Title

Initial Symptoms in Symptomatic and Pre-symptomatic Genetic Frontotemporal Lobar Degeneration

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Abstract

Objectives: The clinical heterogeneity of Frontotemporal Dementia (FTD) complicates identification of biomarkers for clinical trials that may be sensitive during the pre-diagnostic stage. It is not known whether cognitive or behavioural changes during the pre-symptomatic period are predictive of genetic status or conversion to clinical FTD. The first objective was to evaluate the most frequent initial symptoms in patients with genetic FTD. The second objective was to evaluate whether pre-symptomatic mutation carriers demonstrate unique FTD-related symptoms relative to familial mutation non-carriers.

Methods: The current study used data from the Genetic Frontotemporal Dementia Initiative (GENFI) multicentre cohort study collected between 2012-18. Participants included symptomatic carriers (N=185) of a pathogenic mutation in *C9orf72*, *GRN* or *MAPT* and their first-degree biological family members (N=588). Symptom endorsement was documented using informant and clinician-rated scales.

Results: The most frequently endorsed initial symptoms amongst symptomatic patients were apathy (23%), disinhibition (18%), memory impairments (12%), decreased fluency (8%), and impaired articulation (5%). Predominant first symptoms were usually discordant between family members. Relative to biologically related non-carriers, pre-symptomatic *MAPT* carriers endorsed worse mood and sleep symptoms, and *C9orf72* carriers endorsed marginally greater abnormal behaviours. Pre-symptomatic *GRN* carriers endorsed less mood symptoms compared to non-carriers, and worse everyday skills.

Conclusion: Pre-symptomatic mutation carriers exhibited neuropsychiatric symptoms compared to non-carriers that may be considered as future clinical trial endpoints. The heterogeneity of initial symptoms in genetic FTD may be best captured by use of focussed composite indices specific to the most frequent initial symptoms for each genetic group.

Introduction

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder characterized by progressive alterations in behaviour and/or language abilities. Approximately 30% of FTD is familial, where roughly 10% of these patients have a clear autosomal dominant pattern of inheritance caused primarily by mutations in the chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*) and microtubule-associated protein tau (*MAPT;* (Rohrer et al., 2009). While advancements have been made in the development of therapies targeting the underlying pathology (Tsai & Boxer, 2016), currently, no treatments are available to prevent or alter the course of disease progression.

As the early symptoms of FTD are impairing (Rasmussen, Hellzen, Stordal, & Enmarker, 2019), treatments will likely need to intervene during the pre-symptomatic stage, before a patient meets the current international consensus criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Consequently, there is a growing interest in identifying biomarkers and clinical endpoints that can best inform when to administer these interventions and how to track treatment efficacy. A major challenge in designing clinical trials and the designation of clinical endpoints for early intervention is the heterogeneity of genetic FTD at the phenotypic (Benussi, Padovani, & Borroni, 2015), genetic and pathological levels (Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011). For instance, clinical symptoms in FTD range from language disturbances (Gorno-Tempini et al., 2011) to behavioural and neuropsychiatric features (Rascovsky et al., 2011), which occur at various frequencies and ages even within families (Moore et al., In press; Snowden et al., 2015). At present, it is not yet known whether or when neuropsychiatric and

other symptoms associated with FTD may occur during the prodromal period, and whether such symptoms may be specific to the later development of clinical FTD. Now sizable longitudinal cohorts of patients with genetic FTD and their at-risk family members offer a unique opportunity to examine the rates of reported behavioural, neuropsychiatric and cognitive symptoms in mutation carriers vs. non-carriers, to determine whether certain symptoms may be used as clinical endpoints in pre-diagnostic stages of the disease.

To inform such clinical endpoint selection for future clinical trials in at-risk cohorts, the first objective of the current study was to evaluate the most frequent initial symptoms in patients with symptomatic genetic FTD due to *C9orf72*, *GRN* or *MAPT* mutation. The second objective was to evaluate whether pre-symptomatic mutation carriers demonstrate greater or unique behavioural/neuropsychiatric or cognitive symptoms relative to biologically related non-carriers during the pre-diagnostic period.

Method

Participants

The current study used data from the Genetic Frontotemporal Dementia Initiative (GENFI) multicentre cohort study, which consists of research centres across Europe and Canada (http://genfi.org.uk/). This dataset is comprised of (1) known symptomatic carriers of a pathogenic mutation in the *GRN* or *MAPT* genes or with a pathogenic expansion in the *C9orf72* gene (greater than 30 repeats) based on the international consensus diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011), and (2) first-degree biological family members of a

known *GRN*, *MAPT* or *C9orf72* mutation carrier who are at-risk for developing FTD and were not yet demonstrating evidence of progressive cognitive or behavioral symptoms (including both carriers and non-carriers of known mutations). Importantly, the majority of at-risk family members in the GENFI study, and the local GENFI research teams and PIs were not aware of their genetic status at the time of the assessments. After their baseline visit, participants were followed for up to five annual visits. All participants had an identified informant who completed the study measures (see below). The data was part of the GENFI data freeze 4 collected at 22 GENFI sites (2012-2018).

Study Measures

GENFI Symptom List: The 37-symptom list was designed to include a variety of FTD-related symptoms based on standardized rating scales (section S1.0). Based on novel findings in the FTD literature in 03/2015, 31 additional symptoms were included (modified symptom list; section S1.0). Informants of symptomatic patients (typically a spouse or sibling) described the initial symptom and trained research coordinators selected the corresponding symptom from the list. For at-risk family members, clinicians completed the GENFI symptom list (original or modified depending on enrollment date) with the at-risk family member and their study informant, and evaluated the presence of each symptom using a 5-point Likert scale (0=absent, 0.5= questionable/very mild, 1=mild, 2=moderate, 3=severe). Symptom ratings of questionable/very mild, mild, moderate, severe were coded as *symptom endorsement* and absent coded as *symptom absent*.

Cambridge Behavioural Inventory Questionnaire-Revised: Informants of at-risk family members completed the Cambridge Behavioural Inventory-Revised questionnaire (CBI-R; (Wear et al., 2008). Each question is evaluated on a 5-point scale, where higher scores indicate greater symptom endorsement and severity. Symptom domains included memory and orientation, everyday skills, self-care, abnormal behaviour, mood, beliefs, eating habits, sleep, stereotypic and motor behaviours and motivation. Each domain includes 2-8 sub-items. The inclusion of the CBI-R allowed us to examine other symptoms that are not captured by the original (*Sleep, Self-Care*, *Mood* (i.e. agitation, irritability) or modified GENFI symptom list (i.e. *Everyday skills* and *Motivation*).

Years from expected symptom onset was used to determine whether participants who were closer to the age of anticipated symptom onset endorsed greater symptoms. Years from expected symptom onset (YEO) was calculated by subtracting the mean age of symptom onset within the family from the participant's current age (Rohrer et al., 2015). Negative values denote that the participant is at an age *prior* to expected symptom onset; positive values indicate that the participant is at an age *after* expected symptom onset.

