**e-Methods 1.0: GENFI Symptom Domains and Descriptions**

Based on novel findings in the FTD literature, 31 additional symptoms, as indicated by an asterisk, were included in March 2015 (modified symptom list; e-1.0). This symptom list was based on and adapted from a consortium of validated scales including the Clinical Dementia Rating Scale (CDR; [1], FTLD-CDR [2], Social Impairment Rating Scale [3], Neuropsychiatric Inventory [4], Frontal Behavioural Inventory [5], Progressive Aphasia Severity Scale [6], Progressive Supranuclear Palsy Rating Scale [7], and Autonomic Symptoms Questionnaire (used in [8]. Further information can be gathered from the GENFI assessment manuals; see http://genfi.org.uk/.

Behaviour Symptoms

(1) Disinhibition
(2) Apathy
(3) Loss of sympathy/empathy
(4) Ritualistic/compulsive behaviour
(5) Hyperorality and appetite changes
(6) Poor response to social/emotional cues*
(7) Inappropriate trusting behaviour*

Neuropsychiatric Symptoms

(1) Visual hallucinations
(2) Auditory hallucinations
(3) Tactile hallucinations
(4) Delusions
(5) Depression
(6) Anxiety
(7) Irritability/Lability*
(8) Agitation/Aggression*
(9) Euphoria/Elation*
(10) Aberrant motor behaviour*
(11) Hypersexuality*
(12) Hyperreligiosity*
(13) Impaired sleep*
(14) Altered sense of humour*

Language Symptoms

(1) Impaired articulation
(2) Decreased fluency
(3) Impaired grammar/syntax
(4) Impaired word retrieval
(5) Impaired speech repetition
(6) Impaired sentence comprehension
(7) Impaired single word comprehension
(8) Dyslexia
(9) Dysgraphia
(10) Impaired functional communication

Cognitive Symptoms

(1) Memory impairment
(2) Impaired orientation*
(3) Impaired judgement/problem-solving
(4) Problems with community affairs*
(5) Problems at home or with hobbies*
(6) Impaired personal care*
(7) Person recognition difficulty*
(8) Impaired topographical memory*
(9) Visuo-spatial or perceptual impairment
(10) Impaired attention/concentration
(11) Bradyphrenia*

Motor Symptoms
(1) Dysarthria
(2) Dysphagia
(3) Tremor
(4) Slowness
(5) Weakness
(6) Gait disorder
(7) Falls
(8) Functional difficulties using hands*

Autonomic Symptoms
(1) Impaired blood pressure*
(2) Gastrointestinal symptoms*
(3) Impaired thermoregulation*
(4) Urinary symptoms*
(5) Altered responsiveness to pain*

Other Physical Symptoms
(1) Altered perception of sounds or music*
(2) Altered perception of smell or taste*
(3) Persistent unexplained physical symptoms*
(4) Impaired breathing*

Clinical Features
(1) Seizures
(2) Stroke or TIA
(3) Traumatic brain injury
(4) Hypertension
(5) Hypercholesterolaemia
(6) Diabetes mellitus
(7) Smoking*
(8) Excess alcohol use*
(9) Recreational drug use*
(10) Autoimmune disease*

**Supplementary e-Results 2.0: Analysis of symptom endorsement in symptomatic patients who completed the different versions of the GENFI symptom list**

Summary of Results

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 e-1, e-2 and see detailed description of analysis below). 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.

Analysis

Of the symptomatic patients, 76 completed the original and 109 completed the modified GENFI symptom list. Disinhibition (Original: 38.8%; Modified: 4.6), apathy (Original: 28.9%; Modified: 19.3%), decreased fluency (Original: 7.9; Modified: 8.3%), impaired articulation (Original: 5.3%; Modified: 5.5%), memory impairment (Original: 5.3%; Modified: 16.5%) were the most commonly endorsed symptoms in both cohorts. Of note, 5.3% of the "original cohort" endorsed impaired word retrieval. Chi-squared tests or Fisher's exact tests were completed on each cohort to examine differences in symptom endorsement between the genetic groups.

*Original Cohort:* A greater proportion of *MAPT* carriers endorsed disinhibition relative to *C9orf72* and *GRN* carriers ($X^2$=11.1, $p$=0.004). Additionally, only *GRN* carriers endorsed impaired articulation (no *C9orf72* and *MAPT* carriers endorsed impaired articulation, though this contrast was only significant for *C9orf72* carriers [$p$=0.01, Fisher's]). No differences were found for apathy ($X^2$=2.2, $p$=0.3), decreased fluency ($p$=0.47, Fisher's), and memory impairment ($p$=0.27, Fisher's).

