Supplementary tables and figures

Supplementary Table 1. Biomarker availability. The table indicates the number and percentage of subjects for whom each of the biomarkers was included in the models.

	Non-carriers (*n* = 247)	Presymptomatic carriers			Symptomatic carriers			Total
		GRN (*n* = 128)	*C9orf72* (*n* = 102)	*MAPT* (*n* = 45)	*GRN* (*n* = 49)	*C9orf72* (*n* = 54)	*MAPT* (*n* = 24)	
CSF NfL	74 (30%)	47 (37%)	44 (43%)	18 (40%)	13 (27%)	23 (43%)	7 (29%)	226
CSF NPTX2	74 (30%)	47 (37%)	44 (43%)	18 (40%)	15 (31%)	24 (44%)	7 (29%)	229
CSF C1q	74 (30%)	47 (37%)	44 (43%)	18 (40%)	12 (24%)	23 (43%)	7 (29%)	225
CSF C3b	74 (30%)	47 (37%)	44 (43%)	18 (40%)	12 (24%)	23 (43%)	7 (29%)	225
Serum NfL	220 (89%)	107 (84%)	87 (85%)	40 (89%)	40 (82%)	41 (76%)	15 (63%)	550
Serum pNfH	156 (63%)	69 (54%)	69 (68%)	26 (58%)	29 (59%)	33 (61%)	11 (46%)	393
Plasma GFAP	169 (68%)	79 (62%)	67 (66%)	28 (62%)	28 (57%)	31 (57%)	16 (67%)	418

Abbreviations: NfL = neurofilament light chain; NPTX2 = neuronal pentraxin 2; pNfH = phosphorylated neurofilament heavy chain; GFAP = glial fibrillary acidic protein; *GRN* = granulin; *C9orf72* = chromosome 9 open reading frame 72; *MAPT* = microtubule-associated protein tau.

Supplementary Table 2. Relationship between fluid biomarkers and disease severity measures in mutation carriers. All correlation coefficients were derived from Spearman's rho. Grey matter volumes were corrected for total intracranial volume.

		MMSE	CDR® + NACC FTLD-SB	Whole brain	Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe
CSF NfL	r_s	-0.557	0.566	-0.668	-0.640	-0.687	-0.558	-0.399
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Serum NfL	r_s	-0.545	0.629	-0.670	-0.650	-0.604	-0.563	-0.359
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Serum pNfH	r_s	-0.409	0.438	-0.423	-0.437	-0.418	-0.374	-0.238
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CSF NPTX2	r_s	0.287	-0.326	0.388	0.410	0.303	0.293	0.147
	p	p<0.002	<0.001	<0.001	<0.001	<0.001	0.001	0.097
Plasma GFAP	r_s	-0.482	0.375	-0.453	-0.447	-0.418	-0.382	-0.226
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
CSF C1q	r_s	-0.288	0.194	-0.256	-0.337	-0.225	-0.290	-0.236
	p	p<0.001	0.029	0.004	<0.001	0.011	0.001	0.007
CSF C3b	r_s	-0.229	0.248	-0.221	-0.306	-0.189	-0.252	-0.180
	p	0.005	0.005	0.012	<0.001	0.032	0.004	0.042

