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Supplemental information

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Supplemental figure

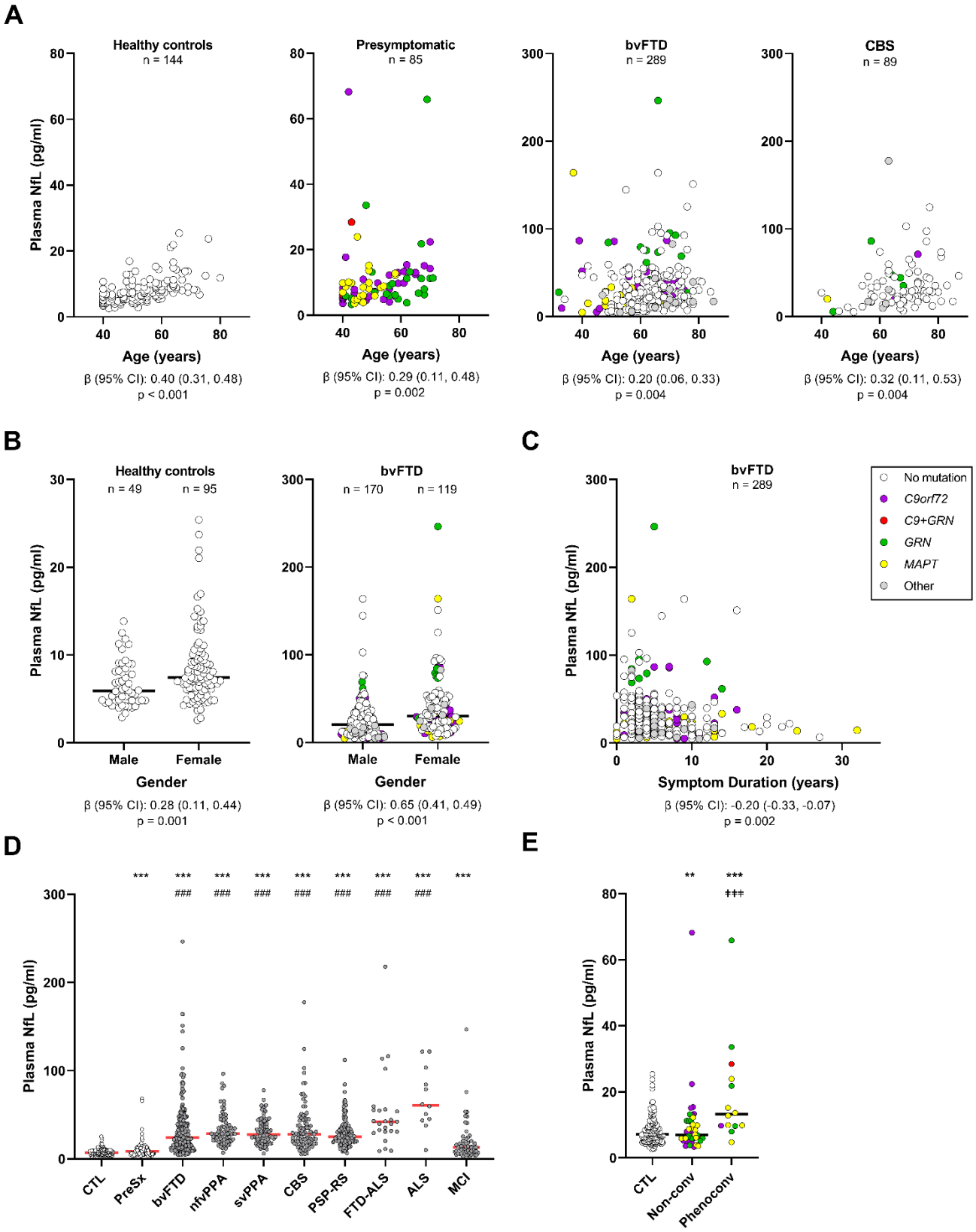

Figure S1. Plasma NfL associates with age, gender and symptom duration in some phenotype groups, and is elevated in presymptomatic mutation carriers and symptomatic groups, Related to Figures 2A and 2B, and to Tables S3–S5 and S7. (**A-C**) Associations of baseline NfL concentrations (the mean of duplicate measures) with age (**A**), gender (**B**) and symptom duration (**C**) were assessed using linear regression models adjusted for age, gender and symptom duration. β coefficients (β), 95% confidence intervals (95% CI) and p values are shown for significant associations. Grey circles represent 11 bvFTD patients and five CBS patients with unknown mutation status, one bvFTD patient with a likely pathogenic *GRN* variant and three with a *TARDBP* mutation, and one CBS patient with an intermediate *C9orf72* repeat expansion. See **Figure 1** to view NfL concentrations on the base 10 logarithm scale and see **Table S2**. (**D, E**) Comparison of baseline plasma NfL between healthy controls or presymptomatic mutation carriers and symptomatic groups (**D**), and between presymptomatic carriers who phenoconverted to controls or to presymptomatic carriers who remained asymptomatic for at least one year (**E**). p values are from analysis adjusted for age and gender. ***$p < 0.001$ and **$p < 0.01$, comparison to controls; $^{###}p < 0.001$ comparison to presymptomatic carriers; $^{\#\#}p < 0.001$, comparison to presymptomatic non-converters. Horizontal bars represent median NfL concentrations. See Figures 2A and 2B to view NfL concentrations on the base 10 logarithm scale, and see Tables S3–S5, S7.

Supplemental tables

Table S1: Breakdown of baseline and longitudinal plasma NfL measures and rates of NfL change in phenotype groups, Related to Table 1

Phenotype group	Number of individuals with baseline plasma NfL	Number of individuals with longitudinal plasma samples	Number of individuals for whom rates of NfL change could be calculated[4]
Controls	144	79	69
All presymptomatic mutation carriers	85	58	52
Non-converters[1]	43	35	35
Phenoconverters[2]	14	14	14
Unknown conversion status[3]	28	9	3
bvFTD	289	39	35
nfvPPA	72	10	7
svPPA	84	2	2
CBS	89	14	6
PSP-RS	124	10	3
MCI	57	18	18

[1]Non-converters were presymptomatic at baseline and known to have remained asymptomatic for at least one year from baseline. [2]Phenoconverters were presymptomatic at baseline but subsequently diagnosed as symptomatic at a later visit. Presymptomatic phenoconverters were comprised of one individual with a *C9orf72* mutation who developed MCI, one with both a *C9orf72* and *GRN* mutation diagnosed with nfvPPA at follow-up, five with a *GRN* mutation and seven with a *MAPT* mutation. All *GRN* mutation carriers phenoconverted to MCI with two patients subsequently developing bvFTD. Four *MAPT* mutation carriers were later diagnosed with MCI, two with bvFTD and one with Parkinson's disease. [3]The 28 presymptomatic individuals with an unknown conversion status had insufficient follow-up data to be categorized as a non-converter or a phenoconverter. [4]Rates of NfL change per year were calculated only for individuals with one or more NfL measurements at least one year from the baseline NfL measurement. See also Table 1.

