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Postural instability/Gait disturbance in Parkinson's Disease has distinct subtypes: an exploratory analysis

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Abstract

Objective—To test the hypothesis that postural instability with falling (PIF) and freezing of gait (FOG) are distinct subtypes of the Postural Instability/Gait Disturbance (PIGD) form of Parkinson's disease (PD).

Methods—We studied 499 PD subjects from the NeuroGenetics Research Consortium using logistic regression to examine, in a cross-sectional analysis, predictors of FOG and PIF. Potential predictors were from four spheres; demographic, clinical motor, clinical non-motor and genetic.

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Results—FOG and PIF were both associated with greater gait subscores and lower tremor subscores on UPDRS ($p \leq 0.02$). However, they differed with regard to demographic, non-motor and genetic predictors. FOG was associated with greater duration of disease, with OR's of 3.01 (95% CI 1.35-6.72) and 4.91 (95% CI 2.29-10.54) for third and fourth quartiles of duration respectively, versus the lowest half of duration. The risk of having psychotic symptoms was also significantly increased (OR 3.02, 95%CI 1.41-6.49; p=.004). FOG was inversely associated with the presence of the *CYP2D6* *4 allele (OR 0.41, 95% CI 0.21-0.80; p=.009) suggesting a protective effect. PIF was associated with depression (OR 1.08, 95% CI 1.01-1.15; p<.02) and was inversely associated with *APOE* ε4 (OR 0.21, 95% CI 0.05-0.87; p=.03), again suggesting a protective effect.

Conclusion—FOG and PIF have different demographic, non-motor and genetic predictors suggesting that they may be pathophysiologically distinct subtypes of PIGD. These findings have implications in discovery of therapeutic targets for these disabling features as well as predicting outcomes of PD.

Keywords

Parkinson's disease; PIGD; Postural instability; freezing of gait; APOE; CYP2D6; depression; psychosis

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Postural instability/gait disturbance (PIGD) is considered by many researchers to be one particular subtype of Parkinson's disease (PD).[1, 2] Its presence has been associated with rapid progression of disease and cognitive dysfunction [2, 3] and it is a major cause of morbidity in advanced disease.[4]

However, clinically, PIGD appears to have several components. The most prominent are postural instability with falling (PIF) and freezing of gait (FOG). It has been shown that these two features cause approximately 80% of falls in PD.[5] In general, PIF and FOG are poorly understood but they have several commonalities including; they occur predominantly in late stages of PD, have limited response to dopaminergic drugs, are episodic and unpredictable.[6]

Falling in PD is common. It is likely that a substantial portion of these falls relate to PIF which results from an underlying balance disorder.[5, 6] One large retrospective study demonstrated that 46% of patients reported one fall and 33% were recurrent fallers eight years into the disease.[7] A recent meta-analysis of six studies and 473 patients found the fall rate was 46% over 3 months with a quarter resulting in injury.[8] As PD progresses, falling becomes increasingly more common, so that in advanced stages of the disease 70% of patients report at least one fall/year.[6, 7]

FOG is a sudden, transient break in walking motion which patients describe as their feet being glued to the floor.[9] As PD progresses, freezing may become accompanied by gait festination, postural instability and falling.[10] It interferes with activities of daily living, causes social isolation and has a negative effect on quality of life. [6, 11] FOG frequency increases with disease progression, from 7% at two years of disease to 58% after ten. [9, 12]

Whether PIF and FOG share pathogenetic mechanisms or neuroanatomic substrates remains unknown. The fact that key associations of PIGD with cognitive dysfunction and disease progression are not consistent [13, 14] would suggest they do not. Such studies have not clearly classified subtypes of PIGD in their cohorts. There have not been detailed comparative examinations of the components of PIGD because they overlap [6] and share similar motor and demographic risk factors; long duration/more severe disease, older age, early onset of gait symptoms, and absence of tremor.[7, 15] However, one study indicated that correlations between FOG and postural instability are at best moderate.[16] In addition, a recent factor analysis approach based on association with motor features lead to a separation of the PIGD into two subtypes, one with FOG and another with postural instability indicating that they may be different.[17]

We hypothesize that PIF and FOG are distinct subtypes of PIGD with different clinical and genetic risk factors. To test this hypothesis we examined combined potential correlates that are demographic, clinical (motor and non-motor) and genetic, for FOG and PIF in PD. We performed a cross-sectional study with the aim of generating testable hypotheses.