*Modified Cohort:* A greater proportion of *MAPT* carriers endorsed disinhibition ($p$=0.03, Fisher's) and memory impairments ($p$=0.04, Fisher's) more often than *C9orf72* and *GRN* carriers. Furthermore, *GRN* carriers endorsed decreased fluency more frequently relative to *C9orf72* and *MAPT* carriers ($p$<0.001, Fisher's). No differences were found for apathy ($p$=1.0, Fisher's) and impaired articulation ($p$=0.09, Fisher's).

Overall, the pattern of results across both cohorts were similar; both groups displayed the same predominant symptoms, and similar differences between the mutation groups. Although no significant group differences were found for impaired articulation in the "modified cohort," both "original" and "modified" cohorts demonstrated analogous pattern of results in which *GRN* carriers showed the highest endorsement (Original: *C9orf72*=0, *GRN*=~17%, *MAPT*=0; Modified: *C9orf72*: 2%, *GRN*=12%, *MAPT*=0). Additionally, in the "modified cohort", memory impairments occurred more frequently amongst the *MAPT* carriers and *GRN* carriers endorsed decreased fluency most often. Different disease subtypes (supplementary Table 1b) and increased samples size in the "modified cohort" (Original: N=76, Modified: N=109) and thus greater recruiting/testing sites and families, may have contributed to these slight differences. Importantly however, the inclusion of additional symptoms in the modified list did not detract reporting of symptoms found only in the original version.

Potential Limitation

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.

**Supplementary e-Methods 3.0: Analysis for CBI-R change score**

To improve the distribution of the residuals we attempted several statistical methods (see below). As the results of the total CBI-R change score were similar across these various techniques, we reported the results from the linear mixed model in the manuscript.

1. To improve the distribution of the residuals in the linear mixed model we included an additional fixed effect (gender) and weighted family membership. These additional predictors did not improve model fit and thus were not included in the current analysis to maintain a parsimonious model.
2. Additionally, we binned the change score into distinct categories (scores 0 or below were categorized as one group, and the remaining scores were grouped based on 20% intervals). Using these categories, we ran a general linear mixed model with multinominal distribution, and a zero inflated model with a random effect. None of these models ran successfully.
3. Using the 6 groups from above, we ran an ordinal regression (with random effects) but this model did not meet the assumption of proportionality. As well, we ran a logistic regression comparing each group to a reference group (no change or improvement in symptoms); the residuals did not improve.
4. Subsequently, we categorized the change score into two groups (group 1= participants whose symptoms deteriorated over time, group 2= participants who symptoms improved or did no change over time) and ran a general linear mixed model with a binary distribution and random effects. The residuals did not improve.

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**Table e-1 Symptom endorsement (%) for symptomatic patients who completed the different versions of the GENFI Symptom List**

| | Original GENFI symptom list | | | | GENFI modified GENFI symptom list | | | |
|---|---|---|---|---|---|---|---|---|
| | **Total (N=76)** | **C9orF72 (N=34)** | **GRN (N=24)** | **MAPT (N=18)** | **Total (N=109)** | **C9orF72 (N=53)** | **GRN (N=41)** | **MAPT (N=15)** |
| **Behavioural** | | | | | | | | |
| **Disinhibition** | 36.8 | 35.3 | 16.7 | 66.7 | 4.6 | 1.9 | 2.4 | 20.0 |
| **Apathy** | 28.9 | 29.4 | 37.5 | 16.7 | 19.3 | 18.9 | 19.5 | 20.0 |
| **Loss of sympathy/empathy** | 1.3 | 2.9 | 0.0 | 0.0 | 1.8 | 0.0 | 4.9 | 0.0 |
| **Ritualistic/compulsive behaviour** | 1.3 | 2.9 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Hyperorality and appetite changes** | 1.3 | 0.0 | 4.2 | 0.0 | 1.8 | 3.8 | 0.0 | 0.0 |
| **Poor response to social/emotional cues**** | | | | | 0.9 | 1.9 | 0.0 | 0.0 |
| **Inappropriate trusting behaviour**** | | | | | 0.9 | 1.9 | 0.0 | 0.0 |
| **Neuropsychiatric** | | | | | | | | |
| **Visual hallucinations** | 1.3 | 2.9 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Auditory hallucinations** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Tactile hallucinations** | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Delusions** | 0.0 | 0.0 | 0.0 | 0.0 | 1.8 | 1.9 | 2.4 | 0.0 |
| **Depression** | 2.6 | 0.0 | 8.3 | 0.0 | 3.7 | 3.8 | 2.4 | 6.7 |
| **Anxiety** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Irritability/Lability**** | | | | | 0.9 | 1.9 | 0.0 | 0.0 |
| **Agitation/Aggression**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Euphoria/Elation**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Aberrant motor behaviour**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |

