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Psychiatric symptoms in preclinical behavioural-variant frontotemporal dementia in *MAPT* mutation carriers

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Abstract

Objective—To characterise psychiatric symptoms in preclinical and early behavioural-variant frontotemporal dementia (bvFTD), a neurodegenerative disorder whose symptoms overlap with and are often mistaken for psychiatric illness.

Methods—The present study reports findings from a systematic, global, prospective evaluation of psychiatric symptoms in 12 preclinical carriers of pathogenic *MAPT* mutations, not yet meeting bvFTD diagnostic criteria, and 46 familial non-carrier controls. Current psychiatric symptoms, informant-reported symptoms and lifetime prevalence of psychiatric disorders were assessed with The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the Neuropsychiatric Inventory Questionnaire. Fisher exact test was used to compare carriers and non-carriers' lifetime prevalence of six DSM-IV disorders: major depressive disorder, panic attacks, alcohol abuse, generalised anxiety disorder, panic disorder, and

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depressive disorder not otherwise specified. Other DSM-IV disorders had insufficient prevalence across our sample for between-group comparisons, but are reported.

Results—Non-carriers had greater prevalence of mood and anxiety disorders than has been reported for a general reference population. Preclinical carriers had lower lifetime prevalence of mood and anxiety disorders than non-carriers, except for depressive disorder not otherwise specified, an atypical syndrome comprising clinically significant depressive symptoms which fail to meet criteria for major depressive disorder.

Conclusion—Findings suggest that early psychiatric symptoms of emergent bvFTD may manifest as emotional blunting or mood changes not cleanly conforming to criteria for a DSM-defined mood disorder.

INTRODUCTION

Behavioural-variant frontotemporal dementia (bvFTD) is a neurodegenerative illness characterised by changes in behaviour, personality, cognition (including social cognition) and emotion. Some symptoms associated with bvFTD overlap and are shared with symptoms of psychiatric disorders. For example, a symptom of both bvFTD and major depressive disorder is decreased interest in the pursuit of previously pleasurable activities. Psychiatric symptoms also emerge in genetic FTD: the phenotypes of schizophrenia and psychosis can be associated with mutations that cause FTD,^{1–4} and visual hallucinations have been reported in *GRN* mutation carriers.⁵ Not surprisingly, brain regions and circuits associated with many psychiatric disorders are affected in bvFTD.⁶⁷ BvFTD is commonly misdiagnosed as a psychiatric disorder.^{8–10} There are anecdotal reports of disparate psychiatric syndromes occurring in early symptomatic illness or even as a prodrome in patients with sporadic and familial FTD,¹¹ but there has not previously been a systematic, prospective evaluation of psychiatric syndromes in FTD. Here, we report the results of a structured clinical psychiatric evaluation performed prospectively in presymptomatic and early symptomatic subjects with *MAPT* mutations associated with bvFTD and matched familial control subjects.

Few studies have reported on the early psychiatric symptoms of bvFTD. Block *et al*¹² presented five cases of *C9orf72* mutation carriers who, prior to FTD onset, met diagnostic criteria for several Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) psychiatric disorders, including obsessive-compulsive disorder, schizophrenia and bipolar disorder, but no longer fit these symptomatic profiles by the time neurodegenerative disease was formally diagnosed. In another study, Gregory¹ noted symptoms of depression and anxiety in prodromal bvFTD patients, but reported that they were ‘short-lived’ and ‘shallow’, not reaching sufficient threshold to culminate in diagnoses. Psychiatric syndromes in *MAPT* mutation carriers have been minimally characterised. Of the mutations associated with FTD, *MAPT* mutations are associated with the most ‘classic’ bvFTD symptom presentation.¹⁴ Evidence to date indicates that early neurodegeneration in *MAPT* mutation carriers occurs in the medial temporal lobes, especially the amygdala, and then spreads to symmetrically target the anterior temporal lobes and ventromedial prefrontal cortex (vmPFC).¹⁴¹⁵

The current study examined the prevalence and course of psychiatric symptoms in *MAPT*-associated preclinical bvFTD by administering a standardised structured psychiatric interview to assess psychiatric symptoms in presymptomatic and early symptomatic carriers of *MAPT* mutations and their non-carrier relatives. We use the term ‘preclinical’ bvFTD to describe *MAPT* mutation carriers who do not meet criteria for possible bvFTD.¹⁶ Carriers may be entirely asymptomatic or may show symptoms that are questionably related to their mutation status (eg, psychiatric changes). Because some but not all carriers may be characterised as prodromal, we thus favour the term ‘preclinical’ to accurately describe our entire carrier group, which consists of both asymptomatic and prodromal carriers.