Table S2: Associations of baseline NfL with age, gender and symptom duration in phenotype groups, Related to Figures 1A–C and Figures S1A–C

Phenotype group/association	β (95% CI)	p value
Controls (n = 144)		
Association with age (per 10 year increase)	0.40 (0.31, 0.48)	**<0.001**
Association with gender (males vs. females)	0.28 (0.11, 0.44)	**0.001**
Presymptomatic mutation carriers (n = 85)		
Association with age (per 10 year increase)	0.29 (0.11, 0.48)	**0.002**
Association with gender (males vs. females)	0.32 (-0.03, 0.67)	0.073
bvFTD patients (n = 289)		
Association with age (per 10 year increase)	0.20 (0.06, 0.33)	**0.004**
Association with gender (males vs. females)	0.65 (0.41, 0.89)	**<0.001**
Association with symptom duration (per 5 year increase)	-0.20 (-0.33, -0.07)	**0.002**
nfvPPA patients (n = 71)		
Association with age (per 10 year increase)	0.03 (-0.19, 0.25)	0.78
Association with gender (males vs. females)	0.38 (0.02, 0.74)	0.038
Association with symptom duration (per 5 year increase)	-0.18 (-0.56, 0.21)	0.36
svPPA patients (n = 84)		
Association with age (per 10 year increase)	0.22 (0.00, 0.43)	0.048
Association with gender (males vs. females)	0.14 (-0.16, 0.43)	0.36
Association with symptom duration (per 5 year increase)	-0.15 (-0.33, 0.02)	0.086
CBS patients (n = 89)		
Association with age (per 10 year increase)	0.32 (0.11, 0.53)	**0.004**
Association with gender (males vs. females)	0.10 (-0.31, 0.52)	0.62
Association with symptom duration (per 5 year increase)	0.07 (-0.15, 0.29)	0.51
PSP-RS patients (n = 124)		
Association with age (per 10 year increase)	0.03 (-0.16, 0.23)	0.75
Association with gender (males vs. females)	0.27 (0.00, 0.54)	0.049
Association with symptom duration (per 5 year increase)	-0.05 (-0.25, 0.16)	0.65
FTD/ALS patients (n = 23)		
Association with age (per 10 year increase)	0.11 (-0.39, 0.61)	0.65
Association with gender (males vs. females)	0.35 (-0.42, 1.13)	0.35
Association with symptom duration (per 5 year increase)	-0.54 (-1.08, 0.01)	0.053
ALS patients (n = 12)		
Association with age (per 10 year increase)	0.11 (-1.12, 1.33)	0.85
Association with gender (males vs. females)	-0.88 (-2.46, 0.70)	0.24
Association with symptom duration (per 5 year increase)	-0.51 (-1.91, 0.88)	0.42
MCI patients (n = 55)		
Association with age (per 10 year increase)	0.33 (0.07, 0.59)	**0.013**
Association with gender (males vs. females)	0.30 (-0.28, 0.88)	0.30
Association with symptom duration (per 5 year increase)	-0.01 (-0.15, 0.14)	0.94

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models that were adjusted for age, gender and symptom duration (only in patients). β values are interpreted as the change in mean NfL concentration (on the base-2 logarithm scale) corresponding to the increase given in parenthesis (for age and symptom duration) or for females in comparison to males (for gender). p values < 0.025 (controls and presymptomatic mutation carriers) or p values <0.0167 (all symptomatic groups) are considered statistically significant after correcting for multiple testing. See also Figures 1A–C and Figures S1A–C.

Table S3: Comparisons of baseline NfL concentrations between controls or presymptomatic mutation carriers and phenotype groups, Related to Figures 2A, 2D and S1D

			Unadjusted analysis		Adjusting for age and gender		AUC (95% CI)	
Phenotype group	n	Median (min, max) NfL concentration (pg/ml)	β (95% CI)	p value	β (95% CI)	p value	Unadjusted analysis	Adjusting for age and gender
Controls	144	7.1 (2.6, 25.4)	0.00 (reference)	N/A	0.00 (reference)	N/A	N/A	N/A
Presymptomatic	85	8.3 (3.3, 68.2)	0.25 (0.06, 0.45)	0.010	0.35 (0.18, 0.52)	**<0.001**	0.58 (0.50, 0.66)	0.64 (0.56, 0.72)
bvFTD	289	24.2 (4.7, 246.4)	1.71 (1.52, 1.90)	**<0.001**	1.64 (1.43, 1.84)	**<0.001**	0.92 (0.89, 0.94)	0.85 (0.82, 0.88)
nfvPPA	72	28.7 (7.1, 96.5)	2.05 (1.86, 2.24)	**<0.001**	1.64 (1.42, 1.85)	**<0.001**	0.98 (0.96, 1.00)	0.87 (0.82, 0.93)
svPPA	84	27.6 (6.0, 77.7)	1.94 (1.76, 2.11)	**<0.001**	1.53 (1.34, 1.72)	**<0.001**	0.98 (0.96, 1.00)	0.89 (0.85, 0.94)
CBS	89	28.1 (5.3, 177.6)	1.93 (1.72, 2.14)	**<0.001**	1.46 (1.23, 1.69)	**<0.001**	0.95 (0.91, 0.98)	0.84 (0.78, 0.89)
PSP-RS	124	25.3 (6.6, 112.0)	1.83 (1.67, 1.99)	**<0.001**	1.46 (1.25, 1.66)	**<0.001**	0.97 (0.95, 0.99)	0.82 (0.77, 0.87)
FTD/ALS	25	42.3 (8.9, 217.9)	2.48 (2.18, 2.78)	**<0.001**	2.31 (2.03, 2.60)	**<0.001**	0.97 (0.94, 1.00)	0.97 (0.95, 1.00)
ALS	12	60.8 (10.0, 121.7)	2.99 (2.60, 3.38)	**<0.001**	2.77 (2.43, 3.10)	**<0.001**	0.98 (0.95, 1.02)	0.97 (0.90, 1.03)
MCI	57	12.9 (2.7, 146.8)	0.83 (0.58, 1.09)	**<0.001**	0.66 (0.42, 0.89)	**<0.001**	0.72 (0.63, 0.81)	0.68 (0.59, 0.78)
Presymptomatic	85	8.3 (3.3, 68.2)	0.00 (reference)	N/A	0.00 (reference)	N/A	N/A	N/A
bvFTD	289	24.2 (4.7, 246.4)	1.46 (1.21, 1.71)	**<0.001**	1.32 (1.06, 1.59)	**<0.001**	0.86 (0.81, 0.90)	0.74 (0.68, 0.80)
nfvPPA	72	28.7 (7.1, 96.5)	1.80 (1.54, 2.05)	**<0.001**	1.48 (1.14, 1.81)	**<0.001**	0.94 (0.90, 0.98)	0.75 (0.68, 0.83)
svPPA	84	27.6 (6.0, 77.7)	1.68 (1.44, 1.92)	**<0.001**	1.32 (1.02, 1.61)	**<0.001**	0.93 (0.89, 0.97)	0.78 (0.71, 0.86)
CBS	89	28.1 (5.3, 177.6)	1.68 (1.40, 1.96)	**<0.001**	1.21 (0.88, 1.55)	**<0.001**	0.90 (0.85, 0.95)	0.72 (0.65, 0.80)
PSP-RS	124	25.3 (6.6, 112.0)	1.58 (1.36, 1.79)	**<0.001**	1.29 (0.98, 1.59)	**<0.001**	0.92 (0.87, 0.96)	0.69 (0.62, 0.76)
FTD/ALS	25	42.3 (8.9, 217.9)	2.23 (1.82, 2.64)	**<0.001**	2.09 (1.65, 2.52)	**<0.001**	0.93 (0.87, 0.99)	0.91 (0.85, 0.97)
ALS	12	60.8 (10.0, 121.7)	2.74 (2.20, 3.27)	**<0.001**	2.53 (1.99, 3.08)	**<0.001**	0.96 (0.90, 1.02)	0.93 (0.83, 1.03)
MCI	57	12.9 (2.7, 146.8)	0.58 (0.24, 0.92)	**0.001**	0.35 (0.01, 0.68)	0.045	0.65 (0.55, 0.75)	0.57 (0.47, 0.68)

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models. β values are interpreted as the difference in the mean NfL concentration (on the base-2 logarithm scale) for the given phenotype group in comparison to controls or presymptomatic mutation carriers. p values < 0.0056 and < 0.0063 are considered statistically significant after correcting for the comparisons of NfL between controls and 9 different overall phenotype groups or presymptomatic mutation carriers and 8 different phenotype groups, respectively. AUC, area under the receiver operating characteristic curve. See also Figures 2A, 2D and S1D.