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| | Original GENFI symptom list | | | | GENFI modified GENFI symptom list | | | |
|---|---|---|---|---|---|---|---|---|
| | **Total (N=76)** | **C9orF72 (N=34)** | **GRN (N=24)** | **MAPT (N=18)** | **Total (N=109)** | **C9orF72 (N=53)** | **GRN (N=41)** | **MAPT (N=15)** |
| **Hypersexuality**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Hyperreligiosity**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Impaired sleep**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Altered sense of humour**** | | | | | 0.9 | 1.9 | 0.0 | 0.0 |
| **Language** | | | | | | | | |
| **Impaired articulation** | 5.3 | 0.0 | 16.7 | 0.0 | 5.5 | 1.9 | 12.2 | 0.0 |
| **Decreased fluency** | 7.9 | 11.8 | 8.3 | 0.0 | 8.3 | 0.0 | 22.0 | 0.0 |
| **Impaired grammar/syntax** | 0.0 | 0.0 | 0.0 | 0.0 | 1.8 | 0.0 | 4.9 | 0.0 |
| **Impaired word retrieval** | 5.3 | 5.9 | 8.3 | 0.0 | 3.7 | 3.8 | 4.9 | 0.0 |
| **Impaired speech repetition** | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Impaired sentence comprehension** | 0.0 | 0.0 | 0.0 | 0.0 | 1.8 | 0.0 | 4.9 | 0.0 |
| **Impaired single word comprehension** | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Dyslexia** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Dysgraphia** | 0.0 | 0.0 | 0.0 | 0.0 | 1.8 | 1.9 | 2.4 | 0.0 |
| **Impaired functional communication** | 1.3 | 0.0 | 0.0 | 5.6 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Cognitive** | | | | | | | | |
| **Memory Impairment** | 5.3 | 5.9 | 0.0 | 11.1 | 16.5 | 15.1 | 9.8 | 40.0 |
| **Impaired judgement/pr** | 1.3 | 2.9 | 0.0 | 0.0 | 3.7 | 3.8 | 2.4 | 6.7 |

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| | Original GENFI symptom list | | | | GENFI modified GENFI symptom list | | | |
|---|---|---|---|---|---|---|---|---|
| | **Total (N=76)** | **C9orF72 (N=34)** | **GRN (N=24)** | **MAPT (N=18)** | **Total (N=109)** | **C9orF72 (N=53)** | **GRN (N=41)** | **MAPT (N=15)** |
| **oblem solving** | | | | | | | | |
| **Visuo-spatial or perceptual impairment** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Impaired attention/concentration** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Impaired Orientation**** | | | | | 2.8 | 1.9 | 4.9 | 0.0 |
| **Problems with community affairs**** | | | | | 0.9 | 1.9 | 0.0 | 0.0 |
| **Problems at home or with hobbies**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Impaired personal care**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Person recognition difficulty**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Impaired topographical memory**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Bradyphrenia **** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Motor** | | | | | | | | |
| **Dysarthria** | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Dysphagia** | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Tremor** | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 1.9 | 0.0 | 0.0 |
| **Slowness** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Weakness** | 0.0 | 0.0 | 0.0 | 0.0 | 3.7 | 7.5 | 0.0 | 0.0 |
| **Gait disorder** | 0.0 | 0.0 | 0.0 | 0.0 | 1.8 | 3.8 | 0.0 | 0.0 |
| **Falls** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Functional Difficulties using hands**** | | | | | 2.8 | 3.8 | 0.0 | 6.7 |
| **Autonomic** | | | | | | | | |
| **Impaired blood** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |

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| | Original GENFI symptom list | | | | GENFI modified GENFI symptom list | | | |
|---|---|---|---|---|---|---|---|---|
| | **Total (N=76)** | **C9orF72 (N=34)** | **GRN (N=24)** | **MAPT (N=18)** | **Total (N=109)** | **C9orF72 (N=53)** | **GRN (N=41)** | **MAPT (N=15)** |
| **pressure**** | | | | | | | | |
| **Gastrointestinal symptoms**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Impaired thermoregulation**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Urinary symptoms**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Altered responsiveness to pain**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Other Physical** | | | | | | | | |
| **Altered perception to sounds or music**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Altered perception of smell or taste**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Persistent unexplained physical symptoms**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Impaired breathing**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Other Disorders** | | | | | | | | |
| **Seizures** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Stroke or TIA** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Traumatic brain injury** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Hypertension** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Hypercholesterolaemia** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Diabetes mellitus** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Smoking**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |

