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Supplementary appendix

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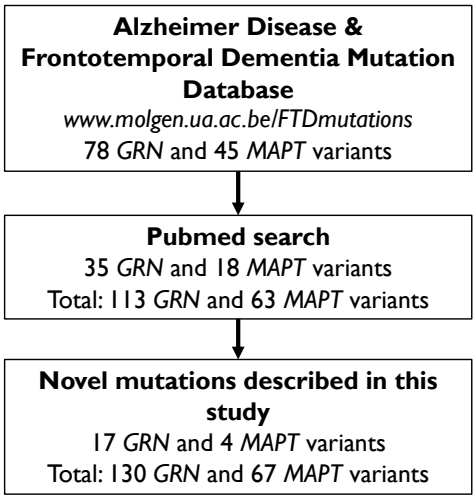
A worldwide cohort study of age at symptom onset and death and disease duration in genetic frontotemporal dementia

Moore et al.

Supplementary Appendix

Section 1) GRN and MAPT pathogenic variants included in the study

Supplementary Figure 1: Flow chart for inclusion of *GRN* and *MAPT* variants in the study.



The 35 GRN and 18 MAPT variants included in the study from the Pubmed search are shown with references in Supplementary Tables 1 (GRN) and 2 (MAPT) below. It was noted that the AD&FTD Mutation Database had not been updated for some time. Novel mutations described in the study are shown in Supplementary Tables 3 and 4.

Inclusion/exclusion criteria

All mutations were reviewed by two geneticists (RG/JB) to examine pathogenicity (as not all *GRN* and *MAPT* variants are pathogenic), and were only included if both agreed on their likely pathogenic nature. For *GRN,* mutations causing haploinsufficiency, due to a frameshift mutation or insertion of a stop codon, were all included as likely pathogenic. The literature on *GRN* missense mutations is less clear as to whether these are likely to be pathogenic or represent risk factors (apart from A9D which affects the signal peptide and is therefore likely to be pathogenic). We only included missense mutations where there was evidence in the literature of a) low progranulin levels (in blood or CSF) similar to those causing haploinsufficiency (rather than intermediate levels as seen in some missense mutations), or b) functional evidence of pathogenicity, and c) no contrary evidence that the mutation was not pathogenic (e.g. the C139R variant has been shown to be associated with Alzheimer's disease (AD) pathology rather than TDP-43 inclusions as would be expected for *GRN* mutations[43]).[6,24,,44] *C9orf72* families with intermediate length expansions (<30 repeats) were not included in the study. Lastly, we did not include in the analysis families with dual mutations e.g. the combination of a *C9orf72* expansion and a pathogenic *GRN* or *MAPT* mutation.

Supplementary Table 1: *GRN* mutations found in Pubmed search.

GRN	Mutation	Predicted protein change	Mutation alias	Reference
Intron 1-12			**delGRN[London]**	1
Exon 2	NM_002087.2:c.58dup:p.(Cys20Leufs*45)	p.C20LfsX45	**C20fs**	2
Exon 2	NM_002087.2:c.78C>A:p.(Cys26*)	p.C26X	**C26X**	2
Exon 2	NM_002087.2:c.117dup:p.(Ser40Glnfs*25)	p.S40QfsX25	**S40fs**	2
Intron 2	NM_002087.2:c.139del:p.(Asp47Thrfs*7)	p.D47TfsX7	**D47fs**	3
Intron 3	NM_002087.2:c.265-2del		**IVS3-2delA**	4
Exon 4	NM_002087.2:c.280del:p.(Asp94Metfs*162)	p.D94MfsX162	**D94fs**	2
Exon 4	NM_002087.2:c.314dup:p.(Cys105Trpfs*14)	p.C105fs	**C105fs**	5
Exon 4	NM_002087.2:c.314G>A:p.(Cys105Tyr)	p.C105Y	**C105Y**	6
Exon 5	NM_002087.2:c.378C>A:p.(Cys126*)	p.C126X	**C126X**	3
Exon 5	NM_002087.2:c.421_422del:p.(Val141Tyrfs*18)	p.V141YfsX18	**V141fs**	2
Exon 5	NM_002087.2:c.445_446del:p.(Cys149Leufs*10)	p.C149fsX10	**C149fs**	7
Exon 6	NM_002087.2:c.481_482del:p.(Arg161Glyfs*36)	p.R161GfsX36	**R161fs**	8
Exon 6	NM_002087.2:c.559del:p.(Leu187Trpfs*69)	p.L187WfsX69	**L187fs (559del)**	2
Exon 7	NM_002087.2:c.607del:p.(Ser203Profs*53)	p.S203PfsX53	**S203fs (607delT)**	2,9
Exon 7	NM_002087.2:c.687T>A:p.(Tyr229*)	p.Y229X	**Y229X**	10
Intron 7	NM_002087.2:c.708+5_8delGTGA		**IVS7+5_8delGTGA**	11, 12
Intron 7	NM_002087.2:c.708+6_9delTGAG		**IVS7+6_9delTGAG**	2, 13, 14
Intron 7	NM_002087.2:c.709-2A>T		**IVS7-2A>T**	15,16
Intron 8	NM_002087.2:c.833_834del:p.(Thr278Serfs*7)	p.T278SfsX7	**T278fs**	17
Intron 8	NM_002087.2:c.836-1G>T		**IVS8-1G>T**	18
Exon 9	NM_002087.2:c.903_904insTG:p.(Gly302Trpfs*60)	p.G302WfsX60	**G302fs**	19
Exon 9	NM_002087.2:c.907del:p.(Ala303Profs*58)	p.A303PfsX58	**A303fs (907delG)**	2
Intron 9	NM_002087.2:c.933+1del		**IVS9+1delG**	20
Exon 10	NM_002087.2:c.975del:p.(Phe326Leufs*35)	p.F326LfsX35	**F326fs**	2
Exon 10	NM_002087.2:c.988_989del:p.(Thr330Alafs*6)	p.T330AfsX6	**T330fs**	2
Exon 10	NM_002087.2:c.1013_1024del:p.(Gly338_Gln341del)	p.Q337_340del	**Q337_340del**	21
Exon 10	NM_002087.2:c.1012_1013delinsC:p.(Gly338Argfs*23)	p.G338RfsX23	**G338fs**	22
Exon 10	NM_002087.2:c.1048dup:p.(Ala350Glyfs*18)	p.A350GfsX18	**A350fs**	23
Exon 10	NM_002087.2:c.1117C>T:p.(Pro373Ser)	p.P373S	**P373S**	24
Intron 10	NM_002087.2:c.1179del:p.(Ala394Leufs*18)	p.A394LfsX18	**A394fs**	25
Exon 11	NM_002087.2:c.1212C>A:p.(Cys404*)	p.C404X	**C404X**	26
Exon 11	NM_002087.2:c.1246dup:p.(Cys416Leufs*30)	p.C416LfsX30	**C416fs**	26
Exon 11	NM_002087.2:c.1354del:p.(Val452Trpfs*39)	p.V452WfsX39	**V452fs**	3
Exon 12	NM_002087.2:c.1612C>T:p.(Arg538*)	p.R538X	**R538X**	2