Table S4: Comparisons of baseline NfL concentrations between controls or presymptomatic mutation carriers and phenotype groups when stratifying by symptom duration, Related to Figures 2A, 2D and S1D

		Unadjusted analysis		Adjusting for age and gender		AUC (95% CI)	
Phenotype group	n	Median (min, max) NfL concentration (pg/ml)	β (95% CI)	p value	β (95% CI)	p value	Unadjusted analysis	Adjusting for age and gender
Controls	144	7.1 (2.6, 25.4)	0.00 (reference)	N/A	0.00 (reference)	N/A	N/A	N/A
bvFTD								
Symptom duration ≤5 years	186	26.9 (4.7, 246.4)	1.84 (1.64, 2.03)	**<0.001**	1.74 (1.54, 1.94)	**<0.001**	0.93 (0.90, 0.96)	0.89 (0.85, 0.92)
Symptom duration >5 years	103	20.4 (4.7, 163.9)	1.48 (1.27, 1.70)	**<0.001**	1.24 (1.00, 1.47)	**<0.001**	0.89 (0.85, 0.93)	0.78 (0.72, 0.84)
nfvPPA								
Symptom duration ≤5 years	55	30.6 (7.1, 96.5)	2.08 (1.86, 2.29)	**<0.001**	1.63 (1.40, 1.86)	**<0.001**	0.98 (0.96, 1.00)	0.86 (0.80, 0.93)
Symptom duration >5 years	17	28.4 (13.5, 43.9)	1.96 (1.66, 2.27)	**<0.001**	1.44 (1.15, 1.72)	**<0.001**	0.99 (0.98, 1.00)	0.90 (0.82, 0.98)
svPPA								
Symptom duration ≤5 years	42	26.4 (11.6, 60.6)	1.91 (1.70, 2.12)	**<0.001**	1.51 (1.31, 1.72)	**<0.001**	0.98 (0.97, 1.00)	0.92 (0.86, 0.97)
Symptom duration >5 years	42	30.2 (6.0, 77.7)	1.96 (1.73, 2.19)	**<0.001**	1.52 (1.29, 1.74)	**<0.001**	0.97 (0.93, 1.00)	0.87 (0.80, 0.95)
CBS								
Symptom duration ≤5 years	63	27.3 (5.3, 124.7)	1.91 (1.68, 2.14)	**<0.001**	1.41 (1.18, 1.64)	**<0.001**	0.94 (0.89, 0.98)	0.85 (0.79, 0.91)
Symptom duration >5 years	26	28.3 (9.2, 177.6)	1.99 (1.71, 2.28)	**<0.001**	1.49 (1.20, 1.79)	**<0.001**	0.97 (0.95, 1.00)	0.80 (0.69, 0.91)
PSP-RS								
Symptom duration ≤5 years	77	26.6 (6.6, 112.0)	1.90 (1.71, 2.09)	**<0.001**	1.45 (1.24, 1.66)	**<0.001**	0.97 (0.95, 0.99)	0.85 (0.80, 0.90)
Symptom duration >5 years	47	23.9 (8.8, 59.2)	1.72 (1.51, 1.93)	**<0.001**	1.24 (0.99, 1.48)	**<0.001**	0.97 (0.94, 0.99)	0.76 (0.68, 0.85)
FTD/ALS								
Symptom duration ≤5 years	19	42.6 (9.2, 217.9)	2.68 (2.35, 3.00)	**<0.001**	2.54 (2.24, 2.84)	**<0.001**	0.98 (0.96, 1.01)	0.98 (0.96, 1.01)
Symptom duration >5 years	6	38.8 (8.9, 54.9)	1.87 (1.34, 2.40)	**<0.001**	1.54 (1.12, 1.95)	**<0.001**	0.92 (0.82, 1.03)	0.94 (0.87, 1.02)
ALS								
Symptom duration ≤5 years	10	70.5 (10.0, 121.7)	3.05 (2.62, 3.47)	**<0.001**	2.82 (2.46, 3.18)	**<0.001**	0.98 (0.94, 1.02)	0.96 (0.88, 1.04)
Symptom duration >5 years	2	48.0 (45.2, 50.8)	2.72 (1.85, 3.59)	**<0.001**	2.50 (1.82, 3.19)	**<0.001**	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
MCI								
Symptom duration ≤5 years	45	10.9 (2.7, 146.8)	0.78 (0.50, 1.06)	**<0.001**	0.64 (0.40, 0.89)	**<0.001**	0.70 (0.59, 0.80)	0.66 (0.55, 0.77)
Symptom duration >5 years	12	13.7 (4.7, 53.3)	1.03 (0.64, 1.42)	**<0.001**	0.72 (0.39, 1.04)	**<0.001**	0.81 (0.66, 0.97)	0.75 (0.58, 0.93)
Presymptomatic	85	8.3 (3.3, 68.2)	0.00 (reference)	N/A	0.00 (reference)	N/A	N/A	N/A
bvFTD								
Symptom duration ≤5 years	186	26.9 (4.7, 246.4)	1.58 (1.32, 1.84)	**<0.001**	1.43 (1.15, 1.70)	**<0.001**	0.88 (0.83, 0.92)	0.79 (0.73, 0.84)
Symptom duration >5 years	103	20.4 (4.7, 163.9)	1.23 (0.95, 1.51)	**<0.001**	0.98 (0.65, 1.31)	**<0.001**	0.83 (0.77, 0.89)	0.66 (0.58, 0.74)
nfvPPA								
Symptom duration ≤5 years	55	30.6 (7.1, 96.5)	1.82 (1.53, 2.11)	**<0.001**	1.46 (1.10, 1.83)	**<0.001**	0.94 (0.89, 0.98)	0.75 (0.67, 0.84)
Symptom duration >5 years	17	28.4 (13.5, 43.9)	1.71 (1.28, 2.13)	**<0.001**	1.30 (0.80, 1.79)	**<0.001**	0.95 (0.91, 0.99)	0.77 (0.65, 0.88)
svPPA								
Symptom duration ≤5 years	42	26.4 (11.6, 60.6)	1.66 (1.36, 1.95)	**<0.001**	1.32 (0.98, 1.66)	**<0.001**	0.94 (0.90, 0.98)	0.81 (0.73, 0.89)