Methods

Subjects

This study was approved by the Institutional Review Boards of participating institutions. PD subjects were enrolled through the NeuroGenetics Research Consortium (NGRC).[18] During single visits uniform and standardized methods were used across sites for diagnosis, subject selection, and data acquisition (demographic and family history). All patients were seen by movement disorder neurologists and met standard clinical diagnostic criteria for PD (modified UK brain bank criteria [19]). Patients were enrolled sequentially, regardless of age at disease onset or family history of PD, and were unrelated to one another. Exclusion criteria included late stage dementia where subjects were unable to complete the visit assessments, history of cerebrovascular disease, findings suggestive of atypical parkinsonism (extraocular movement abnormalities, pyramidal tract signs, ataxia, early dementia), past neuroleptic use, and past history of multiple head injuries. Two of the NGRC sites, Emory University and Albany Medical Center, collected additional clinical data including the total UPDRS, MMSE and Beck Depression Inventory (BDI) and subjects from these sites were included in this analysis.

Molecular genetics

For this analysis, we selected genetic polymorphisms based on prior reports that they impact on risk of developing PD; *MAPT* (microtubule associated protein tau), *SNCA*-REP1 (alpha-synuclein promoter), *APOE* (apolipoprotein E), and *CYP2D6* (cytochrome P450).[20] Genomic DNA was extracted from peripheral blood by standard methods. Genotyping was standardized. REP1, *CYP2D6* and *APOE* genotyping was performed in Albany, New York; *MAPT* was genotyped in Seattle, Washington.

MAPT—H1 haplotype is recessive with respect to PD risk.[21] Thus H2 heterozygotes and homozygotes were combined into one group designated as H2X and compared to H1H1.

H1H1 was set as reference. To distinguish H1 and H2 haplotypes a single H1-H2 SNP (*rs1800547*) that differentiates the two haplotypes was genotyped using a TaqMan assay on an ABI 7900HT Sequence Detection System (Applied Biosystems).[21]

***SNCA* REP1—**Subjects carrying the genotype of the shorter 257 allele are at reduced risk, 259 homozygous (mid-size allele) is neutral, and subjects carrying the longer 261 allele are at increased risk. Three genotypic classes were defined: 257X where X is 257 or 259, 261X where X is 261 or 259, and 259 homozygous. 257-261 heterozygous was excluded because the alleles have opposing effects on PD risk. The low risk 257X group was set as reference. *SNCA* REP1 was PCR-amplified using fluorescently labeled primers, and repeat length was determined by PCR using an ABI PRISM 3100 Genetic Analyzer and Genotyper version 3.7 software (Applied Biosystems, Foster City, CA).[18]

APOE—genotyping was carried out using a standard RFLP method and using a 3100 Genetic Analyzer and Genotyper software.[22] Four genotyping classes were defined: ε4 ε 4, ε 3 ε 4, ε 3 ε 3 and ε 2X (combing the rare ε 2 ε 2 with ε 2 ε 3 and excluding ε 2 ε 4 because ε 2 and ε 4 may have opposing effects on PD risk). ε 3 ε 3 was set as reference.[23]

CYP2D6—a standard RFLP assay was used to detect the presence of the *4 allele by observing whether PCR products were cleaved by the enzyme BstN1.[23]

Statistical analysis

We performed a cross-sectional analysis to examine potential risk factors for FOG and PIF. Our hypothesis was that a different combination of demographic, clinical, and genetic variables would be significant predictors of FOG and PIF, with significance defined as the conventional p<=0.05. Risk factors to be tested were chosen on the basis that there was some suggestive a priori evidence that they would be significant predictor variables (clinical and genetic variables), and/or that they might act as confounders (demographic variables).

The outcomes were considered as dichotomous variables. FOG was defined as a score of >1 on UPDRS Part II item 14 (Freezing when walking), which was measured on a 0 normal to 4 severe scale. This is a subjective measure and the only item specifically related to the occurrence of FOG in the UPDRS. This score represents probable freezing. Subjects were specifically asked if their feet felt “glued” or “stuck” to the floor and a demonstration was provided by the examiner. A score > 1 was selected to eliminate false positives. PIF was defined as a score of >1 on UPDRS Part II item 13 (Falling *not* caused by freezing). We felt this item was the best measure of PIF because falls not related to freezing are, in large part, related to postural instability [7] and the postural instability measure in part III item 29 is a poor predictor of falls.[6] We chose >1 to primarily include recurrent fallers. While it is true that item 13 could pick up other causes of falling (orthostatic hypotension, muscle weakness, anxiety, medications) these would represent a small number.[5, 6]