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| | Original GENFI symptom list | | | | GENFI modified GENFI symptom list | | | |
|---|---|---|---|---|---|---|---|---|
| | **Total (N=76)** | **C9orF72 (N=34)** | **GRN (N=24)** | **MAPT (N=18)** | **Total (N=109)** | **C9orF72 (N=53)** | **GRN (N=41)** | **MAPT (N=15)** |
| **Excess alcohol use**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Recreational drug use**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |
| **Autoimmune disease**** | | | | | 0.0 | 0.0 | 0.0 | 0.0 |

**Table e-2 Demographic details for symptomatic patients completing different versions of the GENFI Symptom List**

| | Original Symptom List | Modified Symptom List |
|---|---|---|
| **N** | 76 | 109 |
| **Genotype** | | |
| **C9orF72** | 34 | 53 |
| **GRN** | 24 | 41 |
| **MAPT** | 18 | 15 |
| **Sex** | | |
| **Female** | 28 | 49 |
| **Male** | 48 | 60 |
| **Handedness** | | |
| **Right** | 71 | 103 |
| **Left** | 5 | 4 |
| **Ambidextrous** | 0 | 2 |
| **Diagnosis** | | |
| **Alzheimer's Disease** | 1 | 0 |
| **Amyotrophic lateral sclerosis (ALS)** | 0 | 6 |
| **Behavioural variant FTD** | 56 | 70 |
| **Corticobasal syndrome** | 1 | 2 |
| **Dementia-NOS** | 3 | 2 |
| **FTD-ALS** | 3 | 6 |
| **Other** | 0 | 2 |
| **Primary progressive aphasia** | 12 | 20 |
| **Progressive supranuclear palsy** | 0 | 1 |
| **Total number of families** | 68 | 103 |
| **Total number of sites** | 12 | 19 |
| **Age (SD)** | 62.9 (8.2) | 61.8 (8.8) |
| **Age of onset (SD)** | 58.3 (8.6) | 57.9 (8.9) |
| **Education, Yrs (SD)** | 12.0 (4.3) | 12.4 (3.7) |

**Table e-3. Baseline (N=588) and Change Score (N=336) for CBI-R Total Score with age substituted for Years to Expected Symptom Onset**

| | **Baseline[#]** | | **Change Score** | |
|---|---|---|---|---|
| | **Estimate (95% CI)** | ***p*-value** | **Estimate (95% CI)** | ***p*-value** |
| **Pre-symptomatic** | 1.48 (0.57, 3.85) | 0.42 | 1.76 (-0.92, 4.44) | 0.2 |
| **Age** | 1.02 (1, 1.03) | 0.02 | 0.046 (0.01, 0.08) | 0.01 |
| **Baseline Score** | - | - | -0.15 (-0.21, -0.1) | <.0001 |
| **GS*Age** | 0.99 (0.97, 1.02) | 0.63 | -0.028 (-0.08, 0.03) | 0.33 |
| **Random Effects** | **Estimate** | ***p*-value** | | |
| **Intercept (family)** | 1.36 | <.0001 | - | - |
| **Scale** | 0.32 | <.0001 | - | - |
| **Residual** | - | - | 10.12 | <.0001 |

- 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
- GS= genetic status; CI=confidence interval; GS*age= genetic status by age interaction
- For the main effect of genetic status and GS*age interaction= reference group are the non-carriers

**Table e-4. CBI-R total change score with outliers by genetic status and by genotype (N=342)**

| | Genotype | |
|---|---|---|
| | **Estimate (95% CI)** | ***p*-value** |
| ***C9orf72*** | -1.98 (-4.24, 0.27) | 0.08 |
| ***GRN*** | 0.39 (-1.20, 1.99) | 0.63 |
| ***MAPT*** | -0.12 (-2.5, 2.28) | 0.92 |
| **YEO** | 0.06 (0.01, 0.11) | 0.01 |
| **Baseline score** | -0.16 (-0.23, -0.09) | <.0001 |
| ***C9orf72**YEO** | -0.17 (-0.28, -0.05) | 0.0062 |
| ***GRN**YEO** | -0.03 (-0.12, 0.07) | 0.57 |
| ***MAPT**YEO** | -0.04 (-0.18, 0.11) | 0.59 |
| **Random Effects** | **Estimate** | **p-value** |
| **Family** | 0.51 | 0.30 |
| **Residual** | 18.7 | <0.001 |

- Statistics are from the Solution for Fixed Effects Table
- YEO= years from expected symptom onset; CI=confidence interval
- For the main effect of genotype and the genetic mutation*YEO interactions= reference group are the non-carriers