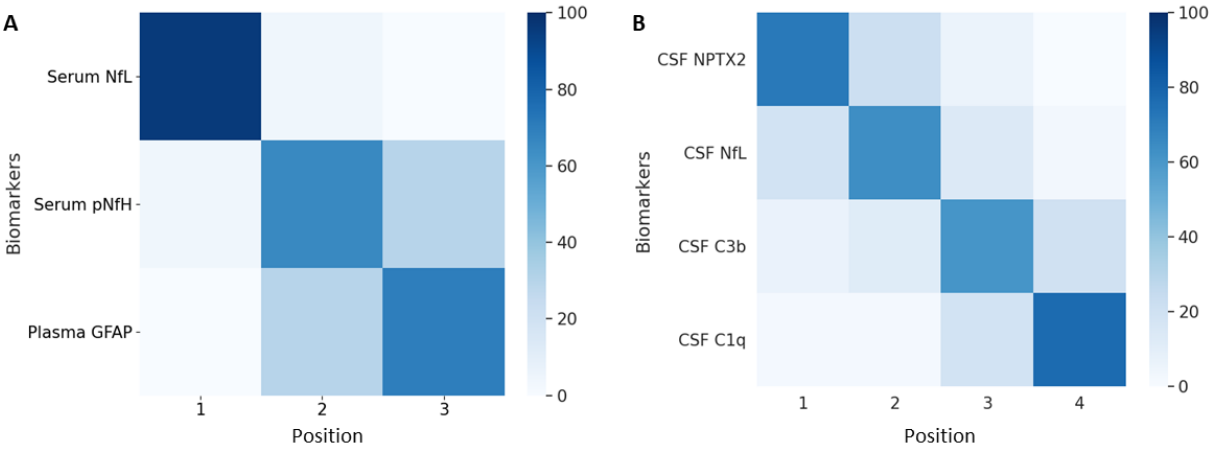
Abbreviations: NfL = neurofilament light chain; NPTX2 = neuronal pentraxin 2; pNfH = phosphorylated neurofilament heavy chain; GFAP = glial fibrillary acidic protein; *GRN* = granulin; *C9orf72* = chromosome 9 open reading frame 72; *MAPT* = microtubule-associated protein tau; MMSE = Mini Mental State Examination; CDR® + NACC FTLD-SB = Clinical Dementia Rating scale plus NACC FTLD-sum of boxes.

Supplementary Table 3. Biomarker levels in genetic subgroups. All variables are shown as medians (interquartile range).