As risk factors, we examined two demographic items: age at diagnosis and duration of disease. Duration of disease was categorized into three groups of subjects, the lowest 50% (the referent group) with <6.8 years, and the upper 50% divided into third and fourth quartiles (6.8-11.8 years, and > 11.8 years). Quartiles were based on the entire population

The bottom two quartiles of duration were collapsed due to some observed instability of models using the first and second quartiles, due to small numbers of some outcomes, eg., PIF. For age at diagnosis the referent group consisted of the youngest quartile (age <61), while the other groups were 61 to 69.2, 69.2 to < 74.9, and 74.9+. Categorical analysis of quartiles for age and duration avoids the assumption, inherent in using age and duration as continuous variables, that these variables have a strictly linear relationship with the odds of the outcome. Categorical analyses make no assumption about the nature of the relationship.

Motor risks included a tremor subscore, a composite of UPDRS part III (motor examination) items including number 20 (tremor at rest) scored for each limb and chin plus 21 (action or postural tremor of the hands). In total there were seven items summed, each scored 0-4, so that the sum had a maximum score of 28. Most items were scored 0, and the mean observed tremor subscore was 2.1, with a median of 2.0 and a standard deviation of 2.3. Gait/balance subscore (referred to as GBS), which was a composite of five items in the UPDRS part III, was also examined as a continuous variable. The items were numbers 27 (arising from a chair), 28 (posture), 29 (postural instability), 30 (gait), 31 (body bradykinesia and hypokinesia). All items were scored 0-4; maximum score of the sum was 20. The observed mean was 4.6, with a median of 4.0 and a standard deviation of 3.4. Both tremor and GBS composite scores were treated as continuous variables in the models given their reasonably continuous distribution and spread. Both tremor and GBS subscores have been shown to have opposite effects on prognosis of PD with tremor having a better prognosis.[2]

Non-motor risks were UPDRS item 41 (does the patient have any sleep disturbance?, 0 = yes, 1 = no), psychotic symptoms as measured dichotomously from item 2 of the UPDRS (thought disorder; >1 indicated the presence of psychotic symptoms, scored 0-4), depression measured by the BDI as a continuous variable (maximum score 63) [24] and cognition measured by the MMSE as a continuous variable (maximum score 30).[25]

Finally, we examined four dichotomous genetic predictors; *APOE* (ε4, ε2 alleles), *CYP2D6* (presence of the *4 allele), REP1 (261 or 257 alleles) and *MAPT* (presence of H1H1).

We used multivariate logistic models for our outcomes. Models were run separately for each outcome, using the full model of all risk factors described above. All 12 predictor variables were retained in models rather than using any backward or forward selection procedure, as the number of predictors were limited, and some residual confounding might be expected from variables selected out via a selection procedure set to a given arbitrary p-value. Variables with p<=0.05 were then highlighted for discussion and interpretation.

Results

Subjects included 499 PD cases; mean (+/- SD) age 67.7 (+/- 10.8) years, mean (+/- SD) duration of disease 8.5 (+/- 6.3) years and 61.9% were men. As expected, the two outcomes overlapped significantly with 23 subjects having both (p<0.001). Nevertheless, when examined independently differences were seen between PIF and FOG in relation to risk factors. No differences were seen regarding gender. Gender was not included in the model.

Overall, 16% of subjects had FOG (56% were male). Table 1 shows data on frequency of all risk factors, odds ratios (OR) and 95% CI. Risk was increased with greater duration of disease. For 6.8-11.8 yrs vs <6.8 yrs, OR 3.01, 95% CI 1.35-6.72 (p=.007) and for >11.8yrs vs <6.8 yrs, OR 4.91, 95% CI 2.29-10.54 (p<.0001). The apparent decreased frequency of FOG seen with age is seen after adjustment for duration of disease. This demonstrates that after adjustment there is no age effect. For motor risk factors FOG was associated with higher GBS subscore, OR 1.33 for each unit increase in score, 95%CI 1.21-1.46 (p<.0001) and lower tremor subscore, OR 0.85 for each unit decrease in score, 95% CI 0.74-0.97 (p=0.02). For non-motor measures, 34% of FOG patients reported psychotic symptoms, where as only 8% of PD patients without FOG had these symptoms, OR 3.02, 95%CI 1.41-6.49 (p=.004). Of genetic correlates, FOG was inversely associated with the presence of the *CYP2D6* *4 allele, OR 0.41, 95% CI 0.21-0.80 (p=.009) suggesting a protective effect.