Statistical Analysis

GENFI Symptom List: Descriptive statistics were used to illustrate the most frequent symptoms endorsed at participants' initial visits. As only a *single* initial symptom was selected for the symptomatic patients, we first investigated whether a different pattern of results was reported for symptomatic patients who used the original vs. modified GENFI symptom list (which included more symptom options), by evaluating the pattern of symptom endorsement at baseline in both

version groups (Table S1a). Across the symptomatic cohort, the most frequent symptoms within each list were items that were present in both versions of the GENFI symptom list: disinhibition, apathy, decreased fluency, memory impairment, impaired articulation and impaired word retrieval. Thus, subsequently, data from both cohorts for the main analysis were combined (see Table S1b for demographic details, and section 2.0 for analysis conducted on the two cohorts separately). Differences amongst the three genetic groups in the frequency of endorsing the most prevalent sub-symptoms were examined using Chi-squared test or Fisher's exact test for the symptomatic patients, and separately comparing pre-symptomatic mutation carriers and non-carriers. Mixed models were not used to account for potential clustering effects of family membership and site, due to the low symptom endorsement (creating small samples) by patients and at-risk family members.

To evaluate changes in symptom endorsement over time in at-risk family members who had at least one follow-up visit, a difference score was calculated by subtracting symptom endorsement at the final visit from symptom endorsement at the first visit (0=not endorsed, 1=symptom endorsed). This resulted in three categories for each symptom: decrease in symptom endorsement over time (score of -1), no change in symptom endorsement over time (score of 0), increase in symptom endorsement over time (score of 1). Calculating change scores enabled all participants to be included in the analysis, regardless of the number of follow-up visits. Chi-squared tests/Fisher's Exact tests were completed to assess group differences.

To evaluate whether the initial symptoms were similar amongst patients from the same family a congruency score was calculated as the number of pairwise comparisons in which family

members shared an initial symptom, divided by the total number of possible pairwise comparisons. A congruency score was also calculated to evaluate the congruency of initial predominant symptoms for specific *GRN* and *MAPT* mutations.

Cambridge Behavioural Inventory Questionnaire-Revised: A generalized linear mixed model with a Laplace likelihood approximation function was used to examine differences in the total CBI-R scores between pre-symptomatic mutation carriers vs. non-mutation carriers at the initial GENFI visit as a function of years from expected symptom onset. This analysis accounted for potential clustering effects based on family membership. Plots of the CBI-R total scores suggested a Poisson distribution; however, due to overdispersion as indicated through the Pearson Chi-Square/DF, a negative binomial distribution with a log link function was used. Predictor variables included random effects [family membership] and fixed effects [genetic status (pre-symptomatic vs. non-carriers), years from expected symptom onset, and an interaction between genetic status and years from expected symptom onset]. Examination of the residuals suggested the use of weights to account for the within-family correlation in the model. Given the variability in contribution of family membership to predicting age of onset by mutation group (Moore et al., In press), a confirmatory analysis was conducted substituting years from expected symptom onset with the participant's age. Of note, as age was highly correlated with years from expected symptom onset ($r=0.84$, $p<0.001$), participant's age could not be included in the model due to multicollinearity. However, when age was substituted for estimated years to symptom onset, the pattern of results was similar (Table S2).

Change scores (symptom score at final visit – score at first visit)/ time interval) were calculated to compare longitudinal data. Participants with studentized residuals greater than +/- 3 were removed (Table S3), and a linear mixed model was used (see section S3.0 on the description of the model formation). Predictor variables included random effects [family membership] and fixed effects [genetic status (pre-symptomatic vs. non-carriers), years from expected symptom onset or participant's age, CBI total score at baseline, and an interaction between genetic status and years from expected symptom onset]. A confirmatory analysis was run substituting participant's age at baseline for the years from expected symptom onset (Table S3). As differences between the pre-symptomatic and non-carriers in the *total* CBI scores may be obscured by opposed group differences in the sub-scale scores, we also examined group differences for each of the sub-scales by using the model developed for the total score. For these models, the same model parameters were used with one exception: the sub-scale score at baseline was used as a fixed effect instead of the CBI total score at baseline. Additionally, for both the baseline and change score analysis, the potential influence of specific FTD-causing mutations was examined by assessing the impact of genetic mutation type as the grouping variable (*C9orF72*, *GRN*, *MAPT*, mutation non-carriers), and post-hoc comparisons were conducted between each genetic group and non-carriers.

Results

Participants

185 patients diagnosed with FTD (*C9orf72* n=87, *GRN* n=65, *MAPT* n=33) from 164 unique families were included in the analysis. Additionally, 637 at-risk family members from 248

families (317 pre-symptomatic mutation carriers, 320 mutation non-carriers) and 588 at risk individuals from 228 families (294 pre-symptomatic carriers, 294 non-carriers) completed the GENFI symptom list and CBI-R scales, respectively (Table 1).

Predominant Initial Symptoms in Symptomatic Patients

Across the entire cohort the most frequently endorsed initial symptoms were apathy (23%), disinhibition (18%), memory impairments (12%) decreased fluency (8%) and impaired articulation (5%; see Table 2). When the most frequent initial symptoms were compared amongst the mutation groups, patients with *MAPT* mutations presented with disinhibition more frequently relative to *C9orf72* and *GRN* carriers, and displayed memory impairments more frequently than *GRN* carriers. *GRN* carriers exhibited impaired articulation and decreased fluency more often than *C9orf72* and *MAPT* carriers. No group differences were observed for apathy.

Symptom Congruency

14 families had at least two related patients in the study cohort; amongst these families, the average percentage congruency for first symptom similarity was 19%. Five families with a MAPT mutation and 7 families with a GRN mutation had at least two related symptom patients in the study cohort and the specific genotype was known (Table S4b). Of the specific genotypes, the average congruency score was 33% for MAPT and 20% for GRN mutations.

Symptom Endorsement in at-risk Family Members (GENFI symptom list)

At baseline greater than 10% of at-risk (pre-symptomatic mutation carriers and non-carriers) reported depression, anxiety, impaired sleep, irritability/lability and memory impairments (Table

2). Additionally, smoking, hypertension, traumatic brain injury and recreational drug use were common *other disorders* amongst the at-risk groups. There were no statistically differences between at-risk groups or genetic group (Tables 2 & 3) in the proportion of participants who endorsed the initial symptoms most commonly reported in affected patients (i.e. apathy, disinhibition decreased fluency, impaired articulation and memory impairments). Overall, at-risk groups (pre-symptomatic vs. non-carriers) and at-risk genetic groups (pre-symptomatic *C9orf72, GRN, MAPT* vs. non-carriers) showed a similar pattern of symptom endorsement over time, with a very low proportion of participants reporting changes in the most common initial symptoms (Table S5).

Symptom Endorsement & Severity in at-risk Family Members (CBI-R questionnaire)

CBI-R scores at baseline: As participants approached the anticipated time to symptom onset there was a significant increase in the reported total symptom score (Table 4). Subscale scores associated with increased years to expected symptom onset included for memory and orientation, eating habits, sleep, motivation, and stereotypic & motor behaviours (marginal effect). There was no association between overall or subscale scores and genetic status, nor between CBI-R scores and genetic status by years to onset interactions.