	Symptom duration >5 years	42	30.2 (6.0, 77.7)	1.71 (1.39, 2.02)	**<0.001**	1.29 (0.92, 1.66)	**<0.001**	0.93 (0.88, 0.98)	0.76 (0.67, 0.85)
CBS									
	Symptom duration ≤5 years	63	27.3 (5.3, 124.7)	1.65 (1.35, 1.96)	**<0.001**	1.15 (0.80, 1.50)	**<0.001**	0.89 (0.83, 0.95)	0.74 (0.66, 0.82)
	Symptom duration >5 years	26	28.3 (9.2, 177.6)	1.74 (1.35, 2.13)	**<0.001**	1.37 (0.88, 1.86)	**<0.001**	0.92 (0.87, 0.98)	0.69 (0.57, 0.81)
PSP-RS									
	Symptom duration ≤5 years	77	26.6 (6.6, 112.0)	1.64 (1.39, 1.90)	**<0.001**	1.23 (0.90, 1.56)	**<0.001**	0.92 (0.88, 0.97)	0.73 (0.65, 0.80)
	Symptom duration >5 years	47	23.9 (8.8, 59.2)	1.46 (1.18, 1.75)	**<0.001**	1.15 (0.74, 1.55)	**<0.001**	0.91 (0.86, 0.96)	0.63 (0.53, 0.73)
FTD/ALS									
	Symptom duration ≤5 years	19	42.6 (9.2, 217.9)	2.42 (1.97, 2.87)	**<0.001**	2.32 (1.86, 2.79)	**<0.001**	0.95 (0.90, 1.00)	0.93 (0.88, 0.99)
	Symptom duration >5 years	6	38.8 (8.9, 54.9)	1.62 (0.88, 2.35)	**<0.001**	1.28 (0.57, 1.99)	**<0.001**	0.86 (0.70, 1.02)	0.84 (0.70, 0.98)
ALS									
	Symptom duration ≤5 years	10	70.5 (10.0, 121.7)	2.79 (2.21, 3.38)	**<0.001**	2.58 (1.99, 3.17)	**<0.001**	0.96 (0.89, 1.02)	0.92 (0.80, 1.04)
	Symptom duration >5 years	2	48.0 (45.2, 50.8)	2.47 (1.25, 3.68)	**<0.001**	2.30 (1.12, 3.47)	**<0.001**	0.98 (0.94, 1.01)	0.97 (0.92, 1.02)
MCI									
	Symptom duration ≤5 years	45	10.9 (2.7, 146.8)	0.53 (0.16, 0.89)	0.006	0.33 (-0.03, 0.69)	0.072	0.63 (0.52, 0.74)	0.56 (0.45, 0.67)
	Symptom duration >5 years	12	13.7 (4.7, 53.3)	0.78 (0.24, 1.32)	0.005	0.48 (-0.06, 1.03)	0.082	0.74 (0.58, 0.90)	0.64 (0.46, 0.81)

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models. β values are interpreted as the difference in the mean NfL concentration (on the base-2 logarithm scale) for the given phenotype group in comparison to controls or to presymptomatic mutation carriers. p values < 0.0031 are considered statistically significant after correcting for the comparisons of NfL between controls and 16 different overall groups. AUC, area under the receiver operating characteristic curve. See also Figures 2A, 2D and S1D.

Table S5. Comparisons of baseline NfL concentrations between controls, presymptomatic mutation carriers who did not phenoconvert after baseline, and presymptomatic mutation carriers who did phenoconvert, Related to Figures 2B and S1E

			Unadjusted analysis		Adjusting for age and gender	
Mutation Status	n	Median (minimum, maximum) NfL concentration (pg/ml)	β (95% CI)	p value	β (95% CI)	p value
Controls	144	7.1 (2.6, 25.4)	0.00 (reference)	N/A	0.00 (reference)	N/A
Presymptomatic non-converters	43	7.0 (3.3, 68.2)	0.12 (-0.11, 0.35)	0.31	0.27 (0.08, 0.46)	**0.006**
Presymptomatic phenoconverters	14	13.2 (4.7, 65.9)	0.52 (0.34, 0.71)	**<0.001**	0.56 (0.41, 0.71)	**<0.001**
Presymptomatic non-converters	43	7.0 (3.3, 68.2)	0.00 (reference)	N/A	0.00 (reference)	N/A
Presymptomatic phenoconverters	14	13.2 (4.7, 65.9)	0.93 (0.40, 1.45)	**<0.001**	0.88 (0.38, 1.38)	**<0.001**

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models. β values are interpreted as the difference in the mean NfL concentration (on the base-2 logarithm scale) for presymptomatic mutation carriers who phenoconverted after baseline to presymptomatic carriers who did not phenoconvert for at least one year from baseline. See also Figures 2B and S1E.

Table S6: Comparisons of baseline NfL concentration between controls or presymptomatic mutation carriers and phenotype groups for patients with a CDR+NACC-FTLD global score of 0 or 0.5, Related to Figures 2C and 2D

			Unadjusted analysis		Adjusting for age and gender		AUC (95% CI)	
Phenotype group	n	Median (min, max) NfL concentration (pg/ml)	β (95% CI)	p value	β (95% CI)	p value	Unadjusted analysis	Adjusting for age and gender
Controls	144	7.1 (2.6, 25.4)	0.00 (reference)	N/A	0.00 (reference)	N/A	N/A	N/A
bvFTD	19	16.1 (4.7, 125.4)	1.27 (0.94, 1.60)	**<0.001**	1.03 (0.76, 1.30)	**<0.001**	0.87 (0.76, 0.97)	0.88 (0.81, 0.95)
nfvPPA	27	29.6 (12.5, 65.2)	2.09 (1.83, 2.35)	**<0.001**	1.59 (1.34, 1.84)	**<0.001**	0.99 (0.98, 1.00)	0.94 (0.91, 0.98)
svPPA	11	17.6 (12.3, 44.6)	1.43 (1.05, 1.81)	**<0.001**	1.04 (0.72, 1.36)	**<0.001**	0.97 (0.94, 1.00)	0.94 (0.89, 0.98)
CBS	26	22.8 (5.6, 124.7)	1.67 (1.38, 1.95)	**<0.001**	1.11 (0.85, 1.36)	**<0.001**	0.93 (0.85, 1.00)	0.88 (0.81, 0.96)
PSP-RS	23	26.0 (6.6, 112.0)	1.82 (1.53, 2.12)	**<0.001**	1.31 (1.05, 1.58)	**<0.001**	0.95 (0.90, 1.00)	0.88 (0.80, 0.97)
Presymptomatic	85	8.3 (3.3, 68.2)	0.00 (reference)	N/A	0.00 (reference)	N/A	N/A	N/A
bvFTD	19	16.1 (4.7, 125.4)	1.02 (0.57, 1.47)	**<0.001**	0.75 (0.30, 1.19)	**0.001**	0.81 (0.69, 0.92)	0.74 (0.63, 0.86)
nfvPPA	27	29.6 (12.5, 65.2)	1.84 (1.48, 2.19)	**<0.001**	1.45 (1.02, 1.87)	**<0.001**	0.95 (0.91, 0.99)	0.83 (0.75, 0.91)
svPPA	11	17.6 (12.3, 44.6)	1.17 (0.65, 1.70)	**<0.001**	0.84 (0.29, 1.39)	**0.003**	0.90 (0.84, 0.97)	0.81 (0.71, 0.91)
CBS	26	22.8 (5.6, 124.7)	1.41 (1.02, 1.80)	**<0.001**	0.86 (0.43, 1.29)	**<0.001**	0.88 (0.79, 0.96)	0.76 (0.66, 0.86)
PSP-RS	23	26.0 (6.6, 112.0)	1.57 (1.16, 1.97)	**<0.001**	1.08 (0.63, 1.54)	**<0.001**	0.90 (0.83, 0.97)	0.78 (0.67, 0.89)

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models. β values are interpreted as the difference in the mean NfL concentration (on the base-2 logarithm scale) for the given phenotype group in comparison to controls or presymptomatic mutation carriers. p values < 0.01 are considered as statistically significant after correcting for multiple testing. AUC, area under the receiver operating characteristic curve. See also Figures 2C and 2D.