Seven percent had PIF (59% male). Table 2 shows data on frequency of risk factors, odds ratios (OR) and 95%CI. This outcome was not associated with duration of disease or age. The same apparent decreased frequency of PIF with age is seen after adjustment for duration of disease. This again indicates no age effect. For motor measures, risk was increased with higher GBS subscore, OR 1.44 per unit increase in score, 95% CI 1.26-1.66 (p<.0001) and lower tremor subscore, OR 0.67 per unit decrease in score, 95% CI 0.51-0.88 (p=.004). For non-motor measures, PIF was directly correlated with depression (BDI) OR 1.08 per unit increase in score, 95% CI 1.01-1.15 (p<.02). A non-significant trend was seen with psychotic symptoms. Of genetic alleles, PIF was inversely associated with *APOE* ε4, OR 0.21, 95% CI 0.05-0.87 (p=.03), suggesting a protective effect.

Discussion

This was a first attempt at examining risk factors from various spheres (demographic, motor, non-motor and genetic) in a single population to demonstrate that FOG and PIF may be distinct subtypes of PIGD in PD. We found that FOG and PIF were both associated with significantly less tremor on examination, consistent with prior studies.[7-9, 12, 14, 15, 17] The inverse association of PIGD with tremor has previously been based on studies where the PIGD was defined by a ratio of tremor and gait subscores in UPDRS.[1, 2] Such measures would introduce bias toward an inverse association. In this study, with our outcomes being components of PIGD, definitions were not based on tremor scores. Nevertheless we found a strong inverse association supporting results of these prior studies.

It was in examining non-motor features and genetic markers that we found differences between the two outcomes. We found PIF to be associated with depression and FOG with psychotic symptoms. Neither was associated with cognitive dysfunction, a feature frequently reported to be associated with PIGD as a whole.[7, 14] However, some studies suggest a strong link between psychosis and dementia [26] indicating a relationship may exist but MMSE may not be sensitive enough to draw this out.[27] Our finding of an association between FOG and psychosis confirms one study.[17] Depression has also been previously associated with PIF.[7]

In relation to genetic risk factors, we found *APOE* ε4 was inversely associated with PIF. Apolipoprotein E, encoded by a polymorphic locus on chromosome 19q13.2, is involved in lipid metabolism and neuronal repair. The gene has three alleles, ε2, ε3, ε4. The ε4 frequency is elevated conferring an increased risk of developing Alzheimer's disease (AD) and earlier age of onset [28] while the ε2 frequency is reduced in the AD population, suggesting protection. Due to the well-known overlaps between PD and AD clinically and pathologically, *APOE* allele status has been examined in PD. It has been reported that the *APOE ε4* allele is associated with an earlier age of onset of PD although this is inconsistent, [22, 29-31] but there does not appear to be an association with the development of dementia. [29, 30, 32] A recent meta-analysis showed that it is ε2, not *ε4,* that is associated with increased PD risk.[33] This is the first report examining it in relation to the risk for gait disorders in PD. That ε4 would be protective would be consistent with ε2 being associated with increased PD risk. The mechanism remains unclear.

We found that the *CYP2D6* *4 allele was inversely associated with FOG. Cytochrome P450 2D6, encoded by a polymorphic locus on chromosome 22, is a detoxifying enzyme that metabolizes exogenous and endogenous compounds and has over 20 alleles. The common allele responsible for “poor metabolizer” status is *4. As PD is believed to be the result of gene-environment interaction, this gene has been of interest in disease susceptibility and age of onset with numerous studies examining the frequency of poor metabolizer status. Results have been inconsistent.[20] The *CYP2D6 *4* allele may be associated with later onset of disease. The only prior examination of the *CYP2D6* allele and an outcome of PD, dementia, revealed the unconfirmed finding that the presence of the *CYP2D6 29B+* allele increased the risk of dementia three fold when it was present in combination with a history of >20 days/ year of pesticide exposure.[34] This is the first time this allele has been examined in relation to FOG. There is biological plausibility to the protective effect of CYP2D6 *4 allele. FOG is a feature seen with toxicant-induced parkinsonism, for example manganese intoxication, the so-called “cock walk” is a form of FOG.[35] The slow metabolizer status could limit the conversion of pre-toxins to toxins. Previous work has suggested that this allele was associated with greater survival in PD [36] which would support our finding.

