58	[1.03-6.46]	0.045	**0.04**
AD	2.89	[1.31-6.35]	0.059	**<0.01**	2.95	[1.26-6.88]	0.060	**0.01**
BD	4.02	[1.89-8.57]	0.101	**<0.01**	4.07	[1.83-9.02]	0.113	**<0.01**
Psychosis								
bvFTD	2.17	[0.59-7.99]	0.022	0.24	3.26	[0.84-12.56]	0.086	0.09
AD	1.44	[0.39-5.26]	0.005	0.58	1.54	[0.37-6.38]	0.010	0.55
BD	3.66	[1.18-11.33]	0.060	**0.02**	5.33	[1.58-17.34]	0.120	**<0.01**
Bipolar disorders								
bvFTD	0.93	[0.15-5.73]	<0.001	0.94	1.62	[0.26-10.20]	0.124	0.60
AD	1.27	[0.28-5.81]	0.002	0.76	1.10	[0.20-5.89]	0.013	0.92
BD	11.85	[3.51-39.96]	0.194	**<0.01**	13.58	[3.85-47.84]	0.200	**<0.01**
Autism Spectrum Disorders								
bvFTD	1.78	[0.46-6.88]	0.012	0.40	1.41	[0.34-5.90]	0.080	0.64
AD	0.23	[0.03-2.08]	0.051	0.19	0.21	[0.18-2.28]	0.084	0.20
BD	1.16	[0.20-6.55]	0.001	0.87	1.46	[0.24-9.10]	0.024	0.68

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