**Table e-5: Symptom endorsement (%) in symptomatic patients and at-risk family members (GENFI symptom list)**

| | Symptomatic Patients N=185 | | | | | Preclinical N=317 | Non-carrier N=320 | |
|---|---|---|---|---|---|---|---|---|
| | **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 | | 2.60 | 1.23 | |
| **Language** | | | | | | | | |
| **Impaired articulation** | 5.4 | 1.1 | 13.8 | 0.0 | $p$=0.001*# GRN > C9orf72 & MAPT | 1.58 | 1.88 | $X^2$= 0.08, $p$=0.77 |
| **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 | |
| **Clinical Features** | | | | | | | | |
| **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; Preclinical=192, Non-carriers N=163)
- *#Fisher's Exact Test was used as the expected count was less than 5

**Table e-6. Initial symptoms of symptomatic patients from the same family**

| Number of participants within each family | Gene | First symptoms reported | Congruency Score (%) |
|---|---|---|---|
| 2 | *GRN* | apathy (n=1), fluency (n=1) | 0 |
| 2 | *GRN* | apathy (n=1) & fluency (n=1) | 0 |
| 2 | *GRN* | apathy (n=1) & articulation (n=1) | 0 |
| 3 | *GRN* | apathy (n=2) & memory impairment (n=1) | 33 |
| 5 | *GRN* | apathy (n=1) & hyperorality and appetite change (n=1), depression (n=1) & articulation (n=2) | 10 |
| 3 | *C9orf72* | disinhibition (n=1) & depression (n=1) & tremor (n=1) | 0 |
| 2 | *C9orf72* | apathy (n=1) & fluency (n=1) | 0 |
| 2 | *C9orf72* | disinhibition (n=1) & memory impairment (n=1) | 0 |
| 2 | *C9orf72* | depression (n=1) & memory impairment (n=1) | 0 |
| 2 | *MAPT* | apathy (n=1) & memory impairment (n=1) | 0 |
| 2 | *MAPT* | disinhibition (n=2) | 100 |
| 2 | *MAPT* | memory (n=2) | 100 |
| 3 | *MAPT* | apathy (n=2) & impaired judgement/problem-solving (n=1) | 33 |
| 3 | *MAPT* | disinhibition (n=2) & depression (n=1) | 33 |

The average congruency score across the cohort was 19%. This was calculated as the number of congruent combinations divided by the number of possible pairwise combinations

**Table e-7. Initial symptoms of symptomatic patients with the same specific genotype**

| Gene | Gene Type | Number of participants | First Symptom Reported | Congruency Score (%) |
|---|---|---|---|---|
| *MAPT* | Q351R | 2 | memory impairment (n=2) | 100 |
| *MAPT* | G272V | 3 | disinhibition (n=2), depression (n=1) | 33 |
| *MAPT* | P301L | 7 | disinhibition (n=3), apathy (n=3), impaired judgement/problem solving (n=1) | 29 |
| *MAPT* | R406W | 7 | disinhibition (n=3), apathy (n=1), memory impairment (n=3) | 29 |
| *MAPT* | IVS10+16 | 9 | disinhibition (n=5), apathy (n=1), memory impairment (n=3) | 36 |
| *GRN* | C149fs | 2 | Disinhibition (n=1), impaired articulation (n=1) | 0 |
| *GRN* | G35fs | 2 | Apathy (n=1), decreased fluency (n=1) | 0 |
| *GRN* | Q130fs (388_391delCAGT) | 2 | Apathy (n=1), impaired grammar/syntax (n=1) | 0 |
| *GRN* | C31fs | 4 | Apathy (n=1), loss of sympathy/empathy (n=1), impaired articulation (n=1), decreased fluency (n=1) | 0 |
| *GRN* | S82fs | 5 | Apathy (n=1), hyperorality and appetite changes (n=1), depression (n=1), impaired articulation (n=2) | 10 |
| *GRN* | IVS7-1G>A | 8 | Apathy (n=2), loss of sympathy/empathy (n=1), decreased fluency (n=1), impaired word retrieval (n=1), impaired sentence completion (n=1), memory impairment (n=2) | 7 |
| *GRN* | T272fs | 24 | Disinhibition (n=1), apathy (n=10), impaired articulation (n=5), decreased fluency (n=4), impaired grammar/syntax (n=1), impaired word retrieval (n=1), dysgraphia (n=1), impaired judgement/problem solving (n=1) | 22 |

The average congruency score was 33% for *MAPT* and 20 for *GRN*. This was calculated as the number of congruent combinations divided by the number of possible pairwise combinations