Genetic Group: As expected, the association between the CBI-R symptom score and anticipated time to symptom onset remained significantly associated when the mutation carrying participants when stratified by genetic group (*C9orf72, GRN, MAPT*, vs. non-carrier). Participants closer to the anticipated symptom onset had higher total scores and for memory and orientation, sleep, motivation, eating habits, and stereotypic and motor behaviours. When adjusting for expected

years to symptom onset and relative to non-carriers, post-hoc contrasts showed that *MAPT* carriers experienced greater mood, sleep, and motivation symptoms; *C9orf72* carriers endorsed greater abnormal behaviour and stereotypic & motor symptoms; and *GRN* carriers had lower mood scores (Table 5; Figure 1).

Longitudinal CBI scores: Improved symptoms over time (negative change scores) were associated with greater symptom scores at baseline when adjusted for expected years to onset and carrier status. This finding held true across all sub-scale scores as well. The only sub-scales with significant associations between change scores and expected years to onset were memory and orientation and stereotypic and motor behaviours (Table 4). There was no significant genetic status by years to symptom onset interaction. However, pre-symptomatic carriers showed a greater deterioration of everyday skills relative to the non-carrier group (Figure 2). *Genetic Group*: The analysis by genetic group was similar: improved symptom scores over time with significant associations between expected years to symptom onset and memory and orientation scores, stereotypic and motor behaviours, but also for eating habits (Table 5). Within the sub-scales, *GRN* and *C9orf72* pre-symptomatic carriers demonstrated worse everyday skills over time relative to mutation non-carriers, but only the GRN carriers' scores met statistical significance (Figure 2).

Discussion

As the first study to compare initial symptoms in symptomatic and at-risk patients with genetic FTD across the three main genetic mutations *MAPT, C9orf72* and *GRN*, our findings demonstrate the overlap and differences in the presence and frequencies of specific FTD-related

symptoms. We also report the first longitudinal differences between pre-symptomatic mutation carriers in comparison to familial non-carriers in the endorsement of cognitive and behavioural/neuropsychiatric symptoms prior to diagnosis. Important to the interpretation of symptom reports and design of clinical trials, we found that pre-symptomatic *MAPT* and *C9orf72* mutation carriers endorsed greater symptoms at the initial assessment (approximately 14 years prior to anticipated age of onset), and over time *GRN* and *C9orf72* mutation carries exhibited poorer everyday skills. The direct comparison of symptoms among mutation groups may be important in the consideration of basket-design clinical trials where, for example, patients with TDP-43 pathology arising from different mutations (*C9orf72* & *GRN*) may be grouped together.

Symptomatic Period

Within the symptomatic cohort, apathy, disinhibition and memory impairments were the most frequently endorsed initial symptoms. While apathy and disinhibition were the most frequent initial symptoms across the mutation groups, some gene specific patterns emerged. The relative proportion of *MAPT* carriers (46%) endorsing disinhibition as the initial complaint relative to *C9orf72* carriers (15%) and *GRN* carriers (8%) is similar to group differences reported by (Snowden et al., 2015) that 93% of *MAPT* carriers exhibited signs of disinhibition over the course of their disease relative to 63% of *C9orf72* and 56% of *GRN* carriers. *GRN* carriers endorsed impaired articulation and decreased fluency most often, which corresponds with the language-based clinical presentation found in some patients in this mutation group (Rademakers et al., 2007; Snowden et al., 2015). *C9orf72* expansion carriers reported motor symptoms most often which is consistent with reports of Amyotrophic Lateral Sclerosis found only in *C9orf72* carriers and absent in *GRN* and *MAPT* (Snowden et al., 2015). Although the symptoms discussed

above are characteristic of the specific gene affected, it is critical to recognize that these symptoms are not endorsed by *all* the participants in each genetic group. Further, the predominant first symptoms differ even within families or specific mutation types. Thus, we suggest a composite symptom index for each mutation group composed of the top three most frequently endorsed symptoms (*C9orf72*: apathy, disinhibition, memory impairment; *GRN*: apathy, decreased fluency, impaired articulation; *MAPT*: disinhibition, apathy, memory impairment) may be considered as an outcome measure or clinical endpoint in future clinical trials.

Although apathy and disinhibition are observed in the diagnostic criteria for behavioural variant FTD (Rascovsky et al., 2011), memory impairments are an exclusionary criterion (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). In our cohort of symptomatic patients, we found that approximately 12% of patients initially experienced memory impairments. Additionally, in our cohort, *MAPT* carriers more frequently displayed memory impairments compared to *GRN* carriers. Early memory complaints have been reported in some *GRN* cases (Kelley et al., 2009; van Swieten & Heutink, 2008), though is usually a more prominent feature later in the disease (Rohrer & Warren, 2011). Previous studies have documented differing rates of initial memory impairments ranging from ~2 to 27% in cohorts of FTD including behavioural variant, semantic variant primary progressive aphasia (PPA) and nonfluent agrammatic variant PPA (Lindau et al., 2000; Pijnenburg, Gillissen, Jonker, & Scheltens, 2004; Shinagawa, Ikeda, Fukuhara, & Tanabe, 2006). Prior studies of small genetic FTD cohorts have found varying rates of initial memory complaints within and across genetic groups. Within our cohort, 24% of *MAPT* carriers reported memory complaints as their initial symptom followed by *C9orf72* carriers (11.5%) and *GRN*

carriers (6%). Previous studies have found that 15% of *MAPT* carriers (N=15; (Borrego-Ecija et al., 2017) report initial memory loss, and 60% (N=5) had memory problems within 12 months of the initial presentation (Piguet et al., 2004). Furthermore, Mahoney et al. (2012) recorded 63% (N=16) of *C9orf72* carriers exhibited early memory impairments (episodic n=6, topographical n=4), and Van Langenhove et al. (2013) found that 42% (N=26) of *C9orf72* carriers reported memory disturbances as initial symptoms. In a cohort of *GRN* carriers (N=33), memory impairment was the second most common early symptom, affecting 30% of the cohort (Rademakers et al., 2007), and Kelley et al. (2009) found that 47% (N=17) had an early memory impairment (impairment new learning or temporal disorientation) within the first year of symptoms. In addition to the sample size, one reason for the variance in rates across studies may be due to different methods of symptom ascertainment, from study partner/caregiver report in this current study, to retrospective chart reviews found in previous reports (Borrego-Ecija et al., 2017; Mahoney et al., 2012; Rademakers et al., 2007).