Table S7: Comparisons of baseline NfL concentration between symptomatic groups, Related to Figures 2A and S1D

			Analysis adjusted for age, gender, and symptom duration						
Phenotype group	n	Median (minimum, maximum) NfL concentration (pg/ml)	p value vs. nfvPPA	p value vs. svPPA	p value vs. CBS	p value vs. PSP-RS	p value vs. FTD/ALS	p value vs. ALS	p value vs. MCI
bvFTD	289	24.2 (4.7, 246.4)	0.40	0.26	0.62	0.71	0.014	**<0.001**	**<0.001**
nfvPPA	72	28.7 (7.1, 96.5)	----	0.93	0.55	0.079	0.063	**<0.001**	**<0.001**
svPPA	84	27.6 (6.0, 77.7)	----	----	0.70	0.13	0.030	**<0.001**	**<0.001**
CBS	89	28.1 (5.3, 177.6)	----	----	----	0.25	0.022	**<0.001**	**<0.001**
PSP-RS	124	25.3 (6.6, 112.0)	----	----	----	----	0.005	**<0.001**	**<0.001**
FTD/ALS	25	42.3 (8.9, 217.9)	----	----	----	----	----	0.16	**<0.001**
ALS	12	60.8 (10.0, 121.7)	----	----	----	----	----	----	**<0.001**
MCI	57	12.9 (2.7, 146.8)	----	----	----	----	----	----	----

p values result from linear regression models that were adjusted for age, gender, and symptom duration. p values < 0.0018 are considered statistically significant after correcting for multiple testing. See also Figures 2A and S1D.

Table S8: Comparisons of baseline NfL concentrations in clinically normal individuals, bvFTD patients and MCI patients according to mutation status, Related to Figure 2E

			Unadjusted analysis		Adjusting for age, gender, and symptom duration	
Phenotype group/Mutation status	n	Median (minimum, maximum) NfL concentration (pg/ml)	β (95% CI)	p value	β (95% CI)	p value
Clinically normal						
No mutation	144	7.1 (2.6, 25.4)	0.00 (reference)	N/A	0.00 (reference)	N/A
C9orf72 mutation	35	8.0 (3.3, 68.2)	0.23 (-0.02, 0.48)	0.073	0.31 (0.10, 0.51)	**0.004**
GRN mutation	26	7.5 (3.3, 65.9)	0.29 (0.01, 0.58)	0.046	0.23 (-0.01, 0.47)	0.066
MAPT mutation	22	8.6 (3.6, 23.9)	0.19 (-0.09, 0.47)	0.19	0.50 (0.27, 0.74)	**<0.001**
bvFTD						
No mutation	188	24.1 (5.0, 163.9)	0.00 (reference)	N/A	0.00 (reference)	N/A
C9orf72, *GRN*, or *MAPT* mutation	86	24.8 (4.7, 246.4)	0.01 (-0.27, 0.28)	0.96	0.07 (-0.20, 0.34)	0.62
C9orf72 mutation	43	24.8 (5.1, 87.0)	-0.13 (-0.47, 0.22)	0.47	-0.08 (-0.42, 0.25)	0.62
GRN mutation	15	68.9 (27.4, 246.4)	1.28 (0.74, 1.82)	**<0.001**	1.17 (0.66, 1.69)	**<0.001**
MAPT mutation	28	17.7 (4.7, 164.0)	-0.47 (-0.88, -0.06)	0.024	-0.34 (-0.77, 0.10)	0.13
MCI						
No mutation	28	13.7 (3.9, 146.8)	0.00 (reference)	N/A	0.00 (reference)	N/A
C9orf72, *GRN*, or *MAPT* mutation	28	11.9 (2.7, 76.0)	-0.08 (-0.74, 0.58)	0.80	0.06 (-0.56, 0.69)	0.84

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models. β values are interpreted as the difference in the mean NfL concentration (on the base-2 logarithm scale) for the given mutation group in comparison to individuals without a mutation. Models involving clinically normal individuals were not adjusted for symptom duration. p values < 0.0083 (six pairwise comparisons for clinically normal individuals; see also Table S9) and <0.0071 (seven pairwise comparisons bvFTD patients; see also Table S9) are considered statistically significant after correcting for multiple testing. See also Figure 2E.

Table S9: Comparisons of baseline NfL concentration among mutation carriers in presymptomatic individuals and patients with bvFTD, Related to Figure 2E

			Adjusting for age and gender and, for bvFTD only, symptom duration	
Phenotype group/Mutation status	n	Median (minimum, maximum) NfL concentration (pg/ml)	p value vs. *GRN* mutation	p value vs. *MAPT* mutation
Presymptomatic				
C9orf72 mutation	35	8.0 (3.3, 68.2)	0.85	0.47
GRN mutation	26	7.5 (3.3, 65.9)	----	0.43
MAPT mutation	22	8.6 (3.6, 23.9)	----	----
bvFTD				
C9orf72 mutation	43	24.8 (5.1, 87.0)	**<0.001**	0.20
GRN mutation	15	68.9 (27.4, 246.4)	----	**<0.001**
MAPT mutation	28	17.7 (4.7, 164.0)	----	----

p values result from linear regression models that were adjusted for age, gender and, only for bvFTD patients, symptom duration. p values < 0.0083 (six pairwise comparisons for clinically normal individuals; see also Table S8) and <0.0071 (seven pairwise comparisons bvFTD patients; see also Table S8) are considered statistically significant after correcting for multiple testing. See also Figure 2E.

Table S10: Disease severity characteristics according to phenotype group, Related to Tables 2 and S11