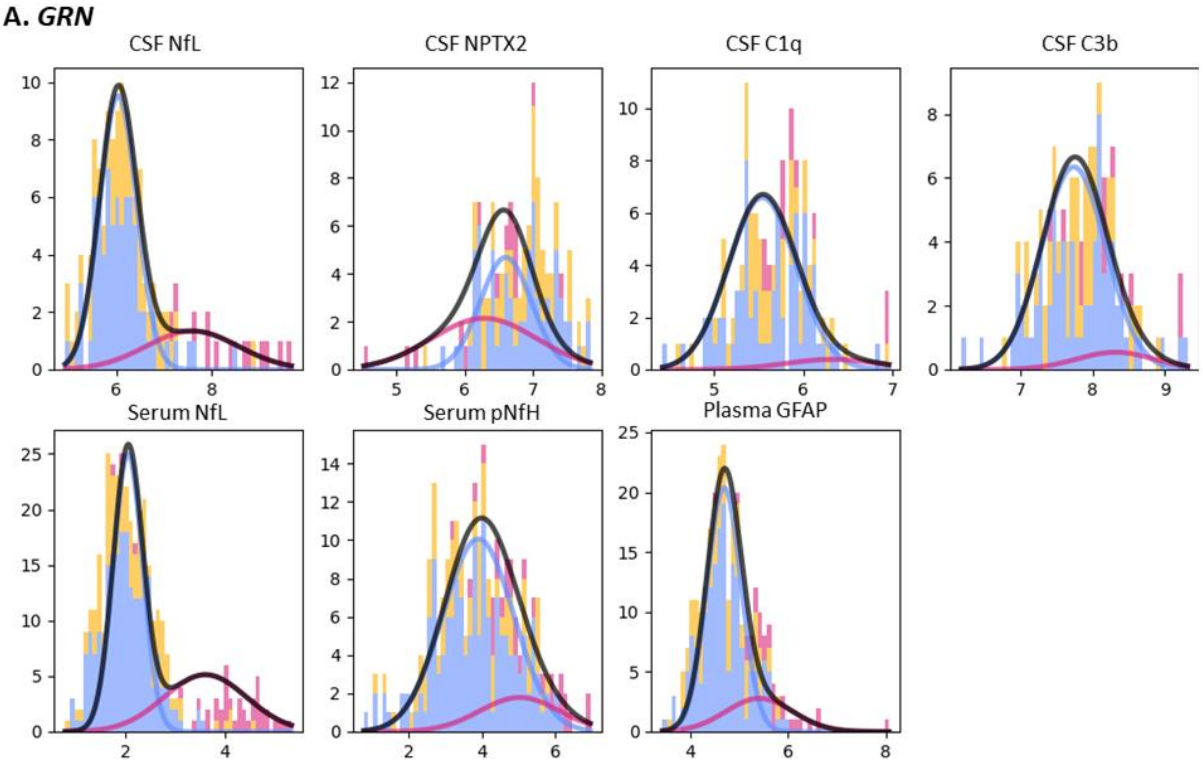
	Presymptomatic carriers			Symptomatic carriers		
	GRN	*C9orf72*	*MAPT*	*GRN*	*C9orf72*	*MAPT*
CSF NfL (pg/ml)	470 (302-682)	456 (302-730)	580 (381-870)	4401 (2339-9231)	2162 (727-2954)	1664 (951-2220)
CSF NPTX2 (pg/ml)	1072 (661-1285)	901 (568-1324)	983 (424-1256)	741 (385-870)	605 (295-881)	483 (217-891)
CSF C1q (ng/ml)	256 (217-374)	241 (181-321)	310 (253-347)	334 (289-442)	324 (228-464)	436 (329-522)
CSF C3b (ng/ml)	2441 (1755-3127)	2280 (1741-3587)	2918 (2110-3674)	3573 (2549-5055)	3148 (2643-4734)	3052 (2544-5100)
Serum NfL (pg/ml)	7.6 (5.2-12.8)	8.5 (6.4-12.5)	6.0 (4.2-8.8)	74.7 (48.8-106.9)	35.6 (15.8-45.3)	22.7 (16.6-31.9)
Serum pNfH (pg/ml)	40.8 (17.3-100.5)	49.5 (22.5-122.5)	32.3 (14.9-55.8)	131.0 (82.4-411.9)	156.0 (82.9-399.1)	110.1 (60.2-172.7)
Plasma GFAP (pg/ml)	109.2 (76.2-158.1)	114.4 (87.8-178.1)	96.7 (71.6-151.8)	266.4 (212.1-402.5)	170.5 (125.1-245.4)	166.6 (99.5-230.0)

Abbreviations: NfL = neurofilament light chain; NPTX2 = neuronal pentraxin 2; pNfH = phosphorylated neurofilament heavy chain; GFAP = glial fibrillary acidic protein; *GRN* = granulin; *C9orf72* = chromosome 9 open reading frame 72; *MAPT* = microtubule-associated protein tau.