Pre-symptomatic Period

Overall, and counter to our predictions, pre-symptomatic carriers and non-carriers endorsed similar rates of initial symptoms endorsed by affected patients (apathy, disinhibition, memory impairments, decreased fluency and impaired articulation). Similarly, pre-symptomatic and non-mutation carriers did not differ in their rates of the most common symptoms endorsed including depression, anxiety and memory impairments, impaired sleep and irritability. Our cohort included biologically related non-mutation carriers which enabled us to control for potential environmental influences (e.g. worry about inheriting an FTD-causing mutation, stress from a family member with FTD) that may impact symptom endorsement. Although biomarkers in

blood and cerebrospinal fluid, grey matter atrophy, white matter hyperintensities and hypometabolism have been detected prior to cognitive impairments during the pre-symptomatic period (Greaves & Rohrer, 2019), the present findings indicate that the behavioural and cognitive symptoms endorsed as initial symptoms by patients may not emerge until just a few years prior to fulminant disease onset. In a recent longitudinal study of 46 pre-symptomatic mutation carriers, 8 of which "converted" to symptomatic during follow-up, cognitive decline during the pre-symptomatic period was evident but were largely driven by the convertors. Additionally, differences in cognitive decline between converters and pre-symptomatic mutation carriers was detectable starting only 2 years prior to symptom onset. This may suggest that cognitive performance may remain relatively stable during the pre-symptomatic period and cognitive decline may begin near or at symptom onset (Jiskoot et al., 2018).

Similar symptom endorsement between pre-symptomatic carriers and non-carriers was also found with a caregiver report (CBI-R), though potential differences could have been obscured in the combination of the three pre-symptomatic genetic groups. Relative to non-carriers, pre-symptomatic *MAPT* carriers endorsed poorer mood and sleep symptoms, and *C9orf72* carriers exhibited marginally greater abnormal behaviours. Moreover, *GRN* pre-symptomatic carriers endorsed *less* mood symptoms relative to non-carriers. Given the natural co-occurrence of sleep and mood alterations, it is not surprising that *MAPT* carriers experienced symptoms in both domains. In line with our current findings, depressive disorder not otherwise specified has been found to be more prevalent amongst *MAPT* pre-symptomatic carriers relative to mutation non-carriers and the general population (Cheran & Silverman, 2018). As well, over a 4-year follow-up, it was reported that *MAPT* pre-symptomatic carriers (n=15) developed more depressive

symptoms than *GRN* carriers (n=31) and healthy controls (n=39; (Jiskoot et al., 2018). In contrast to the current study, other reports have documented inconsistent findings on the prevalence of depressive and other neuropsychiatric symptoms during the pre-symptomatic period. For example, a greater lifetime prevalence of major depressive disorder, generalized anxiety disorder and panic disorder has previously been observed in *non-carriers* (n=46), but not in *MAPT* mutation carriers (n=12; (Cheran & Silverman, 2018). Furthermore, other studies have found that neuropsychiatric features may not emerge until symptom onset. For example, in a Dutch cohort of approximately 80 *MAPT* and *GRN* mutation and non-carriers, mutation carriers who "converted" from pre-symptomatic to symptomatic status (3 *GRN* and 5 *MAPT*) displayed greater depressive and general neuropsychiatric features (as measured through the Neuropsychiatric Inventory) relative to pre-symptomatic mutation carriers and mutation non-carriers at the time of clinical symptom onset (Jiskoot et al., 2019). In our cohort of pre-symptomatic mutation carriers, mood symptoms did not emerge as participants approached their expected time of disease onset; therefore, the endorsement of symptoms by mutation carriers' may reflect a developmental predisposition.

When symptom endorsement was examined longitudinally, pre-symptomatic *GRN* carriers endorsed worse *Everyday Skills* over time compared to non-mutation carriers. Relative to healthy controls and normative data, asymptomatic *GRN* carriers demonstrate poorer performance on a variety of cognitive domains including attention/processing speed ~ 8 years prior to symptom onset(Jiskoot et al., 2016), visuospatial and working memory ~11 years prior to symptom onset (Hallam et al., 2014), verbal fluency, emotion recognition (Rohrer et al., 2008), attention, mental flexibility and language (Barandiaran et al., 2019). With this, it is likely that the decline in

Everyday skills in pre-symptomatic *GRN* carriers reflects subtle changes in a variety of cognitive domains. Therefore, as differences are evident between *GRN* pre-symptomatic mutation carriers and non-carriers everyday skills as measured through the CBI-R may potentially be used as an end point for clinical trials in *GRN* pre-symptomatic individuals.

Clinical trial modeling may need to consider the participants knowledge of their genetic status when considering rates of symptom reporting. In autosomal dominant AD, at-risk participants that did not know their genetic status but who thought they were mutation carriers or who preferred not to answer whether they believe they were carriers showed higher rates of depression, irritability and sleep changes in comparison to participants who thought they were not mutation carriers (Ringman et al., 2015).

Limitations

Potential clustering effects of family membership and testing site could not be accounted for in the clinician-rating scale, due to low symptom endorsement. Furthermore, although the different scales used in the current study allow for the assessment of symptom endorsement by multiple informants, we could not account for potential differences in reporting style based on the sex of the informant or the relationship of the informant to the at-risk family member. An additional potential limitation is the reliance on retrospective caregiver reports to acquire reports of the initial symptom in symptomatic mutation carriers, though the diagnosis of FTD is reliant on caregiver's reports (Rabinovici & Miller, 2010). Moreover, another limitation is the usage of two slightly different versions of the GENFI symptom list. Minor discrepancies in symptom endorsement reported in each version may be the result of varying sample sizes, differing

proportions of FTLD sub-types, and re-categorization of symptoms from the original list into more specific symptoms in the modified list (e.g. including "poor response to social/emotional cues" and "inappropriate trusting behaviour" in the modified list may have been categorized as "disinhibition" in the original list). Importantly though, the inclusion of additional symptoms in the modified symptom list did not detract reporting of symptoms found only in the original version.

Conclusions

In conclusion, and of interest for clinical trial design, we report the frequencies of the most common initial symptoms for the main genetic forms of FTD and suggest that given the heterogeneity between gene groups, family members, and even specific mutations, composite measures of these symptoms may serve as clinical outcomes for detection of early conversion to symptomatic FTD. Of interest, we did not find differences between pre-symptomatic mutation carriers and non-carriers for the most common initial symptoms in affected patients (disinhibition, apathy and memory changes). Future studies with the GENFI and other genetic FTD cohorts examining initial symptoms with additional longitudinal data points will aid in the understanding of the progression of these symptom from the pre-symptomatic, prodromal and the affected diseases stages and further pinpoint the onset of initial symptoms heralding conversion to symptomatic FTD.

Figure 1: Figure 1: CBI-R scores at baseline for (a) abnormal behaviours (b) mood and (c) sleep (d) stereotypic & motor (e) motivation sub-scales. Y-axis represents the scores as modeled through the generalized mixed models, and X-axis represents the expected years to symptom onset. Blue =pre-symptomatic *C9orf72* mutation carriers, red =pre-symptomatic *GRN* mutation carriers, green=pre-symptomatic *MAPT* carriers, and brown =non-carriers.

Figure 2: CBI-R change score for everyday skills sub-scale. Y-axis represents the linear predicted scores for as modeled by linear mixed models and X-axis represents the expected years to symptom onset. Blue =pre-symptomatic *C9orf72* mutation carriers, red =pre-symptomatic *GRN* mutation carriers, green=pre-symptomatic *MAPT* carriers, and brown=non-carriers.