Variable	Median (minimum, maximum) or No. (%) of subjects							
	bvFTD (n = 289)	nfvPPA (n = 72)	svPPA (n = 84)	CBS (n = 89)	PSP-RS (n = 124)	FTD/ALS (n = 25)	ALS (n = 12)	MCI (n = 57)
CDR+NACC-FTLDsb	9 (1, 24)	4 (1, 24)	7 (2, 20)	5 (0, 23)	7 (0, 21)	8 (0, 20)	2 (0, 12)	2 (0, 4)
CDR+NACC-FTLD Domains								
Memory								
0	35 (12.1%)	34 (47.2%)	5 (6.0%)	22 (24.7%)	29 (23.4%)	1 (4.0%)	8 (66.7%)	21 (36.8%)
0.5	86 (29.8%)	21 (29.2%)	33 (39.3%)	40 (44.9%)	54 (43.5%)	12 (48.0%)	2 (16.7%)	31 (54.4%)
≥1	168 (58.1%)	17 (23.6%)	46 (54.8%)	27 (30.3%)	41 (33.1%)	12 (48.0%)	2 (16.7%)	5 (8.8%)
Orientation								
0	98 (33.9%)	52 (72.2%)	44 (52.4%)	52 (58.4%)	58 (46.8%)	6 (24.0%)	9 (75.0%)	43 (75.4%)
0.5	70 (24.2%)	7 (9.7%)	18 (21.4%)	14 (15.7%)	44 (35.5%)	10 (40.0%)	2 (16.7%)	14 (24.6%)
≥1	121 (41.9%)	13 (18.1%)	22 (26.2%)	23 (25.8%)	22 (17.7%)	9 (36.0%)	1 (8.3%)	0 (0.0%)
Judgment and Problem Solving								
0	2 (0.7%)	21 (29.2%)	5 (6.0%)	17 (19.1%)	12 (9.7%)	1 (4.0%)	4 (33.3%)	18 (31.6%)
0.5	32 (11.1%)	26 (36.1%)	14 (16.7%)	24 (27.0%)	36 (29.0%)	4 (16.0%)	5 (41.7%)	37 (64.9%)
≥1	255 (88.2%)	25 (34.7%)	65 (77.4%)	48 (53.9%)	76 (61.3%)	20 (80.0%)	3 (25.0%)	2 (3.5%)
Community Affairs								
0	13 (4.5%)	20 (27.8%)	6 (7.1%)	20 (22.5%)	9 (7.3%)	2 (8.0%)	6 (50.0%)	33 (57.9%)
0.5	47 (16.3%)	28 (38.9%)	22 (26.2%)	24 (27.0%)	28 (22.6%)	2 (8.0%)	2 (16.7%)	23 (40.4%)
≥1	229 (79.2%)	24 (33.3%)	56 (66.7%)	45 (50.6%)	87 (70.2%)	21 (84.0%)	4 (33.3%)	1 (1.8%)
Home and Hobbies								
0	16 (5.5%)	26 (36.1%)	8 (9.5%)	16 (18.0%)	15 (12.1%)	2 (8.0%)	7 (58.3%)	37 (64.9%)
0.5	52 (18.0%)	23 (31.9%)	34 (40.5%)	24 (27.0%)	24 (19.4%)	4 (16.0%)	2 (16.7%)	20 (35.1%)
≥1	221 (76.5%)	23 (31.9%)	42 (50.0%)	49 (55.1%)	85 (68.5%)	19 (76.0%)	3 (25.0%)	0 (0.0%)
Personal Care								
0	122 (42.2%)	62 (86.1%)	65 (77.4%)	51 (57.3%)	61 (49.2%)	13 (52.0%)	9 (75.0%)	57 (100.0%)
0.5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥1	167 (57.8%)	10 (13.9%)	19 (22.6%)	38 (42.7%)	63 (50.8%)	12 (48.0%)	3 (25.0%)	0 (0.0%)
Behavior/Comportment/Personality								
0	0 (0.0%)	32 (44.4%)	11 (13.1%)	45 (50.6%)	33 (26.6%)	2 (8.0%)	5 (41.7%)	16 (28.1%)
0.5	19 (6.6%)	25 (34.7%)	21 (25.0%)	18 (20.2%)	38 (30.6%)	3 (12.0%)	5 (41.7%)	25 (43.9%)
≥1	270 (93.4%)	15 (20.8%)	52 (61.9%)	26 (29.2%)	53 (42.7%)	20 (80.0%)	2 (16.7%)	16 (28.1%)
Language								
0	88 (30.4%)	0 (0.0%)	0 (0.0%)	23 (25.8%)	18 (14.5%)	5 (20.0%)	5 (41.7%)	36 (63.2%)
0.5	98 (33.9%)	7 (9.7%)	13 (15.5%)	29 (32.6%)	50 (40.3%)	8 (32.0%)	6 (50.0%)	19 (33.3%)
≥1	103 (35.6%)	65 (90.3%)	71 (84.5%)	37 (41.6%)	56 (45.2%)	12 (48.0%)	1 (8.3%)	2 (3.5%)
MoCA	20 (1, 30)	22 (1, 30)	17 (0, 27)	23 (1, 30)	22 (2, 30)	19 (2, 26)	23 (10, 29)	25 (14, 30)
Unknown	22	11	4	18	10	1	3	0
SNQ	17 (8, 22)	18 (8, 22)	18 (10, 21)	19 (14, 22)	19 (12, 22)	18.5 (10, 22)	19 (14, 22)	19 (12, 22)

Unknown	53	15	15	13	19	7	0	1
MINT	27 (0, 32)	29 (0, 32)	8 (0, 29)	30 (17, 32)	29 (5, 32)	28 (7, 32)	29 (16, 32)	30 (1, 32)
Unknown	38	15	17	14	11	3	0	1
NAT	7 (0, 10)	8 (0, 10)	9 (1, 10)	9 (0, 10)	9 (0, 10)	7.5 (1, 10)	9 (5, 10)	10 (4, 10)
Unknown	74	15	14	30	42	7	2	8
Phonemic fluency	13 (0, 45)	11 (0, 28)	15 (0, 37)	17 (3, 39)	12 (0, 36)	13 (0, 36)	19 (3, 32)	23 (8, 44)
Unknown	34	18	5	13	9	4	2	1
Category fluency	19 (0, 53)	19 (0, 46)	10 (0, 38)	22 (0, 48)	17 (0, 40)	18 (0, 48)	22 (7, 41)	33.5 (4, 48)
Unknown	37	16	9	11	6	4	2	1
Digit Span Forward	6 (0, 14)	5.5 (1, 10)	7 (1, 13)	7 (0, 14)	7 (1, 13)	6.5 (3, 12)	6 (4, 14)	7 (4, 12)
Unknown	26	14	13	12	11	1	1	0
Digit Span Backward	4 (0, 12)	4 (0, 10)	6 (0, 12)	4 (0, 11)	4 (0, 10)	5 (0, 9)	5 (3, 9)	6 (2, 12)
Unknown	32	14	11	13	12	2	1	0
Trails B	111 (29, 300)	134 (25, 300)	96 (37, 300)	172 (32, 300)	212 (37, 300)	194 (53, 300)	116 (35, 300)	84 (31, 300)
Unknown	110	22	10	33	42	8	3	1

CDR+NACC-FTLDsb, CDR® Dementia Staging Instrument plus behavior and language domains from the National Alzheimer's Disease Coordinating Center FTLD module sum of boxes; MoCA, Montreal Cognitive Assessment; SNQ, Social Norms Questionnaire; MINT, Multilingual Naming Test; NAT, Northwestern Anagram Test; Trails B, Trail Making Test Part B. See also Tables 2 and S11.