**Table e-8. Baseline symptom endorsement on the GENFI symptom list (%) by gene mutation type in at-risk[t] family members**

| | *C9orf72* | | | *GRN* | | | *MAPT* | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Preclinical (n=117)** | **Non-carrier (n=115)** | **Contrast (test statistic, *p*-value)** | **Preclinical (n=144)** | **Non-carrier (n=144)** | **Contrast (test statistic, *p*-value)** | **Preclinical (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: preclinical carriers and non-carriers
- No differences were found between the preclinical mutation groups (Disinhibition: Fisher's Exact Test p=0.21; Apathy: Fisher's Exact Test, p=0.23; Memory $X^2$=2.14, p=0.4; Fluency: Fisher's Exact Test p=0.64; Articulation : Fisher's Exact Test p=1.0)

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**Table e-9. Symptom endorsement (%) between the first and final visit for at-risk individuals (GENFI symptom list)**

| | Pre-symptomatic Mutation Carriers | | | | | | Non-carriers | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total (N=196)** | **Mean time interval, Yrs (SD)** | **Mean YEO (SD)[#]** | ***C9orf72 (n=58)*** | ***GRN (n=95)*** | ***MAPT (n=43)*** | **Total (N=202)** | **Mean time interval, Yrs (SD)** | **Mean YEO (SD)[#]** | ***C9orf72 (n=62)*** | ***GRN (n=103)*** | ***MAPT (n=37)*** | **Group Contrasts** | **Genotype Contrasts** |
| **Disinhibition** | | | | | | | | | | | | | | |
| **No change** | 96.9 | 2.6 (1.3)<br>Min: 0.8<br>Max: 5.6 | -14.1 (11.2) | 98.3 | 96.8 | 95.3 | 98.0 | 2.5 (1.5)<br>Min: 0.8<br>Max: 5.6 | -11.6 (13.3) | 98.4 | 97.1 | 100 | *p*=0.8 | *C9orf72*: *p*=1.0 |
| **Increase symptom endorsement** | 2.0 | 2.4 (1.7)<br>Min: 0.9<br>Max: 4.5 | -7.4 (17.1) | 1.7 | 2.1 | 2.3 | 1.0 | 3.3 (1.7)<br>Min: 2.1<br>Max: 4.5 | -6.4 (21.4) | 1.6 | 1.0 | 0.0 | | *GRN:* *p*=0.847 |
| **Decrease in symptom endorsement** | 1.0 | 3.4 (2.8)<br>Min: 1.4<br>Max: 5.4 | -0.8 (14.3) | 0.0 | 1.0 | 2.3 | 1.0 | 3.0 (2.7)<br>Min: 1.1<br>Max: 4.9 | -19.0 (1.0) | 0.0 | 1.9 | 0.0 | | *MAPT*: *p*=1.0 |
| **Apathy** | | | | | | | | | | | | | | |
| **No change** | 95.4 | 2.6 (1.3)<br>Min: 0.8<br>Max: 5.6 | -14.2 (11.2) | 94.8 | 95.8 | 95.3 | 95.5 | 2.5 (1.4)<br>Min: 0.8<br>Max: 5.6 | -11.7 (13.2) | 95.2 | 96.1 | 94.6 | *p*= 0.9 | *C9orf72*: *p*=1.0 |
| **Increase symptom endorsement** | 2.0 | 3.4 (1.8)<br>Min: 1.7<br>Max: 5.2 | -1.0 (11.9) | 0.0 | 3.2 | 2.3 | 2.5 | 3.5 (2.3)<br>Min: 1.0<br>Max: 5.6 | 0.6 (13.46) | 0.0 | 2.9 | 5.4 | | *GRN:* *p*=1.0 |
| **Decrease in symptom endorsement** | 2.6 | 3.1 (1.8)<br>Min: 1.1<br>Max: 5.0 | -9.2 (12.5) | 5.2 | 1.1 | 2.3 | 2.0 | 2.1 (1.9)<br>Min: 1.0<br>Max: 4.9 | -21.9 (3.4) | 4.8 | 1.0 | 0.0 | | *MAPT*: *p*=0.8 |
| **Decreased fluency** | | | | | | | | | | | | | | |
| **No change** | 96.4 | 2.6 (1.4)<br>Min: 0.8<br>Max: 5.6 | -13.9 (11.4) | 98.3 | 97.9 | 90.7 | 96.5 | 2.5 (1.5)<br>Min: 0.78<br>Max: 5.6 | -11.9 (13.3) | 95.2 | 96.1 | 100 | *p*=0.9 | *C9orf72*: *p*=0.746319 |
| **Increase symptom endorsement** | 2.6 | 1.8 (1.0)<br>Min: 0.9<br>Max: 3.3 | -17.7 (7.0) | 1.7 | 2.1 | 4.7 | 2.0 | 1.0 (0.1)<br>Min: 1.0<br>Max: 1.1 | -1.4 (10.3) | 1.6 | 2.9 | 0.0 | | *GRN:* *p*=1.0 |
| **Decrease in symptom endorsement** | 1.0 | 2.2 (1.2)<br>Min: 1.4<br>Max: 3.1 | 0.2 (12.8) | 0.0 | 0.0 | 4.7 | 1.5 | 3.2 (2.0)<br>Min: 1.0<br>Max: 4.9 | -7.4 (10.2) | 3.2 | 1.0 | 0.0 | | *MAPT*: *p*=0.247 |
| **Memory impairments** | | | | | | | | | | | | | | |
| **No change** | 85.7 | 2.6(1.3)<br>Min: 0.9<br>Max: 5.4 | -14.0 (11.0) | 86.2 | 87.4 | 81.4 | 85.1 | 2.5 (1.5)<br>Min: 0.8<br>Max: 5.6 | -12.6 (12.5) | 82.3 | 85.4 | 89.2 | $X^2$=0.7, *p*=0.7 | *C9orf72*: *p*=0.5 |
| **Increase** | 8.7 | 3.0 (1.8) | -11.6 | 10.3 | 6.3 | 11.6 | 7.4 | 2.7 (1.8) | -4.2 (14.8) | 8.1 | 6.8 | 8.1 | | *GRN:* |