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Table 1: Demographics Table for Symptomatic and At-risk Family Members

	Symptomatic Patients					At-risk Family Members					
	Total	***C9orf72***	***GRN***	***MAPT***	**Contrasts**	**Pre-symptomatic[&]**	**Non-carrier[&]**	**Contrasts[&]**	**Pre-symptomatic[^]**	**Non-carrier[^]**	**Contrasts[^]**
N	185	87	65	33		317	320		294	294	
Handedness					p=0.02[*#]			p=0.16[*#]			p=0.14[*#]
Right	174	80	65	29		282	298		275	262	
Left	9	5	0	4		31	20		17	28	
Ambidextrous	2	2	0	0		4	2		2	4	
Sex					X^2=6.2, p=0.045			X^2=0.90, p=0.34			X^2=0.86, p=0.35
Male	108	57	30	21		123	136		112	123	
Female	77	30	35	12		194	184		182	171	
Genotype								X^2=0.21, p=0.90			X^2=0.58, p=0.75
C9orf72						117	115		104	103	
GRN						144	144		138	132	
MAPT						56	61		52	59	
Maximum number of visits											
1						121	118		124	122	
2						80	98		80	95	

3						72	58		60	38	
4						30	27		22	23	
5						10	15		7	16	
6						4	4		1	0	
Time interval for change score (SD)						2.6 (1.4) [n=196]	2.5 (1.5) [n=202]	t(394.7) = -0.6, p=0.54	2.5 (1.3) [n=170]	2.4 (1.5) [n=172]	t(340)= -0.7, *p*=0.49
Age (SD)	62.3 (8.5)	63.7 (8.3)	63.5 (6.9)	56.2 (9.5)	F(2,184)=11.5, *p*<0.001[#] C9> MAPT GRN > MAPT	44.0 (11.8)	46.3 (14.0)	t(619)=2.3, *p*=0.03	44.0 (11.9)	46.7 (14.1)	t(570.1)=2.6, *p*=0.01
Age at onset (SD)	58.1 (8.8)	58.8 (9.0)	60.6 (7.2)	51.1 (7.7)	F(2,184)=11.5, *p*<0.001[#] C9>MAPT GRN >MAPT						
Education, Yrs, (SD)	12.2 (4.0)	12.6 (4.0)	11.2 (4.0)	13.2 (3.6)	F(2,184)=3.5, *p*=0.03[#]	14.3 (3.3)	13.9 (3.6)	t(635)= -1.5, *p*=0.13	14.3 (3.3)	13.9 (3.6)	t(586)= -1.58, p=0.1

					MAPT> GRN (p=0.065)						
Years from expected symptom onset (SD)[**]						-14.4 (11.8)	-13.2 (14.1)	t(618.5) = 1.17, p=0.24	-14.5 (12.0)	12.9 (14.2)	t(569.3)= 1.51, p=0.13

- Chi-squared, Fisher's Exact tests (if expected cell count was less than 5), independent sample t-tests or one-way analysis of variance were used to discern group differences for relevant variables
- [#] Bonferroni correction applied
- [&]At-risk participants who completed the GENFI symptom list
- [^]At-risk participants who completed the CBI questionnaire
- [*#]Fisher's Exact Test was used
- [**]Years from expected symptom onset was calculated by subtracting the participant's age at the time of participation from the mean age of symptom onset within the family

Table 2: Symptom endorsement (%) in symptomatic patients and at-risk family members (GENFI symptom list)

	Symptomatic Patients					Pre-symptomatic	Non-carrier	
	Total (N=185)	**C9orF72 (N=87)**	**GRN (N=65)**	**MAPT (N=33)**	**Group Contrasts**	**Symptom Endorsement (%)**	**Symptom Endorsement (%)**	**Group Contrasts**
Behavioural								
Disinhibition	17.8	14.9	7.7	45.5	X^2= 22.2, p<0.001 MAPT > C9orf72 & GRN	3.5	1.9	X^2= 1.6, p=0.2
Apathy	23.2	23.0	26.2	18.2	X^2= 0.8, p=0.7	4.10	4.38	X^2=0.9, p=1.0
Loss of sympathy/empathy	1.6	1.1	3.1	0.0		2.52	1.88	
Ritualistic/compulsive behaviour	1.1	2.3	0.0	0.0		1.89	1.25	
Hyperorality and appetite changes	1.6	2.3	1.5	0.0		1.26	1.25	
Poor response to social/emotional cues**	0.9	1.9	0.0	0.0		3.13	1.23	

Inappropriate trusting behaviour**	0.9	1.9	0.0	0.0		3.65	0.61	
Neuropsychiatric								
Visual hallucinations	1.1	2.3	0.0	0.0		1.89	0.00	
Auditory hallucinations	0.0	0.0	0.0	0.0		0.32	1.25	
Tactile hallucinations	0.5	1.1	0.0	0.0		0.63	0.00	
Delusions	1.1	1.1	1.5	0.0		0.32	0.94	
Depression	3.2	2.3	4.6	3.0		14.20	13.75	
Anxiety	0.0	0.0	0.0	0.0		16.09	13.13	
Irritability/Lability**	0.9	1.9	0.0	0.0		11.98	14.11	
Agitation/Aggression**	0.0	0.0	0.0	0.0		5.21	3.68	
Euphoria/Elation**	0.0	0.0	0.0	0.0		2.60	0.61	
Aberrant motor behaviour**	0.0	0.0	0.0	0.0		3.13	0.61	
Hypersexuality**	0.0	0.0	0.0	0.0		0.52	0.0	
Hyperreligiosity**	0.0	0.0	0.0	0.0		1.04	0.0	
Impaired sleep**	0.0	0.0	0.0	0.0		14.58	12.27	
Altered sense of humour**	0.9	1.9	0.0	0.0		2.604167	1.226994	
Language								
Impaired articulation	5.4	1.1	13.8	0.0	p=0.001$^{*\#}$	1.58	1.88	X^2= 0.08, p=0.77

					GRN > C9orf72 & MAPT			
Decreased fluency	8.1	4.6	16.9	0.0	p=0.005*# GRN > C9orf72 & MAPT	2.52	3.13	X^2=0.21, p=0.65
Impaired grammar/syntax	1.1	0.0	3.1	0.0		0.95	1.25	
Impaired word retrieval	4.3	4.6	6.2	0.0		7.26	10.63	
Impaired speech repetition	0.5	1.1	0.0	0.0		0.00	0.31	
Impaired sentence comprehension	1.1	0.0	3.1	0.0		0.95	0.31	
Impaired single word comprehension	0.5	1.1	0.0	0.0		0.95	0.31	
Dyslexia	0.0	0.0	0.0	0.0		1.89	1.56	
Dysgraphia	1.1	1.1	1.5	0.0		1.26	2.50	
Impaired functional communication	1.1	1.1	0.0	3.0		0.63	0.31	
Cognitive								