Non-carrier family members were used as familial controls, as their shared genetic and environmental backgrounds minimised potential variability. We performed a global assessment of preclinical *MAPT* mutation carriers to obtain valuable insights into psychiatric syndromes in incipient bvFTD, which are contextualised through comparison to environmentally and genetically homogeneous familial controls.

MATERIALS AND METHODS

Subjects

Fifty-eight subjects (n=58) were recruited from multiple generations of at-risk branches within six families with *MAPT* mutations, who comprise the *MAPT* cohort at Columbia University. Forty of these subjects descend from a large extended family with an exon 10+14 C>T *MAPT* mutation in which FTD was originally linked to chromosome 17.¹⁷¹⁸ Other enrolled families carried other *MAPT* mutations (see below). Subjects were enrolled in a multisite observational research study with centres in the USA and Ireland, within which they underwent clinical and cognitive assessment and contributed blood samples from which DNA was isolated. Genomic DNA was extracted from peripheral blood using standard procedures. The *MAPT* gene was sequenced as previously described, and familial *MAPT* mutations were identified.¹⁹ Twelve (eight women and four men) of the 58 subjects were determined to be carriers of the following mutations: P301L (one subject), exon 10+16 mutation (IVS10 +16 C>T) (one subject), exon 10+15 (IVS10 +15 A>C) (two subjects), V337M (four subjects) and exon 10+14 (IVS10 +14 C>T) (four subjects) all of which have been established as pathogenic.²⁰ All preclinical subjects were assigned a clinical dementia rating (CDR) of 0 (asymptomatic) or 0.5 (questionably symptomatic) by an evaluating physician.²¹ The expanded CDR with behaviour and language items was used to better capture symptoms that could arise as a result of FTD.²² Six of the 12 carriers were assigned a Global CDR score of 0, and 6 were given a Global CDR score of 0.5, indicating questionable cognitive impairment. Two of the 46 control subjects received a CDR score of 0.5 (table 1), likely reflecting the difficulty distinguishing questionable behavioural and psychiatric changes between controls and preclinical bvFTD. No subjects received a CDR score >0.5. All subjects provided written informed consent prior to participation. All sites of the study were approved by their respective institutional ethical boards to conduct study procedures.

Experimental design

The Structured Clinical Interview for the DSM-IV Non-Patient Edition (SCID-I/NP),²³ a clinician-administered, semi-structured interview used to screen for and diagnose DSM-IV disorders, was used to globally assess psychiatric symptoms and identify lifetime prevalence of threshold and subthreshold disorders. Structured psychiatric interviews such as the SCID are considered the gold-standard measurement of psychiatric diagnoses in research studies. All subjects underwent psychiatric evaluation by personnel blinded to carrier status whenever possible and certified in administering the SCID-I/NP (EDH at the Columbia University Medical Center, SS at University of Michigan and BDK at the Dublin Neurological Institute).²³ SCID-I/NP data were reviewed in a blinded manner and each disorder was coded by the following variables: lifetime prevalence (whether subthreshold or full threshold diagnostic criteria were ever met), current diagnosis (whether the disorder was active at the time of evaluation) and remission (whether the disorder was in partial or full remission, if applicable, at the time of evaluation). The SCID-I/NP allows diagnoses of all major Axis I, but not Axis II, disorders, including not otherwise specified (NOS) diagnoses.²³ The Neuropsychiatric Inventory Questionnaire (NPI-Q), a widely used informant-based measure of current psychiatric symptoms in dementia populations, was also administered to informants of participating subjects, usually a spouse or close relative. The NPI-Q is designed to capture specific symptoms (eg, hallucinations or apathy) and is not used to make DSM diagnoses. It is briefer and less broad in scope than the SCID-I/NP, and we therefore hypothesised it would be less sensitive to early psychiatric symptoms of FTD.