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| | Pre-symptomatic Mutation Carriers | | | | | | Non-carriers | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total (N=196)** | **Mean time interval, Yrs (SD)** | **Mean YEO (SD)#** | ***C9orf72 (n=58)*** | ***GRN (n=95)*** | ***MAPT (n=43)*** | **Total (N=202)** | **Mean time interval, Yrs (SD)** | **Mean YEO (SD)#** | ***C9orf72 (n=62)*** | ***GRN (n=103)*** | ***MAPT (n=37)*** | **Group Contrasts** | **Genotype Contrasts** |
| **symptom endorsement** | | Min: 0.8<br>Max: 5.56 | (14.2) | | | | | Min: 0.9<br>Max: 5.6 | | | | | | $X^2$=0.2, *p*=0.9 |
| **Decrease in symptom endorsement** | 5.6 | 3.0 (2.0)<br>Min: 1.0<br>Max: 5.5 | -13.9 (13.1) | 3.4 | 6.3 | 7.0 | 7.4 | 2.1 (1.5)<br>Min: 1.0<br>Max: 5.3 | -7.9 (17.3) | 9.7 | 7.8 | 2.7 | | *MAPT*: *p*=0.7 |
| **Articulation Impairments** | | | | | | | | | | | | | | |
| **No change** | 96.9 | 2.6 (1.4)<br>Min: 0.8<br>Max: 5.6 | -14.0 (11.3) | 98.3 | 95.8 | 97.7 | 96.5 | 2.5 (1.5)<br>Min: 0.8<br>Max: 5.6 | -11.5 (13.2) | 100 | 93.2 | 100 | *p*= 0.7 | *C9orf72*: *p*=0.483 |
| **Increase symptom endorsement** | 2.6 | 2.8 (1.7)<br>Min: 1.0<br>Max: 5.5 | -5.8 (13.9) | 1.7 | 3.2 | 2.3 | 2.0 | 2.8 (2.1)<br>Min: 1.0<br>Max: 4.9 | -4.6 (14.7) | 0.0 | 3.9 | 0.0 | | *GRN:* *p*=0.791 |
| **Decrease in symptom endorsement** | 0.5 | -- | -- | 0.0 | 1.1 | 0.0 | 1.5 | 1.3 (0.4)<br>Min: 1.<br>Max: 1.7 | -27.3 (5.4) | 0.0 | 2.9 | 0.0 | | *MAPT*: *p*=1.0 |

- Number of participants for each maximum visit: Maximum of 2 visits: N=178 (n=80 pre-symptomatic; n=98 non-carrier); Maximum of 3 visits: N=130 (n=72 pre-symptomatic; 58 non-carriers); Maximum of 4 visits: N=57 (n=30 pre-symptomatic; 27 non-carriers); Maximum of 5 visits: N=25 (n=10 pre-symptomatic; n=15 non-carriers); Maximum of 6 visits: N= 8 (n=4 pre-symptomatic; n=4 non-carriers)
- *Sub-symptoms are coded as 0=no change in symptom endorsement, 1=increase in symptom endorsement, -1 decrease in symptom endorsement
- #YEO=Years from expected symptom onset. Values represent estimates from the initial visit. Mean YEO is only reported for categories where n>1 to prevent disclosure of genetic status