Memory Impairment	11.9	11.5	6.2	24.2	p=0.46*#	10.41	12.50	X^2= 0.69, p= 0.41
Impaired judgement/problem solving	2.7	3.4	1.5	3.0		1.58	1.56	
Visuo-spatial or perceptual impairment	0.0	0.0	0.0	0.0		0.95	0.31	
Impaired attention/concentration	0.0	0.0	0.0	0.0		5.99	8.75	
Impaired Orientation**	2.8	1.9	4.9	0.0		2.08	0.0	
Problems with community affairs**	0.9	1.9	0.0	0.0		1.04	0.6	
Problems at home or with hobbies**	0.0	0.0	0.0	0.0		1.04	1.23	
Impaired personal care**	0.0	0.0	0.0	0.0		0.52	0.0	
Person recognition difficulty**	0.0	0.0	0.0	0.0		1.04	3.07	
Impaired topographical memory**	0.0	0.0	0.0	0.0		2.60	2.45	
Bradyphrenia**	0.0	0.0	0.0	0.0		2.60	3.68	
Motor								
Dysarthria	0.5	1.1	0.0	0.0		0.63	0.94	
Dysphagia	0.5	1.1	0.0	0.0		1.26	0.94	

Tremor	0.5	1.1	0.0	0.0		2.21	5.63	
Slowness	0.0	0.0	0.0	0.0		0.32	1.56	
Weakness	2.2	4.6	0.0	0.0		0.63	0.00	
Gait disorder	1.1	2.3	0.0	0.0		0.32	0.94	
Falls	0.0	0.0	0.0	0.0		0.00	0.63	
Functional Difficulties using hands**	2.8	3.8	0.0	6.7		1.0	0.0	
Autonomic								
Impaired blood pressure**	0.0	0.0	0.0	0.0		5.73	4.29	
Gastrointestinal symptoms**	0.0	0.0	0.0	0.0		2.60	5.52	
Impaired thermoregulation**	0.0	0.0	0.0	0.0		4.17	5.52	
Urinary symptoms**	0.0	0.0	0.0	0.0		4.69	4.29	
Altered responsiveness to pain**	0.0	0.0	0.0	0.0		1.04	1.84	
Other Physical								
Altered perception to sounds or music**	0.0	0.0	0.0	0.0		0.52	1.84	
Altered perception of smell or taste**	0.0	0.0	0.0	0.0		2.1	2.5	

Persistent unexplained physical symptoms**	0.0	0.0	0.0	0.0		2.1	0.0	
Impaired breathing**	0.0	0.0	0.0	0.0		0.5	1.2	
Other Disorders								
Seizures	0.0	0.0	0.0	0.0		1.58	0.94	
Stroke or TIA	0.0	0.0	0.0	0.0		0.32	0.63	
Traumatic brain injury	0.0	0.0	0.0	0.0		9.46	11.56	
Hypertension	0.0	0.0	0.0	0.0		12.62	11.56	
Hypercholesterolaemia	0.0	0.0	0.0	0.0		9.78	11.56	
Diabetes mellitus	0.0	0.0	0.0	0.0		2.21	2.19	
Smoking**	0.0	0.0	0.0	0.0		27.08	34.97	
Excess alcohol use**	0.0	0.0	0.0	0.0		4.69	4.91	
Recreational drug use**	0.0	0.0	0.0	0.0		9.38	11.0	
Autoimmune disease**	0.0	0.0	0.0	0.0		5.73	6.75	

- **Indicates sub-symptoms collected using the modified GENFI symptom list (Symptomatic: N=109; Pre-symptomatic=192, Non-carriers N=163)
- *# Fisher's Exact Test was used as the expected count was less than 5

Table 3. Baseline symptom Endorsement on the GENFI symptom list (%) by gene mutation type in at-risk[t] family members

	C9orf72			*GRN*			*MAPT*		
	Pre-symptomatic (n=117)	**Non-carrier (n=115)**	**Contrast (test statistic, *p*-value)**	**Pre-symptomatic (n=144)**	**Non-carrier (n=144)**	**Contrast (test statistic, *p*-value)**	**Pre-symptomatic (n=56)**	**Non-carrier (n=61)**	**Contrast (test statistic, *p*-value)**
Sub-symptoms*									
Disinhibition	6.0	1.7	0.17[#]	2.1	2.1	1.00[#]	1.8	1.6	1.00[#]
Apathy	6.8	6.1	X^2=0.05, *p*=0.82	2.8	3.5	1.00[#]	1.8	3.3	1.00[#]
Decreased fluency	1.7	6.1	0.10[#]	2.8	0.7	0.37[#]	3.6	3.3	1.00[#]
Impaired articulation	1.7	0.9	1.00[#]	1.4	3.5	0.44[#]	1.8	0	0.48[#]
Memory impairment	13.7	13.9	X^2=0.002, *p*=0.96	8.3	11.8	X^2=0.96, *p*=0.33	8.9	11.5	X^2=0.21, *p*=0.65

- *Reflects the sub-symptoms that were most frequently endorsed as "first symptoms" by symptomatic patients
- [#] Fisher's Exact Test was used as the expected count was less than 5
- [t] At-risk: pre-symptomatic carriers and non-carriers

Table 4: CBI total and sub-scale scores at baseline and overtime for at-risk[ŧ] individuals

	Baseline[#]			Change Score		
	N	**Estimate (95% CI)**	***p*-value**	**N**	**Estimate (95% CI)**	***p*-value**
Total Score	588			336		
Pre-symptomatic		1.28 (0.84, 1.94)	0.26		0.35 (-0.63, 1.32)	0.49
YEO		1.02 (1, 1.03)	0.02		0.03 (-0.007, 0.07)	0.11
Baseline score		-	-		-0.15 (-0.21, -0.1)	<.0001
GS*YEO		1 (0.98, 1.03)	0.65		-0.01 (-0.06, 0.05)	0.85
Memory and Orientation	588			334		
Pre-symptomatic		0.94 (0.62, 1.44)	0.79		-0.02 (-0.25, 0.21)	0.85
YEO		1.03 (1.01, 1.04)	0.001		0.01 (0.002, 0.02)	0.02
Baseline score		-	-		-0.18 (-0.23, -0.13)	<.0001
GS*YEO		1 (0.97, 1.02)	0.73		-0.002 (-0.02, 0.01)	0.73
Everyday Skills	588			334		
Pre-symptomatic		0.74 (0.18, 3.11)	0.68		0.06 (0.01, 0.10)	0.01
YEO		1.03 (0.98, 1.09)	0.27		0.0005 (-0.001, 0.002)	0.52
Baseline score		-	-		-0.5 (-0.54, -0.46)	<.0001
GS*YEO		1 (0.92, 1.09)	0.92		0.001 (-0.001, 0.003)	0.35
Abnormal Behaviour	588			334		
Pre-symptomatic		1.62 (0.92, 2.85)	0.09		-0.03 (-0.19, 0.13)	0.71
YEO		1.00 (0.98, 1.02)	0.94		0.004 (-0.002, 0.01)	0.19
Baseline score		-	-		-0.23 (-0.28, -0.18)	<.0001
GS*YEO		1.01 (0.98, 1.04)	0.53		-0.006 (-0.01, 0.003)	0.21
Mood	588			334		
Pre-symptomatic		1.16 (0.74, 1.84)	0.51		0.17 (-0.07, 0.40)	0.16