Table S11: Associations of baseline NfL with disease indicators in symptomatic groups from unadjusted analysis, Related to Tables 2 and S10

	Association between NfL and:									
Phenotype group	CDR+NACC-FTLDsb	MoCA	SNQ	NAT	MINT	Phonemic fluency	Category fluency	Digit span forward	Digit span backward	Trails B
FTD groups	n = 658	n = 593	n = 543	n = 483	n = 563	n = 579	n = 579	n = 582	n = 576	n = 441
β (95% CI)	0.04 (0.02, 0.05)	-2.05 (-2.60, -1.50)	-0.76 (-1.02, -0.51)	-0.77 (-1.03, -0.51)	-2.09 (-2.87, -1.30)	-3.90 (-4.63, -3.17)	-3.78 (-4.66, -2.90)	-0.50 (-0.72, -0.28)	-0.82 (-1.03, -0.60)	21.32 (12.49, 30.15)
p value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
bvFTD	n = 289	n = 267	n = 236	n = 215	n = 251	n = 255	n = 252	n = 263	n = 257	n = 179
β (95% CI)	0.06 (0.04, 0.09)	-2.46 (-3.20, -1.72)	-1.13 (-1.49, -0.76)	-0.98 (-1.32, -0.63)	-2.66 (-3.55, -1.77)	-4.73 (-5.73, -3.73)	-5.09 (-6.27, -3.92)	*-0.40 (-0.69, -0.11)*	-0.93 (-1.25, -0.62)	*15.92 (4.23, 27.61)*
p value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	*0.007*	**<0.001**	*0.008*
nfvPPA	n = 72	n = 61	n = 57	n = 57	n = 57	n = 54	n = 56	n = 58	n = 58	n = 50
β (95% CI)	0.02 (-0.02, 0.06)	-1.83 (-4.18, 0.52)	-0.80 (-1.87, 0.26)	-0.56 (-1.64, 0.52)	-0.40 (-2.84, 2.03)	-1.69 (-4.18, 0.81)	-1.01 (-4.70, 2.68)	*-0.95 (-1.63, -0.27)*	-0.48 (-1.28, 0.31)	30.90 (-1.76, 63.56)
p value	0.27	0.13	0.14	0.30	0.74	0.18	0.58	*0.007*	0.23	0.063
svPPA	n = 84	n = 80	n = 69	n = 70	n = 67	n = 79	n = 75	n = 71	n = 73	n = 74
β (95% CI)	0.05 (0.01, 0.10)	-2.84 (-4.67, -1.00)	-0.76 (-1.72, 0.20)	-1.34 (-2.18, -0.49)	-4.88 (-7.64, -2.13)	*-3.18 (-5.92, -0.44)*	-4.68 (-7.32, -2.05)	*-0.90 (-1.79, -0.01)*	-1.34 (-2.16, -0.53)	19.75 (-5.65, 45.16)
p value	0.015	**0.003**	0.12	**0.002**	**<0.001**	*0.024*	**<0.001**	*0.048*	**0.002**	0.13
CBS	n = 89	n = 71	n = 76	n = 59	n = 75	n = 76	n = 78	n = 77	n = 76	n = 56
β (95% CI)	*0.06 (0.01, 0.10)*	*-1.53 (-2.95, -0.10)*	0.00 (-0.46, 0.47)	-0.62 (-1.27, 0.03)	-0.34 (-1.10, 0.41)	-3.17 (-5.13, -1.21)	-0.81 (-3.17, 1.55)	-0.09 (-0.73, 0.55)	*-0.56 (-1.05, -0.07)*	17.79 (-6.24, 41.81)
p value	*0.012*	*0.037*	0.99	0.062	0.37	**0.002**	0.50	0.79	*0.025*	0.14
PSP-RS	n = 124	n = 114	n = 105	n = 82	n = 113	n = 115	n = 118	n = 113	n = 112	n = 82
β (95% CI)	0.03 (-0.00, 0.05)	*-1.36 (-2.66, -0.05)*	*-0.64 (-1.22, -0.05)*	-0.21 (-0.93, 0.51)	-0.99 (-2.23, 0.25)	*-2.57 (-4.43, -0.71)*	*-2.71 (-4.63, -0.80)*	*-0.75 (-1.29, -0.20)*	-0.70 (-1.17, -0.23)	38.27 (14.04, 62.51)
p value	0.094	*0.041*	*0.035*	0.56	0.12	*0.007*	*0.006*	*0.008*	**0.004**	**0.002**
MCI	n = 57	n = 57	n = 56	n = 49	n = 56	n = 56	n = 56	n = 57	n = 57	n = 56
β (95% CI)	0.28 (-0.01, 0.57)	*-1.16 (-1.94, -0.38)*	-0.26 (-0.77, 0.25)	-0.28 (-0.69, 0.12)	-0.79 (-1.85, 0.27)	-0.66 (-2.43, 1.10)	-1.32 (-3.38, 0.74)	-0.01 (-0.47, 0.46)	-0.14 (-0.65, 0.37)	*15.16 (1.71, 28.60)*
p value	0.062	*0.005*	0.32	0.17	0.14	0.45	0.20	0.98	0.58	*0.028*

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from unadjusted linear regression models. β values are interpreted as the change in the mean value of the given disease indicator for each doubling of NfL concentration. p values < 0.005 are considered statistically significant after correcting for multiple testing are shown in bold. Nominally significant p values <0.05 are shown in italic. The FTD group includes patients with bvFTD, nfvPPA, svPPA, CBS or PSP-RS. CDR+NACC-FTLDsb, CDR® Dementia Staging Instrument plus behavior and language domains from the National Alzheimer's Disease Coordinating Center FTLD module sum of boxes; MoCA, Montreal Cognitive Assessment; SNQ, Social Norms Questionnaire; MINT, Multilingual Naming Test; NAT, Northwestern Anagram Test; Trails B, Trail Making Test Part B. See also Tables 2 and S10.

Table S12: Associations between baseline NfL concentrations and rates of change over time of disease indicators, Related to Table 2

	Association between baseline NfL and rate of change over time in the given disease indicator									
	bvFTD patients					Combined group of bvFTD, nfvPPA, svPPA, CBS, and PSP-RS patients				
		Unadjusted analysis		Adjusting for age, gender, symptom duration, and years of education			Unadjusted analysis		Adjusting for age, gender, symptom duration, and years of education	
Disease indicator	n	β (95% CI)	p value	β (95% CI)	p value	n	β (95% CI)	p value	β (95% CI)	p value
CDR+NACC-FTLDsb	52	1.33 (0.76, 1.90)	**<0.001**	1.16 (0.48, 1.85)	**0.001**	90	1.07 (0.59, 1.56)	**<0.001**	1.12 (0.56, 1.68)	**<0.001**
MoCA	40	-2.05 (-2.94, -1.17)	**<0.001**	-2.03 (-3.02, -1.03)	**<0.001**	69	-1.85 (-2.60, -1.10)	**<0.001**	-2.01 (-2.84, -1.18)	**<0.001**
SNQ	33	-0.10 (-0.74, 0.54)	0.75	0.29 (-0.43, 1.02)	0.42	52	-0.52 (-1.24, 0.19)	0.15	0.00 (-0.77, 0.78)	1.00
NAT	29	-0.61 (-1.48, 0.27)	0.16	-0.97 (-2.12, 0.18)	0.093	44	-0.70 (-1.33, -0.06)	0.032	-0.67 (-1.49, 0.15)	0.11
MINT	38	-1.37 (-2.40, -0.35)	0.010	-1.30 (-2.47, -0.13)	0.030	71	-0.90 (-1.62, -0.19)	0.013	-0.97 (-1.78, -0.17)	0.019
Phonemic fluency	38	-1.69 (-2.85, -0.52)	0.006	-0.88 (-2.20, 0.44)	0.19	71	-1.45 (-2.34, -0.57)	**0.002**	-1.47 (-2.50, -0.43)	0.006
Category fluency	39	-3.95 (-5.21, -2.69)	**<0.001**	-3.38 (-4.83, -1.93)	**<0.001**	72	-3.28 (-4.32, -2.23)	**<0.001**	-3.06 (-4.23, -1.89)	**<0.001**
Digit span forward	39	-0.24 (-0.75, 0.27)	0.35	-0.03 (-0.65, 0.58)	0.91	72	-0.21 (-0.61, 0.18)	0.28	-0.08 (-0.51, 0.36)	0.73
Digit span backward	39	-0.63 (-1.16, -0.09)	0.024	-0.51 (-1.15, 0.13)	0.11	73	-0.35 (-0.76, 0.07)	0.10	-0.46 (-0.93, 0.01)	0.057
Trails B	25	27.26 (6.64, 47.88)	0.012	33.59 (6.35, 60.83)	0.018	51	9.22 (-5.93, 24.37)	0.23	13.52 (-68.91, 190.90)	0.13