**Table e-10: Sensitivity and Specificity Scores (%) for Gene Composite Indices**

| | C9orf72/MAPT Composite Index | | GRN Composite Index | |
|---|---|---|---|---|
| **Gene Group** | **Sensitivity (95% CI)** | **Specificity (95% CI)** | **Sensitivity (95% CI)** | **Specificity (95% CI)** |
| *Symptomatic vs. Non-carrier | | | | |
| *C9orf72* | 96.4 (89.9-99.3) | 80.4 (71.4-87.6) | 89.3 (80.6-95.0) | 91.2 (83.9-95.9) |
| *GRN* | 96.6 (88.1-99.6) | 80.4 (71.4-87.6) | 98.3 (90.8-100.0) | 91.2 (83.9-95.9) |
| *MAPT* | 93.6 (78.6-99.2) | 80.4 (71.4-87.6) | 80.7 (62.5-92.6) | 91.2 (83.9-95.9) |
| **Preclinical vs. Non-carriers (Beginning -5 years of expected symptom onset) | | | | |
| *C9orf72* | 20.0 (6.8 - 40.7) | 80.4 (71.4 - 87.6) | 12.0 (2.6 - 31.2) | 91.2 (83.9 - 95.9) |
| *GRN* | 14.3 (4.8 - 30.3) | 80.4 (71.4 - 87.6) | 8.6 (1.8 - 23.1) | 91.2 (83.9 - 95.9) |
| *MAPT* | 18.2 (2.3 - 51.8) | 80.4 (71.4 - 87.6) | 9.1 (0.2 - 41.3) | 91.2 (83.9 - 95.9) |
| ^Preclinical vs. Non-carriers (Beginning -2 years of expected symptom onset) | | | | |
| *C9orf72* | 20.0 (4.3 - 48.1) | 78.4 (67.3 - 87.1) | 13.3 (1.7 - 40.5) | 90.5 (81.5 - 96.1) |
| *GRN* | 15.4 (4.4 - 34.9) | 78.4 (67.3 - 87.1) | 11.5 (2.5 - 30.2) | 90.5 (81.5 - 96.1) |
| *MAPT* | 28.6 (3.7 - 71.0) | 78.4 (67.3 - 87.1) | 14.3 (0.4 - 57.9) | 90.5 (81.5 - 96.1) |
| ^^Preclinical vs. Non-carriers (Beginning 0 years of expected symptom onset) | | | | |
| *C9orf72* | 23.1 (5.0 - 53.8) | 76.2 (63.8 - 86.0) | 15.4 (1.9 - 45.5) | 90.5 (80.4 - 96.4) |
| *GRN* | 22.2 (6.4 - 47.6) | 76.2 (63.8 - 86.0) | 16.7 (3.6 - 41.4) | 90.5 (80.4 - 96.4) |
| *MAPT* | 33.3 (4.3 - 77.7) | 76.2 (63.8 - 86.0) | 16.7 (0.4-64.1) | 90.5 (80.4 - 96.4) |

*As symptomatic carriers were older than non-carriers the following comparison only includes non-carriers who were at least -5 years from symptom onset. Symptomatic carriers: *C9orf92*: n=84, *GRN*: n=58, *MAPT*: n=31; *Non-carriers* n=102

**Preclinical: *C9orf92*: n=25, *GRN*: n=35, *MAPT*: n=11; *Non-carriers* n=102

^Preclinical: *C9orf92*: n=15, *GRN*: n=26, *MAPT*: n=7; *Non-carriers* n=74

^^Preclinical: *C9orf92*: n=13, *GRN*: n=18, *MAPT*: n=6; *Non-carriers* n=63

CI= 95% confidence intervals

**Table e-11: Mean (SD) Composite Scores for At-Risk Groups**

| | C9orf72/MAPT Composite Index | | GRN Composite Index | |
|---|---|---|---|---|
| | **Preclinical** | **Non-carrier** | **Preclinical** | **Non-carrier** |
| At-risk from -5 years to expected onset | | | | |
| *C9orf72* | 0.2 (0.5) | 0.3 (0.6) | 0.2 (0.5) | 0.1 (0.5) |
| *GRN* | 0.2 (0.5) | | 0.1 (0.6) | |
| *MAPT* | 0.3 (0.6) | | 0.2 (0.6) | |
| At-risk from -2 years to expected onset | | | | |
| *C9orf72* | 0.3 (0.6) | 0.3 (0.7) | 0.2 (0.6) | 0.1 (0.5) |
| *GRN* | 0.2 (0.5) | | 0.2 (0.36) | |
| *MAPT* | 0.4 (0.8) | | 0.3 (0.8) | |
| At-risk from -0 years to expected onset | | | | |
| *C9orf72* | 0.3 (0.6) | 0.3 (0.7) | 0.2 (0.6) | 0.1 (0.5) |
| *GRN* | 0.3 (0.6) | | 0.3 (0.8) | |
| *MAPT* | 0.5 (0.8) | | 0.3 (0.8) | |

Only one symptom was selected as the initial symptom for affected patients

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