Statistical analysis

All statistical analyses were conducted using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). The prevalence of DSM-IV psychiatric disorders evaluated by the SCID-I/NP were summarised with frequency and percent by mutation carrier status (see table 2). We compared group differences in the six psychiatric disorders (major depressive disorder, panic attack, substance abuse of alcohol, generalised anxiety disorder, panic disorder and depressive disorder NOS) for which there were at least five participants who had met criteria for the diagnosis in their lifetime (a number chosen to give us adequate power for analyses). Disorders with fewer than five diagnosed participants were excluded. The lifetime prevalence of psychiatric disorders in carriers and non-carriers was compared using Fisher exact test. The lifetime prevalence of the six psychiatric disorders in the carriers and non-carriers was also compared with the prevalence reported in published reference populations.^{24,25} Explicit lifetime prevalence of depressive disorder NOS was not available for the reference populations, thus minor depression was used as a next best point-of-comparison to lifetime prevalence of depressive disorder NOS in our cohort. Among the non-carriers, the prevalence of the six disorders was compared between first-degree relatives of known *MAPT* mutation carriers and relatives who were more distantly related, to determine whether familial proximity to an affected family member was associated with the incidence of psychiatric illnesses in our sample. All statistical tests were conducted at 5% significance level, and were corrected for multiplicity of the six psychiatric disorders by the false discovery rate.²⁶

RESULTS

The demographic characteristics of the sample are summarised by group in table 1. Among the 18 psychiatric disorders for which there was lifetime prevalence in the sample, 12, including obsessive-compulsive disorder and bipolar disorder, had fewer than five subjects with lifetime history and were insufficiently powered for analysis (table 2). These disorders were excluded from further analysis.

Analysis of lifetime prevalence of psychiatric disorders in the carrier and non-carrier groups revealed significant between-group differences. We analysed lifetime prevalence to maximise our detection of psychiatric illness. Among the six psychiatric disorders compared, major depressive disorder was significantly more prevalent in the non-carrier group. Depressive disorder NOS was more prevalent in the carrier group. Individuals with depressive disorder NOS reported significant depressive symptoms, including depressed mood or anhedonia, that did not meet full criteria for major depressive disorder. These diagnoses did not fit a specific pattern, but included subjects who reported symptoms meeting criteria for major depressive disorder, except for whom symptoms lasted only a few days, subjects with significant isolated anhedonia, and subjects with significant depressed mood or increased mood reactivity and lability, but without meeting full DSM-IV major depressive disorder criteria. Compared with the general population, the non-carrier control group had significantly greater lifetime prevalence of major depressive disorder and panic disorder (table 3). Though the carrier group only consisted of 12 subjects, we exploratorily compared them to general population and found that carriers had significantly greater lifetime prevalence of depressive disorder NOS, though this finding did not survive correction for multiple comparisons (table 3).

To discern whether any of the differences in lifetime prevalence of psychiatric disorders within our sample were related to familial proximity to an affected relative, we compared lifetime prevalence of psychiatric disorders between first-degree relatives of known carriers and those more distantly related. Panic disorder was less prevalent in subjects who are first-degree relatives of known carriers as compared with more distantly related relatives, although this finding did not survive correction for multiple comparisons (table 4).

Using the NPI-Q at the time of the evaluation, informants for mutation carriers reported a greater prevalence of agitation, apathy, disinhibition, elation, and irritability compared with non-carriers (table 1).²⁷

DISCUSSION

This study had four major findings. First, the mutation-negative members of *MAPT* mutation families had a high prevalence of mood and anxiety disorders compared with the general population. Second, the preclinical mutation-positive *MAPT* family members had a significantly lower incidence of major depressive disorder, and non-significant trends of lower incidence of most anxiety disorders than matched family control subjects. Third, the exception to this finding was that the *MAPT* mutation carriers had a higher prevalence of depressive disorder NOS than both their family controls and the general population. Finally,

many psychiatric disorders, including schizophrenia and related psychotic disorders, were either rare or not present in our sample. This is in contrast to previous studies showing a high prevalence of psychosis in *C9orf72* mutation carriers.³ We discuss these findings below.