YEO		1.01 (0.99, 1.03)	0.26		-0.002 (-0.01, 0.01)	0.7
Baseline score		-	-		-0.23 (-0.27, -0.18)	<.0001
GS*YEO		1 (0.97, 1.02)	0.67		-0.005 (-0.02, 0.008)	0.43
Beliefs	588			340		
Pre-symptomatic		0.66 (0.01, 30.74)	0.83		-0.006 (-0.01, 0.001)	0.11
YEO		0.96 (0.87, 1.07)	0.47		0.00008 (-0.0002, 0.0004)	0.6
Baseline score		-	-		-0.38 (-0.41, -0.34)	<.0001
GS*YEO		0.96 (0.8, 1.15)	0.65		-0.0002 (0.0006, 0.0003)	0.45
Eating habits	588			334		
Pre-symptomatic		0.97 (0.38, 2.45)	0.94		0.02 (-0.08, 0.11)	0.74
YEO		1.05 (1.01, 1.09)	0.01		0.003 (-0.0009, 0.006)	0.14
Baseline score		-	-		-0.31 (-0.35, -0.27)	<.0001
GS*YEO		0.98 (0.93, 1.03)	0.43		0.0002 (-0.01, 0.01)	0.93
Sleep	588			334		
Pre-symptomatic		1.61 (0.98, 2.65)	0.06		0.001 (-0.15, 0.16)	0.99
YEO		1.03 (1.01, 1.05)	0.01		-0.0009 (-0.007, 0.005)	0.76
Baseline score		-	-		-0.28 (-0.33, -0.22)	<.0001
GS*YEO		1.01 (0.98, 1.04)	0.49		-0.002 (-0.01, 0.007)	0.73
Stereotypic and motor behaviours				335		
Pre-symptomatic		1.55 (0.85, 2.83)	0.15		0.02 (-0.16, 0.19)	0.85
YEO		1.02 (1, 1.05)	0.06		0.008 (0.001, 0.01)	0.02
Baseline score		-	-		-0.31 (-0.37, -0.25)	<.0001
GS*YEO		1 (0.97, 1.04)	0.85		-0.002 (-0.01, 0.008)	0.68

Motivation	587			330		
Pre-symptomatic		1.79 (0.82, 3.91)	0.14		0.03 (-0.13, 0.20)	0.7
YEO		1.05 (1.01, 1.08)	0.004		0.002 (-0.005, 0.008)	0.59
Baseline score		-	-		-0.26 (-0.33, -0.19)	<.0001
GS*YEO		0.98 (0.94, 1.02)	0.3		0.003 (-0.006, 0.01)	0.51

- Statistics are from the Solution for Fixed Effects Table
- [#]Baseline data was modeled with a negative binomial distribution with a log link function. Estimates and confidence intervals of fixed effects are exponentiated (base e) and indicate the incident rates. Estimates below 1 indicate an inverse relationship between the variable and outcome
- [t] At-risk: pre-symptomatic carriers and non-carriers No participants endorsed self-care symptoms at baseline and only 1 non-carrier endorsed a change in self-care symptoms.
- GS= genetic status; YEO=Years from expected symptom onset; CI=confidence interval; GS*EYO= genetic status by estimated years to onset interaction
- For the main effect of genetic status and GS*EYO interaction= reference group are the non-carriers

Table 5: CBI total and sub-scale scores at baseline and over time for at-risk family members by genetic group (no outliers included)

	Baseline[#]			Change Score		
	N	**Estimate (95% CI)**	***p*-value**	**N**	**Estimate (95% CI)**	***p*-value**
Total Score	588			336		
C9orf72	104	1.34 (0.78, 2.31)	0.29		0.28 (-1.42, 1.97)	0.75
GRN	138	0.95 (0.52, 1.73)	0.86		0.38 (-0.8, 1.56)	0.53
MAPT	52	1.96 (0.88, 4.38)	0.1		0.39 (-1.37, 2.15)	0.66
YEO		1.02 (1, 1.03)	0.02		0.03 (-0.01, 0.07)	0.11
Baseline score		-	-		-0.15 (-0.21, -0.1)	<.0001
***C9orf72**YEO**		1 (0.98, 1.03)	0.8		0.01 (-0.08, 0.11)	0.78
***GRN**YEO**		1 (0.97, 1.03)	0.87		-0.02 (-0.08, 0.05)	0.63
***MAPT**YEO**		1 (0.96, 1.05)	0.85		-0.01 (-0.12, 0.1)	0.86
Memory and Orientation	588			334		
C9orf72	104	0.88 (0.51, 1.52)	0.65	49	-0.02 (-0.41, 0.37)	0.92
GRN	138	1.03 (0.56, 1.89)	0.92	85	-0.03 (-0.3, 0.25)	0.85
MAPT	52	0.89 (0.39, 2.03)	0.78	33	-0.01 (-0.42, 0.41)	0.98
YEO		1.03 (1.01, 1.04)	0.001		0.01 (0.002, 0.02)	0.02
Baseline score		-	-		-0.18 (-0.23, -0.13)	<.0001
***C9orf72**YEO**		0.98 (0.96, 1.01)	0.29		-0.003 (-0.02, 0.02)	0.74
***GRN**YEO**		1.01 (0.98, 1.04)	0.47		-0.002 (-0.02, 0.01)	0.78
***MAPT**YEO**		0.99 (0.95, 1.03)	0.59		0.0003 (-0.02, 0.03)	0.98
Everyday Skills	588			335		
C9orf72	104	0.77 (0.09, 6.56)	0.81	50	0.07 (-0.01, 0.14)	0.09
GRN	138	0.71 (0.1, 4.92)	0.72	85	0.11 (0.05, 0.16)	0.0001