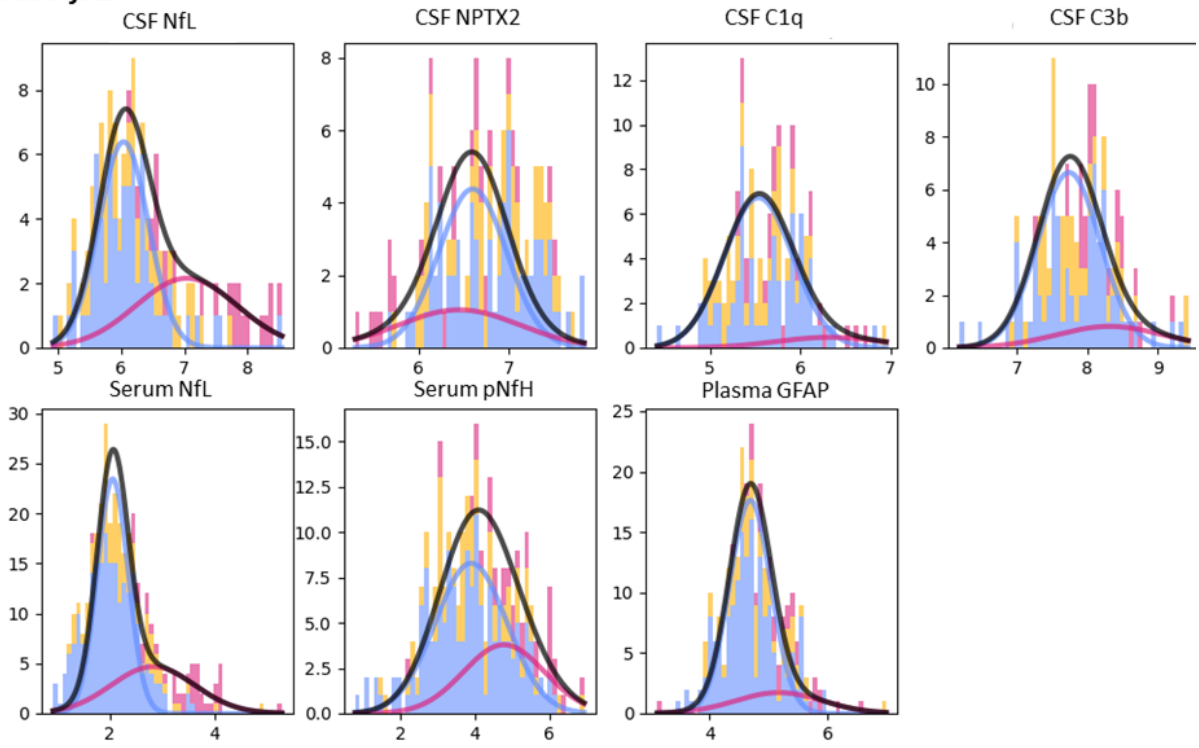
Supplementary Figure 1. Positional variance diagrams showing the sequence of biomarker abnormalities for (A) CSF-only (*n* = 225) and (B) blood-only models (*n* = 342). For these models, subjects were selected based on the availability of all four CSF biomarkers or all three blood biomarkers, .which ensured equal sample sizes for each of the biomarkers. The colour intensity of each of the squares represents the number of bootstrap resampling iterations in which the biomarker was placed at a certain position. The darkest square for each biomarker therefore signifies the mode, i.e. the position where the biomarker was placed most frequently. The spread obtained from bootstrap resampling represents the standard error of the distribution and signifies uncertainty in the estimation of the ordering. The ordering of biomarkers is based on their position in the entire dataset (without bootstrap resampling), which is akin to mean position. Abbreviations: NfL = neurofilament light chain; NPTX2 = neuronal pentraxin 2; pNfH = phosphorylated neurofilament heavy chain; GFAP = glial fibrillary acidic protein.