Among the sample's non-carriers, we observed higher lifetime prevalence of major depressive disorder, generalised anxiety disorder, and panic disorder than the respective lifetime prevalence percentages reported within the general population (table 3).²⁴ We speculate that the increased prevalence of mood and anxiety disorders we observed in our mutation-negative *MAPT* family members compared with the general population could be related to the stress of belonging to a family with familial FTD, the uncertainty of personal carrier status, or the burden of caring for affected family members. Significant stress is a risk factor for mood and anxiety disorders.²⁸ This finding emphasises the importance of selecting appropriate control groups for studies of psychiatric symptoms in neurodegenerative disorders. Comparison of carriers with non-carrier relatives contextualises early changes observed in carriers and minimises variability due to environment or genetic factors.

Mutation carriers showed a significantly lower prevalence of major depressive disorder and a non-significant trend of lower prevalence of panic attacks, panic disorder and generalised anxiety disorder than *MAPT* family control subjects (see table 2). Decreased emotional responsiveness to stimuli that would pre-morbidly have generated an emotional response is a recognised symptom of clinical bvFTD (ie, emotional blunting),²⁹ and it is a component of bvFTD symptoms including personality change,³⁰ apathy¹⁶ and anosodiaphoria.³¹ While it may be counterintuitive to think that neurodegeneration could provide 'protection' from psychiatric illness, many psychiatric disorders represent a pathological exaggeration of a normal emotional response. In this way, the relative lack of DSM-defined depressive and anxiety disorders in our mutation carriers could represent early blunting of emotional responsiveness, which we observe in fully symptomatic FTD. In our laboratory, and in related research, we have observed this phenomenon in patients with neurodegenerative illness and brain injury. Cognitively asymptomatic carriers of autosomal-dominant mutations related to Alzheimer's disease reported fewer depressive symptoms than their non-carrier relatives and had lower odds of experiencing behavioural symptoms.³² Veterans of the Vietnam War with vmPFC injury show decreased depressive symptoms,³ and those with injury to the amygdala or vmPFC show a lower prevalence of post-traumatic stress disorder than matched control subjects.³⁴ In patients with FTD, corticobasal syndrome and Alzheimer's disease, atrophy of the vmPFC is selectively associated with apathy.^{35,36} The lower lifetime prevalence of major depressive disorder (and possibly some anxiety disorders) observed in the mutation carriers in the current study could reflect a decreased ability for the mutation carriers to mount a normal or exaggerated emotional response. In support of this assertion, stimuli that trigger emotion in healthy subjects do not evoke normal corresponding physiological responses, such as skin conductance, in patients with bvFTD.³⁷

It is of note that the lower prevalence of psychiatric illness in the carrier group seems to extend across several mood and anxiety disorders. The generalised nature of this effect may be supportive of the 'factor structure,' characterised in recent research as an alternative method of classifying psychiatric illness.^{38–40} Research in large numbers of psychiatric

patients has elucidated several broad ‘factors’ that appear to underlie the large number of specific DSM Axis I and II psychiatric disorders.^{38–40} A few factors have been consistently identified, the most common of which have been labelled ‘internalising’ and ‘externalising’. Internalising psychiatric disorders are characterised by a dysphoric focus on one’s own responsibility for problems, especially interpersonal problems. Mood and anxiety disorders, including major depressive disorder, generalised anxiety disorder, social phobia, panic disorder and post-traumatic stress disorder, are internalising psychiatric disorders. Externalising disorders, by contrast, involve a conscious violation of social rules and norms, exploitation of others, and include antisocial personality disorder, conduct disorder and substance abuse. In our study, all disorders for which the carrier group had lower prevalence than the non-carrier group were internalising disorders. The lower prevalence of internalising psychiatric disorders may indicate disruption of underlying brain regions and neural networks associated with this factor. Future studies can explore the usefulness of the factor model versus DSM-defined disorders in characterising neurodegeneration-associated psychiatric symptoms, such as those observed in our cohort.