MAPT	52	1.08 (0.05, 22.27)	0.96	32	0.03 (-0.06, 0.11)	0.53
YEO		1.03 (0.97, 1.09)	0.34		0.001 (0, 0)	0.57
Baseline score		-	-		-0.5 (-0.55, -0.45)	<.0001
***C9orf72**YEO**		1 (0.89, 1.13)	0.96		0.003 (0, 0.01)	0.21
***GRN**YEO**		1.05 (0.93, 1.2)	0.42		0.003 (0, 0.01)	0.07
***MAPT**YEO**		0.96 (0.82, 1.11)	0.57		0.0002 (0, 0.01)	0.95
Abnormal Behaviour	588			334		
C9orf72	104	2.16 (1.09, 4.26)	0.03	48	-0.02 (-0.3, 0.25)	0.86
GRN	138	0.83 (0.36, 1.91)	0.67	86	-0.03 (-0.22, 0.15)	0.73
MAPT	52	2.07 (0.8, 5.38)	0.14	33	-0.02 (-0.3, 0.26)	0.89
YEO		1 (0.98, 1.02)	0.9		0.004 (0, 0.01)	0.19
Baseline score		-	-		-0.23 (-0.28, -0.18)	<.0001
***C9orf72**YEO**		1.02 (0.98, 1.06)	0.37		-0.006 (-0.02, 0.01)	0.47
***GRN**YEO**		1 (0.96, 1.04)	0.99		-0.007 (-0.02, 0)	0.23
***MAPT**YEO**		0.99 (0.95, 1.04)	0.77		-0.0033 (-0.02, 0.01)	0.71
Mood	587			334		
C9orf72	104	1.22 (0.7, 2.12)	0.49	49	-0.07 (-0.47, 0.34)	0.75
GRN	137	0.46 (0.23, 0.93)	0.03	84	0.18 (-0.11, 0.47)	0.2
MAPT	52	2.75 (1.29, 5.89)	0.01	33	0.38 (-0.05, 0.81)	0.08
YEO		1.01 (0.99, 1.03)	0.26		-0.002 (-0.01, 0.01)	0.7
Baseline score		-	-		-0.23 (-0.28, -0.18)	<.0001
***C9orf72**YEO**		1 (0.97, 1.03)	0.80		-0.018 (-0.04, 0)	0.11
***GRN**YEO**		0.97 (0.94, 1)	0.05		-0.003 (-0.02, 0.01)	0.73
***MAPT**YEO**		1.01 (0.97, 1.05)	0.58		0.0031 (-0.02, 0.03)	0.81
Beliefs				340		
C9orf72				49	-0.004 (-0.02, 0.01)	0.56

GRN				86	-0.01 (-0.02, 0.0014)	0.097
MAPT				33	-0.01 (-0.02, 0.01)	0.46
YEO					0.00007 (-0.0002, 0.0004)	0.62
Baseline score					-0.38 (-0.41, -0.34)	<.0001
***C9orf72**YEO**					-0.00017 (-0.0009, 0.0005)	0.64
***GRN**YEO**					-0.00017 (-0.0007, 0.0004)	0.52
***MAPT**YEO**					-0.0001 (-0.0009, 0.0007)	0.86
Eating habits	588			335		
C9orf72	104	0.61 (0.16, 2.32)	0.46	49	-0.02 (-0.2, 0.16)	0.83
GRN	138	1.57 (0.46, 5.39)	0.47	86	0 (-0.13, 0.1247)	0.99
MAPT	52	0.68 (0.1, 4.82)	0.70	32	0.1 (-0.09, 0.29)	0.29
YEO		1.05 (1.01, 1.09)	0.01		0.0041 (0.0001, 0.008)	0.04
Baseline score		-	-		-0.35 (-0.39, -0.31)	<.0001
***C9orf72**YEO**		0.96 (0.89, 1.03)	0.25		-0.006 (-0.02, 0.005)	0.28
***GRN**YEO**		1 (0.94, 1.07)	0.91		-0.00002 (-0.007, 0.007)	0.996
***MAPT**YEO**		0.95 (0.87, 1.05)	0.35		0.003 (-0.008, 0.01)	0.6
Sleep	588			334		
C9orf72	104	1.4 (0.75, 2.64)	0.29	49	-0.13 (-0.39, 0.13)	0.33
GRN	138	1.16 (0.56, 2.39)	0.68	86	0.05 (-0.14, 0.23)	0.62
MAPT	52	3.37 (1.46, 7.74)	0.004	32	0.02 (-0.26, 0.3)	0.89
YEO		1.03 (1.01, 1.05)	0.01		-0.0009 (-0.007, 0.005)	0.76

Baseline score		-	-		-0.28 (-0.33, -0.22)	<.0001
***C9orf72**YEO**		1.01 (0.97, 1.05)	0.56		-0.008 (-0.02, 0.006)	0.25
***GRN**YEO**		1 (0.96, 1.04)	0.86		0.003 (-0.008, 0.01)	0.63
***MAPT**YEO**		1.03 (0.98, 1.08)	0.26		-0.005 (-0.02, 0.01)	0.54
Stereotypic and motor behaviours	588			335		
C9orf72	104	2.15 (1.05, 4.39)	0.04[&]	49	-0.12 (-0.42, 0.18)	0.44
GRN	138	1.07 (0.46, 2.52)	0.87	86	0.08 (-0.13, 0.28)	0.47
MAPT	52	1 (0.31, 3.23)	0.999	32	0.002 (-0.31, 0.32)	0.99
YEO		1.02 (1, 1.05)	0.05		0.0079 (0.001, 0.01)	0.02
Baseline score		-	-		-0.3 (-0.37, -0.24)	<.0001
***C9orf72**YEO**		1.03 (0.98, 1.07)	0.23		-0.01 (-0.03, 0.007)	0.23
***GRN**YEO**		1 (0.96, 1.05)	0.96		0.0001 (-0.01, 0.01)	0.99
***MAPT**YEO**		0.94 (0.89, 1)	0.05		0.002 (-0.02, 0.02)	0.86
Motivation	587			330		
C9orf72	104	1.91 (0.72, 5.06)	0.19	49	0.093 (-0.19, 0.38)	0.52
GRN	138	0.93 (0.31, 2.75)	0.9	84	0.02 (-0.19, 0.22)	0.88
MAPT	52	3.68 (1, 13.52)	0.05[&]	31	0.0004 (-0.3, 0.3)	1
YEO		1.05 (1.02, 1.08)	0.003		0.002 (-0.0047, 0.008)	0.62
Baseline score		-	-		-0.26 (-0.33, -0.19)	<.0001
***C9orf72**YEO**		0.98 (0.93, 1.04)	0.51		0.005 (-0.0109, 0.02)	0.54
***GRN**YEO**		0.97 (0.92, 1.02)	0.26		0.006 (-0.0057, 0.02)	0.31
***MAPT**YEO**		0.97 (0.9, 1.04)	0.41		-0.006 (-0.0247, 0.01)	0.49

- Statistics are from the Solution for Fixed Effects Table

- [#]Baseline data was modeled with a negative binomial distribution with a log link function. Estimates and confidence intervals of fixed effects are exponentiated (base e) and indicate the incident rates. Estimates below 1 indicate an inverse relationship between the variable and outcome
- [&]Overall effect of genetic group was not statistically significant at $p<0.05$ (based on Type III Tests of Fixed Effects)
- The model could not be run on some subscales after outliers were removed due to low symptom endorsement. At baseline, for the self-care sub-scale, 3 participants (3 pre-symptomatic) had scores above zero after outliers were removed. At baseline, for the beliefs sub-scale, 4 participants (1 pre-symptomatic, 2 non-carrier) had scores above zero after outliers were removed. For the change score, for the self-care scale, 1 non-carrier endorsed a change in symptom.
- For the main effect of genetic group and Gene*EYO interaction= reference group are the non-carriers
- YEO= Years from estimated symptom onset; CI=confidence interval

Appendix

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