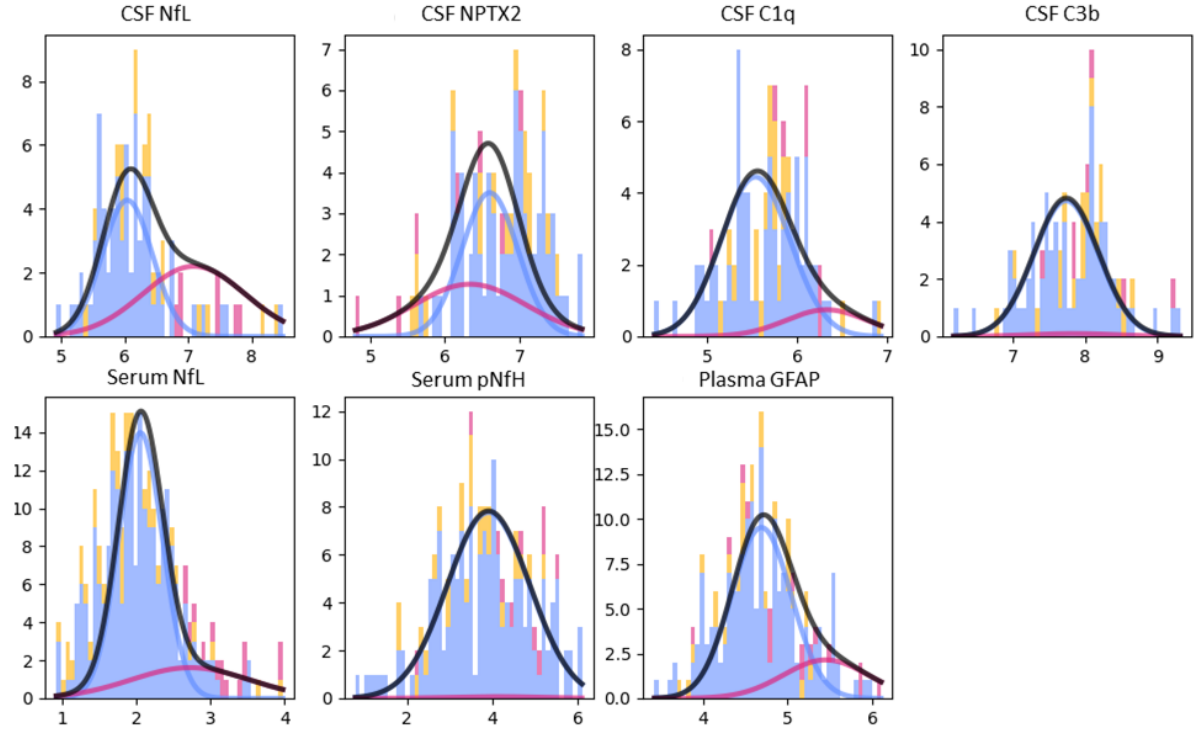
Supplementary Figure 2. Gaussian mixture modelling (GMM) distributions for each biomarker in genetic subgroups. Distributions were computed using co-initialised DEBM in **(A)** *GRN*, **(B)** *C9orf72* and **(C)** *MAPT* mutation carriers. Histogram bins are shown for non-carriers (blue), presymptomatic carriers (orange) and symptomatic carriers (dark pink). The blue Gaussian represents the distribution of normal biomarker values based on non-carriers, whereas the dark pink Gaussian shows the distribution for abnormal biomarker values, estimated by the GMM. The amplitudes of these Gaussians are based on an estimated mixing parameter. Black curves show the total estimated biomarker distribution, i.e. the summation of blue and dark pink Gaussians. All biomarker values were log-transformed. Abbreviations: NfL = neurofilament light chain; NPTX2 = neuronal pentraxin 2; pNfH = phosphorylated neurofilament heavy chain; GFAP = glial fibrillary acidic protein; *GRN* = granulin; *C9orf72* = chromosome 9 open reading frame 72; *MAPT* = microtubule-associated protein tau.