The current study also found that depressive disorder NOS had a higher prevalence in the mutation carriers than the family controls, and a higher prevalence than minor depression in the general population. We did not find a single pattern of depressive symptoms in these subjects. Rather, we observed different syndromes, the unifying factor being depressive symptoms that did not meet criteria for major depressive disorder. In some cases, this was because the number of symptoms was insufficient, that is, persistent depressed mood without other symptoms of major depressive disorder. In other cases, the symptoms met criteria for major depressive disorder, but the duration was insufficient. Of note, for both carriers and non-carriers, all cases of depressive disorder NOS represented current symptoms. Our finding suggests that while many patients with preclinical bvFTD simply have early versions of symptoms that are commonly observed in bvFTD, such as apathy and emotional blunting, a sub-set of preclinical bvFTD patients have emotional symptoms that significantly differ from typical symptoms of bvFTD, for example, depressed mood. Early dysfunction of networks involved in emotion in FTD may manifest as mood changes that do not meet criteria for a DSM-defined disorder. This finding has precedent in other neurodegenerative disorders, such as Huntington’s Disease, in which early frontal involvement can manifest as internalising psychiatric symptoms that do not fit criteria for a specific DSM-defined mood disorder,⁴¹ and which can progress to more usual symptoms of frontal dysfunction including apathy and emotional blunting as the illness progresses. We have observed a similar pattern with some other symptoms of bvFTD. In unpublished data we collected on sexual symptoms of bvFTD, while most partners of patients report that patients show decreased sexual drive and activity, some partners report that during the preclinical stage, patients show increased drive and activity. The unusual nature of depressive symptoms in mutation carriers with incipient FTD could also be partially attributable to decreased insight or emotional perception, or to impaired symptom recall (although as a group, carriers performed within normal limits on neuropsychological testing of recall). Further research can better define the psychiatric syndromes observed in preclinical bvFTD, and determine if they vary systematically by FTD mutation type and brain regions involved.

Based on anecdotal reports of psychiatric symptoms in preclinical bvFTD, and because the SCID is a more detailed measure of psychiatric symptoms than the NPI-Q, we hypothesised that the SCID would be more sensitive to early symptoms of FTD than the NPI-Q. In support of this hypothesis, in our study the NPI-Q did not distinguish any significant between-group differences in depression or anxiety. However, we found significant differences between the carriers and control subjects in several NPI-Q domains characteristic of bvFTD, including apathy and disinhibition, indicative that some of the carriers may be experiencing early symptoms. It is worth pointing out that in the NPI-Q, unlike in the SCID, domains are not derived from the DSM, and while there is some category overlap (eg, depression and anxiety), these may not be entirely comparable. For instance, in the SCID, major depressive disorder includes apathy and depressed mood, while these symptoms are separated in the NPI-Q. A question to address in future studies is: which type of measure (cognitive, psychiatric, behavioural and so on) best detects earliest symptoms associated with bvFTD?

To our knowledge, this is the first prospective evaluation of all major Axis I psychiatric syndromes in subjects with preclinical FTD. Research on psychiatric syndromes in FTD has several challenges, some of which we addressed, and some of which we were unable to address. While evaluating personnel were blinded to the carrier status of subjects as much as possible, some subjects had previously undergone clinical genetic testing and knew their mutation status, which could affect their psychiatric status in ways hard to predict. As previously noted, the selection of control groups is crucial. Psychiatric symptoms are common in the general population and may be even more common in members of families with familial FTD. For these reasons, we used family controls. It is important to note our small sample size. This was in part because we focused on a specific gene, *MAPT*. There is evidence that mutations in other genes, such as *C9orf72*, have distinct psychiatric presentations, including schizophrenia-like psychosis.³¹² Therefore, the generalisability of our findings may be limited. Another complicating factor is that the background prevalence of specific psychiatric syndromes and symptoms varies. For example, mood symptoms are relatively common, while somatic hallucinations are rare. The current study may have been powered to detect changes in mood disorders in our group, but not to detect differences in rarer psychiatric syndromes and symptoms. Future research can address these issues by assembling larger groups of patients and attempting to group psychiatric symptoms by common factors. Finally, we did not assess axis II disorders, which could also have been a feature of preclinical FTD.