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models. β values are interpreted as the change in the mean rate of change per year in the given outcome for each doubling of NfL concentration. p values < 0.005 are considered statistically significant after correcting for multiple testing. The FTD group includes patients with bvFTD, nfvPPA, svPPA, CBS or PSP-RS. CDR+NACC-FTLDsb, CDR® Dementia Staging Instrument plus behavior and language domains from the National Alzheimer's Disease Coordinating Center FTLD module sum of boxes; MoCA, Montreal Cognitive Assessment; SNQ, Social Norms Questionnaire; MINT, Multilingual Naming Test; NAT, Northwestern Anagram Test; Trails B, Trail Making Test Part B. See also Table 2.

Table S13: Comparison of rate of change in NfL concentrations with controls for presymptomatic mutation carriers and patients with MCI, bvFTD, PPA or parkinsonian disorders, Related to Figures 3 and 4

			Unadjusted analysis		Adjusting for age and gender	
Mutation Status	n	Median (minimum, maximum) rate of change per year in NfL concentration (pg/ml)	β (95% CI)	p value	β (95% CI)	p value
Controls	69	0.3 (-6.4, 4.9)	0.00 (reference)	N/A	0.00 (reference)	N/A
All pre-symptomatic mutation carriers	52	0.6 (-10.1, 24.9)	1.12 (-0.01, 2.24)	0.052	1.30 (0.13, 2.48)	0.029
C9orf72 mutation	17	0.6 (-10.1, 11.3)	-0.11 (-1.29, 1.07)	0.86	0.33 (-0.94, 1.59)	0.61
GRN mutation	14	0.7 (-1.0, 7.7)	1.63 (0.63, 2.62)	**0.002**	1.35 (0.31, 2.38)	0.012
MAPT mutation	20	0.5 (-2.3, 4.9)	0.63 (-0.12, 1.37)	0.097	0.69 (-0.11, 1.49)	0.092
Non-converters	35	0.5 (-3.7, 11.3)	0.33 (-0.39, 1.05)	0.36	0.42 (-0.34, 1.18)	0.28
Phenoconverters	14	2.2 (-1.0, 24.9)	1.88 (1.02, 2.73)	**<0.001**	1.91 (1.04, 2.78)	**<0.001**
MCI	18	1.9 (-0.9, 54.6)	9.32 (5.44, 13.21)	**<0.001**	8.87 (5.04, 12.71)	**<0.001**
bvFTD	35	2.8 (-3.8, 48.9)	4.82 (2.49, 7.15)	**<0.001**	5.50 (3.16, 7.84)	**<0.001**
No mutation	4	2.6 (1.1, 6.8)	N/A	N/A	N/A	N/A
C9orf72, *GRN* or *MAPT* mutation	31	3.0 (-3.8, 48.9)	5.06 (2.59, 7.52)	**<0.001**	5.87 (3.39, 8.35)	**<0.001**
C9orf72 mutation	13	1.2 (-3.8, 12.0)	1.75 (0.46, 3.03)	0.008	1.79 (0.43, 3.15)	0.011
GRN mutation	4	15.9 (3.2, 25.8)	N/A	N/A	N/A	N/A
MAPT mutation	14	2.2 (-0.5, 48.9)	5.32 (2.28, 8.37)	**<0.001**	5.40 (2.38, 8.42)	**<0.001**
nfvPPA and svPPA	9	3.5 (1.0, 42.3)	13.64 (9.92, 17.36)	**<0.001**	12.43 (8.31, 16.55)	**<0.001**
CBS and PSP-RS	9	0.4 (-16.0, 18.4)	2.27 (-0.22, 4.77)	0.074	2.14 (-0.57, 4.86)	0.12

β=regression coefficient; CI=confidence interval. β values, 95% CIs, and p values result from linear regression models. β values are interpreted as the difference in the mean rate of change per year in NfL concentration for the given group in comparison to controls. p values < 0.0039 are considered statistically significant after correcting for multiple testing. Rates of NfL change per year were calculated only for individuals with one or more NfL measurements at least one year from baseline. There was one presymptomatic mutation carrier with a mutation in *C9orf72* and in *GRN* for whom NfL rate of change could be calculated; this individual was only included in the "All pre-symptomatic mutation carriers" group. See also Figures 3 and 4.

Table S14: Comparisons of rate of change in NfL concentrations between presymptomatic mutation carriers and other phenotype groups, Related to Figure 3

			Analysis adjusted for age and gender (and symptom duration when relevant)				
Phenotype group	n	Median (minimum, maximum) rate of change per year in NfL concentration (pg/ml)	p value vs. phenoconverters	p value vs. MCI	p value vs. bvFTD	p value vs. nfvPPA and svPPA	p value vs. CBS and PSP-RS
Presymptomatic non-converters	35	0.5 (-3.7, 11.3)	0.008	0.032	**0.001**	**0.003**	0.38
Presymptomatic phenoconverters	14	2.2 (-1.0, 24.9)	----	0.40	0.40	0.23	0.85
MCI	18	1.9 (-0.9, 54.6)	----	----	0.26	0.64	0.11
bvFTD	35	2.8 (-3.8, 48.9)	----	----	----	0.025	0.66
nfvPPA and svPPA	9	3.5 (1.0, 42.3)	----	----	----	----	0.032
CBS and PSP-RS	9	0.4 (-16.0, 18.4)	----	----	----	----	----

p values result from linear regression models that were adjusted for age, gender, and symptom duration. p values < 0.0033 are considered statistically significant after correcting for multiple testing. Presymptomatic non-converters refers to presymptomatic mutation carriers who did not phenoconvert for at least one year from baseline. Presymptomatic phenoconverters refers to presymptomatic mutation carriers who phenoconverted after baseline. Rates of NfL change per year were calculated only for individuals with one or more NfL measurements at least one year from baseline. See also Figure 3.

Table S15: Comparisons of rate of change in NfL concentration among pre-symptomatic individuals according to mutation status, Related to Figure 4

			Adjusting for age and gender	
Phenotype group	n	Median (minimum, maximum) rate of change per year in NfL concentration (pg/ml)	p value vs. *GRN* mutation	p value vs. *MAPT* mutation
C9orf72 mutation	17	0.6 (-10.1, 11.3)	0.66	0.55
GRN mutation	14	0.7 (-1.0, 7.7)	----	0.63
MAPT mutation	20	0.5 (-2.3, 4.9)	----	----

p values result from linear regression models that were adjusted for age and gender. p values < 0.0167 are considered statistically significant after correcting for multiple testing. Rates of NfL change per year were calculated only for individuals with one or more NfL measurements at least one year from baseline. See also Figure 4.