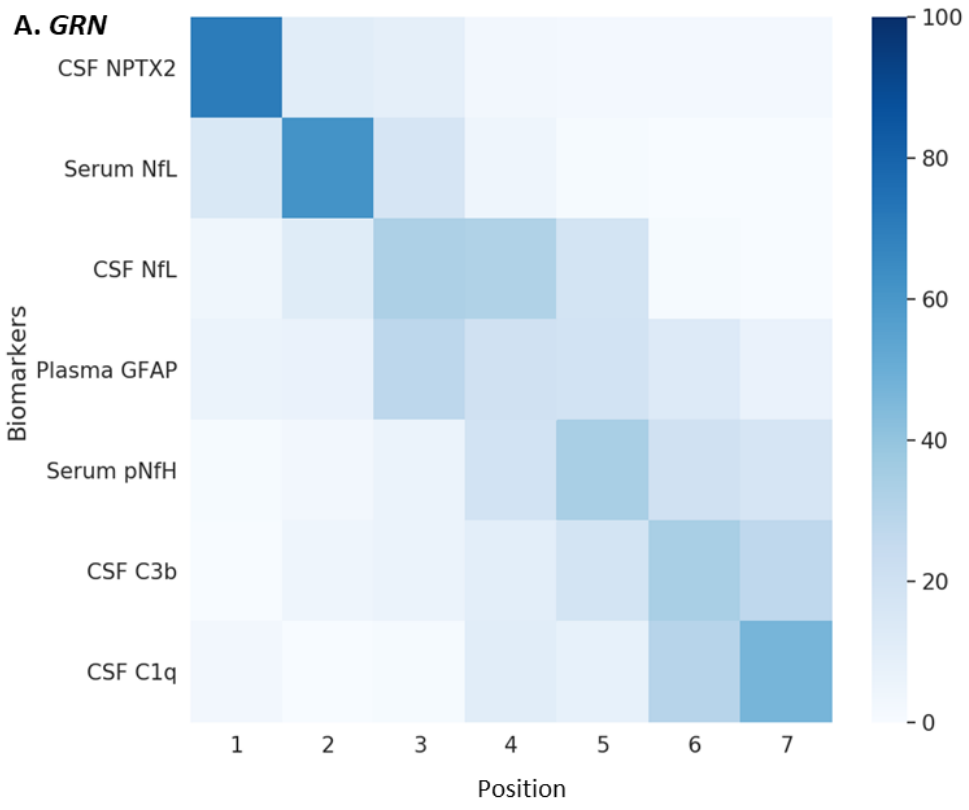
B. *C9orf72*

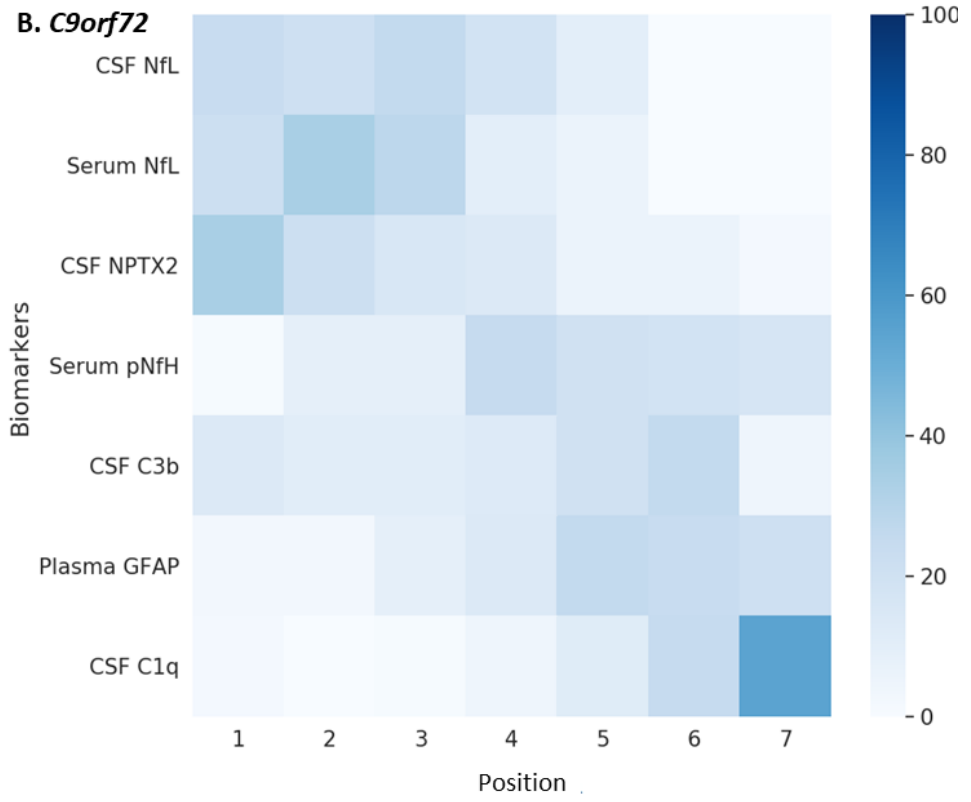


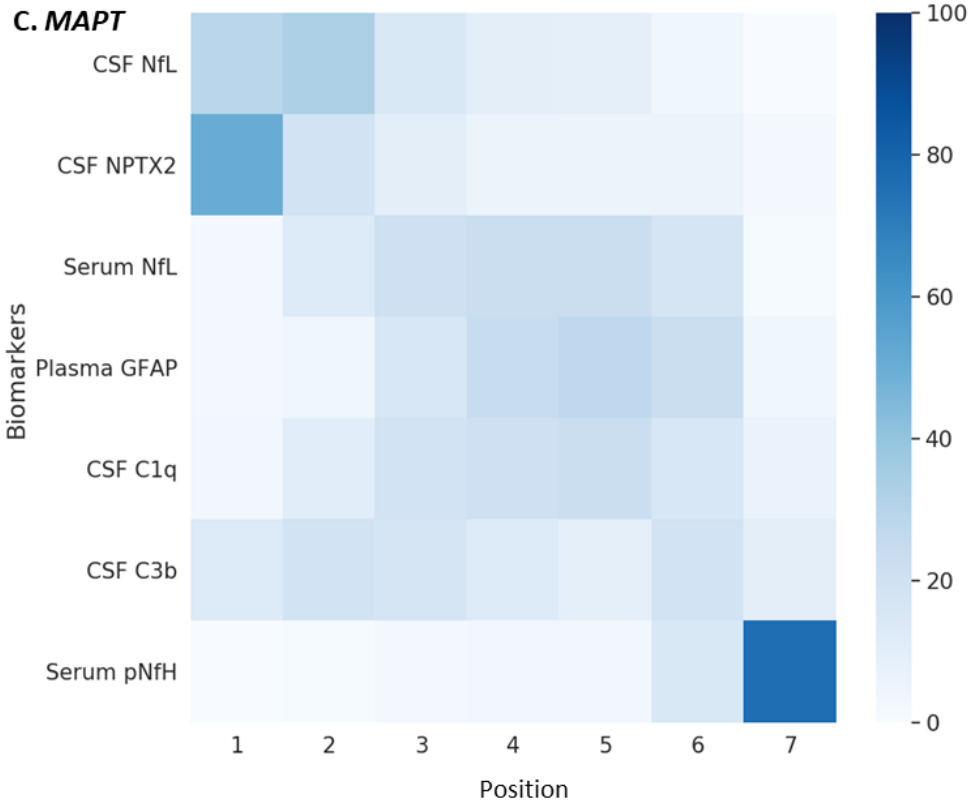
C. *MAPT*



Supplementary Figure 3. Positional variance diagrams showing the estimated sequence of biomarker abnormalities for each genetic subgroup. Sequences were obtained through co-initialised discriminative event-based modelling for **(A)** *GRN* mutation carriers; **(B)** *C9orf72* mutation carriers; **(C)** *MAPT* mutation carriers. The colour intensity of each of the squares represents the number of bootstrap resampling iterations in which the biomarker was placed at a certain position. The darkest square for each biomarker therefore signifies the mode, i.e. the position where the biomarker was placed most frequently. The spread obtained from bootstrap resampling represents the standard error of the distribution and signifies uncertainty in the estimation of the ordering. The ordering of biomarkers is based on their position in the entire dataset (without bootstrap resampling), which is akin to mean position. Abbreviations: NfL = neurofilament light chain; NPTX2 = neuronal pentraxin 2; pNfH = phosphorylated neurofilament heavy chain; GFAP = glial fibrillary acidic protein; *GRN* = granulin; *C9orf72* = chromosome 9 open reading frame 72; *MAPT* = microtubule-associated protein tau.




B. C9orf72
CSF NfL
Serum NfL
CSF NPTX2
Serum pNfH
CSF C3b
Plasma GFAP
CSF C1q
Biomarkers
1
2
3
4
5
6
7
Position
100
80
60
40
20
0


C. MAPT
CSF NfL
CSF NPTX2
Serum NfL
Plasma GFAP
CSF C1q
CSF C3b
Serum pNfH
Biomarkers
1
2
3
4
5
6
7
Position
100
80
60
40
20
0