In conclusion, we found that compared with family control subjects, preclinical *MAPT* mutation carriers had a lower incidence of DSM-defined major depressive disorder and anxiety disorders, but a higher incidence of depressive symptoms that did not fit DSM criteria for major depressive disorder. It is unclear how these symptoms will change over time, though longitudinal characterisation of the Columbia *MAPT* cohort is underway. Psychiatric disorders were relatively common in *MAPT* mutation non-carriers compared with the general population. Psychiatric symptoms possibly related to early bvFTD were detected by both the SCID and the NPI-Q, but only the SCID detected significant differences in mood and anxiety symptoms. These findings suggest that while bvFTD can have an early psychiatric presentation, DSM diagnostic categories are likely not the best grouping of these

symptoms. Psychiatric factors may be more closely associated with specific brain regions and circuits than specific psychiatric disorders. Future research will hopefully move toward defining psychiatric syndromes in early FTD and other neurodegenerative disorders on the basis of brain regions and circuits involved.

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Table 1

Sample demographics and group comparison of NPI-Q data

Sample demographics	Non-carriers (n=46)		Carriers (n=12)		P value [*]
	CDR=0 (n=44)	CDR=0.5 (n=2)	CDR=0 (n=6)	CDR=0.5 (n=6)	
	Mean (SD)		Mean (SD)		
Education (years)	15.05 (2.41)	17 (1.41)	15.33 (2.07)	15.17 (2.4)	0.882
MMSE score	29.7 (0.63)	30 (0)	29.33 (1.21)	27.67 (2.25)	0.005 ^{**}
Age (years)	43.68 (13.47)	55 (8.49)	38.83 (11.82)	58.67 (5.32)	0.304
Sex					
Female	19 (43.18)	1 (50)	2 (33.33)	2 (33.33)	0.743
Male	25 (56.82)	1 (50)	4 (66.67)	4 (66.67)	

NPI-Q domains	Non-carriers (n=43) ^{††}		Carriers (n=12)		P value [‡]
	CDR=0 (n=41)	CDR=0.5 (n=2)	CDR=0 (n=6)	CDR=0.5 (n=6)	
	Prevalence % (n)		Prevalence % (n)		
Agitation/aggression	4.88% (n=2)	0%	0%	83.33% (n=5)	0.002 ^{**}
Anxiety ^{††}	12.2% (n=5)	0%	20% (n=1)	60% (n=3)	0.053
Apathy/indifference	2.44% (n=1)	0%	0%	66.67% (n=4)	0.004 ^{**}
Appetite/eating	12.2% (n=5)	0%	0%	50% (n=3)	0.337
Delusions	2.44% (n=1)	0%	0%	0%	1
Depression/dysphoria	12.2% (n=5)	0%	20% (n=1)	33.33% (n=2)	0.337
Disinhibition	4.88% (n=2)	0%	0%	83.33% (n=5)	0.002 ^{**}
Elation/euphoria	0%	0%	0%	50% (n=3)	0.006 ^{**}
Hallucinations	0%	0%	0%	16.67% (n=1)	0.203
Irritability/lability	7.32% (n=3)	0%	0%	66.67% (n=4)	0.025 ^{**}
Motor disturbances	2.44% (n=1)	0%	0%	33.33% (n=2)	0.102
Nighttime behaviours	7.32% (n=3)	0%	0%	33.33% (n=2)	0.266

NPI-Q severity total [§]	Mean (SD)	Mean (SD)	Mean (SD)	P value [‡]
	1.37 (4.07)	0 (0)	0.4 (0.89)	12.8 (7.19)
				0.004 ^{**}

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** P<0.01.

* P value from Wilcoxon's test.

[†] P value from Fisher's exact test.

^{‡‡} NPI-Q data unavailable for three non-carriers.

[§] NPI-Q data incomplete for 1 CDR=0.5 carrier.

CDR, clinical dementia rating; MMSE, Mini Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire.