Neither *SNCA* REP 1 nor *MAPT* were found to be associated with gait disorders in PD. Both, which are associated with protein aggregation,[37] have been consistently associated with the risk of developing PD and this has been borne out by genome wide association studies.[38] The expanded repeat for REP 1, associated with overexpression of protein, has been shown to increase risk of PD by ∼25%.[18] H1H1 diplotype of *MAPT* is associated with increased risk of PD by 46% [21] despite the fact that PD is not a tauopathy. It was reasonable to examine these in association with gait disorders, particularly with *MAPT,* since the H1 haplotype is associated with progressive supranuclear palsy, a disease characterized by PIF. Nevertheless, our results are consistent with the finding that these genes tend to associate more with non-motor features. *MAPT* has been found to associate with dementia in PD [37] and the SNCA gene has also been associated with dementia [39] as well although this remains to be shown for the REP 1 polymorphism. [40]

There are multiple potential implications of our findings. The discovery of separate subtypes of PIGD with different clinical and genetic risk factors possibly indicates separate

pathophysiological mechanisms and neuroanatomic substrates. Focused study of these individual subtypes instead of a single PIGD subtype could lead to a better understanding of these mechanisms and natural history. In turn, new treatment targets could be developed. An important impact of the discovery of risk factors is the potential for prediction of these outcomes. In clinical practice one could provide patients with more accurate prognostic information. Prediction can also be important to planning management and perhaps guide development of preventative therapies. Clinical trials could target those at greater risk and would be smaller, but still have the power to detect outcomes while being less expensive. An example, is a protective trial with selegiline where data exist suggesting it may potentially delay onset of FOG.[12]

This study has several strengths. They include the consecutive nature of data collection on PD patients; diagnosis of PD and outcomes by movement disorder specialists; use of standardized measures such as UPDRS, BDI, MMSE and the availability of genetic data in 499 PD patients. Our sample is relatively large for this type of clinical study.

Methodological limitations include the cross-sectional design, i.e., we do not know if some risk factors (e.g., presence of psychotic symptoms) preceded the occurrence of the outcome. In addition, our measures of the outcomes, PIF and FOG, were based on historical information which may not always be accurate. However, for FOG in particular, it is difficult to assess freezing objectively in the clinic as it tends to occur more at home.[16] Longitudinal studies with more objective measures should be used in confirmatory studies. In addition, it would be of interest to examine on and off FOG. The use of MMSE for cognition, UPDRS for sleep and psychotic symptoms and BDI for depression are good screens for symptoms and are commonly utilized in similar pilot studies but are not comprehensive. Based on these results more detailed measures of relevant features could provide more insight into the relationships of various symptoms. Another potential issue is that with stratification some categories were small. A final issue concerns our lack of adjustment for multiple tests (or comparisons). Ours is not a study with a large number of tests conducted with no a priori hypothesis (eg, gene association studies with thousands of genes tested), where such multiple comparison adjustments are commonly applied. Instead, we have a relatively small number of largely unrelated predictor variables, about each of which we have a priori hypothesis. Standard statistical methods would not include any multiple comparison adjustments for this type of study design. Given these caveats, we encourage the readers to interpret the findings with caution and consider them preliminary until they are confirmed in a longitudinal, hypothesis driven study with more detailed measures of the clinical features and examination of other potential genetic predictors.

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Table 1

Data from the Freezing of Gait (FOG) analysis. Shown on this table are the number of patients with and without FOG (row depicted “Number”) and the number (%) for dichotomous variables or mean scores (+/- SD) of continuous variables for the predictors for those with FOG (column named “FOG”) and without FOG (column named “No FOG”).

