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.

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

	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

	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

	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

	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)

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) Min: 0.8 Max: 5.6	-14.1 (11.2)	98.3	96.8	95.3	98.0	2.5 (1.5) Min: 0.8 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) Min: 0.9 Max: 4.5	-7.4 (17.1)	1.7	2.1	2.3	1.0	3.3 (1.7) Min: 2.1 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) Min: 1.4 Max: 5.4	-0.8 (14.3)	0.0	1.0	2.3	1.0	3.0 (2.7) Min: 1.1 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) Min: 0.8 Max: 5.6	-14.2 (11.2)	94.8	95.8	95.3	95.5	2.5 (1.4) Min: 0.8 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) Min: 1.7 Max: 5.2	-1.0 (11.9)	0.0	3.2	2.3	2.5	3.5 (2.3) Min: 1.0 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) Min: 1.1 Max: 5.0	-9.2 (12.5)	5.2	1.1	2.3	2.0	2.1 (1.9) Min: 1.0 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) Min: 0.8 Max: 5.6	-13.9 (11.4)	98.3	97.9	90.7	96.5	2.5 (1.5) Min: 0.78 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) Min: 0.9 Max: 3.3	-17.7 (7.0)	1.7	2.1	4.7	2.0	1.0 (0.1) Min: 1.0 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) Min: 1.4 Max: 3.1	0.2 (12.8)	0.0	0.0	4.7	1.5	3.2 (2.0) Min: 1.0 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) Min: 0.9 Max: 5.4	-14.0 (11.0)	86.2	87.4	81.4	85.1	2.5 (1.5) Min: 0.8 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:*

	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 Max: 5.56	(14.2)					Min: 0.9 Max: 5.6						X^2=0.2, *p*=0.9
Decrease in symptom endorsement	5.6	3.0 (2.0) Min: 1.0 Max: 5.5	-13.9 (13.1)	3.4	6.3	7.0	7.4	2.1 (1.5) Min: 1.0 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) Min: 0.8 Max: 5.6	-14.0 (11.3)	98.3	95.8	97.7	96.5	2.5 (1.5) Min: 0.8 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) Min: 1.0 Max: 5.5	-5.8 (13.9)	1.7	3.2	2.3	2.0	2.8 (2.1) Min: 1.0 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) Min: 1. 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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