Table 2

Group differences in lifetime prevalence of psychiatric disorders

Diagnosis of lifetime prevalence								
SCID DSM-IV disorder	Non-carriers (n=46)		Carriers (n=12)		Total sample			
	n	%	n	%	n	OR	P value	FDR
Major depressive disorder	19	41.30	0	0.00	19	N/A	0.0054**	0.0325*
Panic attack	10	21.74	1	8.33	11	0.33	0.4285	0.6428
Alcohol abuse	7	15.22	3	25.00	10	1.86	0.4166	0.6428
Depressive disorder NOS	4	8.70	4	33.33	8	5.25	0.0489*	0.1468
Generalised anxiety disorder	7	15.22	1	8.33	8	0.51	1.0000	1.0000
Panic disorder	7	15.22	1	8.33	8	0.51	1.0000	1.0000
Bipolar I	1	2.17	0	0.00	1	N/A		
Substance-induced mood disorder	1	2.17	0	0.00	1	N/A		
Substance abuse	3	6.52	1	8.33	4	1.30		
Social phobia	0	0.00	1	8.33	1	N/A		
Specific phobia	3	6.52	0	0.00	3	N/A		
Obsessive-compulsive disorder	2	4.35	0	0.00	2	N/A		
Post-traumatic stress disorder	1	2.17	0	0.00	1	N/A		
Anxiety disorder NOS	2	4.35	1	8.33	3	2.00		
Eating disorder	1	2.17	0	0.00	1	N/A		
Adjustment disorder	0	0.00	2	16.67	2	N/A		
Attention deficit disorder	1	2.17	1	8.33	2	4.09		

Only the top six disorders were analysed for significance.

OR: carriers to non-carriers; P value: from Fisher's exact test.

* P<0.05;

** P<0.01.

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FDR, false discovery rate; NOS, not otherwise specified; SCID, Structured Clinical Interview.

Table 3

Comparison of lifetime prevalence of psychiatric disorders in our sample with general population

SCID DSM-IV disorder	Non-carriers (n=46)		General population reference group (1-4)			
	Present	%	Sample (n)	%	OR	FDR
Major depressive disorder	19	41.30	9282	16.60	3.54	<0.0001** 0.0004**
Panic attack	10	21.74	9282	23.50	0.90	0.8632 1.0000
Alcohol abuse	7	15.22	9282	13.20	1.18	0.6636 0.9954
Depressive disorder NOS ^{††}	4	8.70	8098	10.00	0.86	1.0000 1.0000
Generalised anxiety disorder	7	15.22	9282	5.70	2.97	0.0151** 0.0302**
Panic disorder	7	15.22	9282	4.70	3.64	0.0056** 0.0168**

SCID DSM-IV disorder	Carriers (n=12)		General population reference group (1-4)			
	Present	%	Sample (n)	%	OR	FDR
Major depressive disorder	0	0	9282	16.60	0.00	0.2366 0.4732
Panic attack	1	8.33	9282	23.50	0.30	0.3163 0.4744
Alcohol abuse	3	25.00	9282	13.20	2.19	0.2079 0.4732
Depressive disorder NOS ^{††}	4	33.33	8098	10.00	4.50	0.0259* 0.1554
Generalised anxiety disorder	1	8.33	9282	5.70	1.50	0.5059 0.5059
Panic disorder	1	8.33	9282	4.70	1.84	0.4391 0.5059

OR: carriers to non-carriers; P value: from Fisher exact test; FDR: P values adjusted for multiplicity by false discovery rate.

* P<0.05;

** P<0.01.

^{††} Lifetime prevalence of DD-NOS in sample was compared with lifetime prevalence of minor depression in the general population.²⁴²⁵

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FDR, false discovery rate; NOS, not otherwise specified; SCID, Structured Clinical Interview.

Table 4

Lifetime prevalence of psychiatric disorders within non-carriers by degree of relation to known carrier

Non-carriers (n=46)						
		First degree relative [†] (n=18)		Not first degree relative [†] (n=28)		
Diagnosis of lifetime prevalence						
SCID DSM-IV disorder	n	%	n	%	P value	FDR
Major depressive disorder	5	27.78	14	50	0.2199	0.4263
Panic attack	4	22.22	6	21.43	1	1
Alcohol abuse	1	5.56	6	21.43	0.2196	0.4263
Depressive disorder NOS	3	16.67	1	3.57	0.2842	0.4263
Generalised anxiety disorder	2	11.11	5	17.86	0.6879	0.82548
Panic disorder	0	0.00	7	25	0.0324 [*]	0.1944

* P<0.05.

[†]To a known carrier P value: from Fisher's exact test; FDR: P values adjusted for multiplicity by false discovery rate.

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FDR, false discovery rate; NOS, not otherwise specified; SCID, Structured Clinical Interview.