Predictors	**FOG**	**No FOG**	**Odds ratio**	**95% CI**	**P-value**
	# (%) or mean (+/- SD)	**# (%) or mean (+/- SD)**			
Number	82 (16%)	417 (84%)			
PD Duration					
<6.8 yrs	14 (17%)	232 (56%)	Reference		
6.8-11.8	24 (29%)	104 (25%)	3.01	1.35-6.72	0.007
>11.8	44 (54%)	81 (19%)	4.91	2.29-10.54	<0.0001
Age					
< 61 yrs	17 (21%)	109 (26%)	Reference		
61.0-69.2	17 (21%)	103 (25%)	0.67	0.28-1.58	0.36
69.2-74.9	20 (24%)	104 (25%)	0.42	0.17-1.07	0.07
>74.9	28 (34%)	101 (24%)	0.51	0.21-1.21	0.13
Motor predictors					
Posture/gait subscore	7.92 (+/- 4.02)	4.05 (+/- 2.86)	1.33	1.21-1.46	<0.0001
Tremor subscore	1.63 (+/- 2.53)	2.17 (+/- 2.30)	0.85	0.74-0.97	0.02
Non-motor predictors					
BDI2	11.71 (+/- 7.39)	8.74 (+/- 6.64)	1.03	0.99-1.07	0.21
Psychotic symptoms	28 (34%)	34 (8%)	3.02	1.41-6.49	0.004
Sleep	43 (52%)	172 (41%)	0.96	0.53-1.75	0.89
MMSE	27.00 (+/- 3.14)	28.12 (+/- 2.20)	1.02	0.91-1.15	0.71
Genetic predictors					
APOE 4	21 (26%)	90 (22%)	1.05	0.53-2.09	0.9
APOE 2	16 (20%)	73(18%)	1.05	0.51-2.16	0.89
CYP2D6*4	22 (27%)	150 (36%)	0.41	0.21-0.80	0.009
REP 257	34 (42%)	175 (42%)	1.16	0.62-2.18	0.64
REP 261	15 (18%)	51 (12%)	1.76	0.75-4.14	0.2

Predictors	FOG	No FOG	Odds ratio	95% CI	P-value
	# (%) or mean (+/- SD)	# (%) or mean (+/- SD)			
MAPT H1H1	53 (65%)	284 (68%)	0.61	0.33-1.12	0.11

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Table 2

Data from the Postural instability with falling (PIF) analysis. Shown on this table are the number of patients with and without PIF (row depicted by "Number") and the number (%) for dichotomous variables or mean scores (+/- SD) of continuous variables for the predictors for those with PIF (column named "PIF") and without PIF (column named "No PIF").

Predictors	**PIF**	**No PIF**	**Odds ratio**	**95% CI**	**P-value**
	# (%) or mean (+/- SD)	**# (%) or mean (+/- SD)**			
Number	32 (7%)	467 (93%)			
PD Duration					
< 6.8 yrs	7 (22%)	239 (51%)			
6.8-11.8	4 (13%)	124 (27%)	0.62	0.14-2.77	0.53
>11.8	21 (65%)	104 (22%)	2.24	0.73-6.95	0.16
Age					
< 61 yrs	7 (22%)	119 (26%)			
61.0-69.2	8 (25%)	112 (24%)	1.16	0.32-4.26	0.82
69.2-74.9	10 (31%)	114 (24%)	0.53	0.13-2.22	0.38
>74.9	7 (22%)	122 (26%)	0.28	0.06-1.29	0.1
Motor predictors					
Posture/gait subscore*	9.25 (+/- 3.72)	4.37 (+/- 3.14)	1.44	1.26-1.66	<0.0001
Tremor subscore*	1.00 (+/- 2.00)	2.15 (+/- 2.35)	0.67	0.51-0.88	0.004
Non-motor predictors					
BDI2*	13.25 (+/- 8.59)	8.96 (+/- 6.64)	1.08	1.01-1.15	<0.02
Psychotic symptoms	12 (38%)	50 (10%)	2.34	0.77-7.08	0.13
Sleep	16 (50%)	199 (43%)	0.74	0.28-1.95	0.55
MMSE*	26.69 (+/-3.34)	28.02 (+/- 2.31)	1.05	0.88-1.25	0.57
Genetic predictors					
APOE 4	3 (9%)	108 (23%)	0.21	0.05-0.87	0.03
APOE 2	5 (16%)	84 (18%)	0.85	0.26-2.82	0.79
CYP2D6*4	12 (38%)	160 (34%)	0.8	0.31-2.10	0.65
REP 257	10 (31%)	199 (43%)	0.46	0.17-1.27	0.13
REP 261	5 (16%)	61 (13%)	0.71	0.18-2.85	0.63

Predictors	PIF	No PIF	Odds ratio	95% CI	P-value
	# (%) or mean (+/- SD)	# (%) or mean (+/- SD)			
MAPT H1H1	25 (78%)	312 (67%)	1.22	0.44-3.41	0.62