Supplementary Table 2: *MAPT* mutations found in Pubmed search.

MAPT	Mutation	Predicted protein change	Mutation alias	Reference
Exon 2	NM_001123066.3:c.163G>A:p.(Gly55Arg)	p.G55R (p.G55R)	**G55R**	27
Intron 9	NM_001123066.3:c.1828-15T>C		**IVS9-15T>C**	28
Exon 10	NM_001123066.3:c.1856T>G:p.(Leu619Arg)	p.L284R (p.L619R)	**L284R**	29
Exon 10	NM_001123066.3:c.1858A>C:p.(Ser620Arg)	p.S285R (p.S620R)	**S285R**	22
Exon 10	NM_001123066.3:c.1876T>C:p.(Cys626Arg)	p.C291R (p.C626R)	**C291R**	30
Exon 10	NM_001123066.3:c.1897A>G:p.(Lys633Glu)	p.K298E (p.K633E)	**K298E**	31
Exon 10	NM_001123066.3:c.1915G>A:p.(Gly639Ser)	p.G304S (p.G639S)	**G304S**	32
Intron 10	NM_001123066.3:c.1920+4A>C		**IVS10+4A>C**	28
Intron 10	NM_001123066.3:c.1920+15A>C		**IVS10+15A>C**	33
Exon 11	NM_001123066.3:c.1999C>T:p.(Pro667Ser)	p.P332S (p.P667S)	**P332S**	34
Exon 12	NM_001123066.3:c.2013G>C:p.(Gln671His)	p.Q336H (p.Q671H)	**Q336H**	35
Exon 12	NM_001123066.3:c.2057A>G:p.(Gln686Arg)	p.Q351R (p.Q686R)	**Q351R**	36
Exon 12	NM_001123066.3:c.2071T>A:p.(Ser691Thr)	p.S356T (p.S691T)	**S356T**	37
Exon 12	NM_001123066.3:c.2093T>C:p.(Val698Ala)	p.V363A (p.V698A)	**V363A**	38
Exon 12	NM_001123066.3:c.2095C>T:p.(Pro699Ser)	p.P364S (p.P699S)	**P364S**	39,40
Exon 12	NM_001123066.3:c.2101G>A:p.(Gly701Arg)	p.G366R (p.G701R)	**G366R**	39
Exon 13	NM_001123066.3:c.2120A>G:p.(Glu707Gly)	p.E372G (p.E707G)	**E372G**	41
Exon 13	NM_001123066.3:c.2233A>C:p.(Asn745His)	p.N410H (p.N745H)	**N410H**	42

Supplementary Table 3: Novel *GRN* mutations reported in this study.

GRN	Mutation	Predicted protein change	Mutation alias
Intron 1-12			**delGRN[Tubingen]** (chr17:42,426,438-42,430,018)
Exon 2	NM_002087.2:c.87dup:p.(Cys30Leufs*35)	p.C30LfsX35	**C30fs**
Intron 2	NM_002087.2:c.139-4C>T		**IVS2-4C>T**
Exon 3	NM_002087.2:c.232dup:p.(Ser78Phefs*41)	p.S78FfsX41	**S78fs**
Exon 4	NM_002087.2:c.295_308del:p.(Cys99Profs*15)	p.Cys99fsX15	**C99fs**
Intron 4	NM_002087.2:c.349+1G>C		**IVS4+1G>C**
Intron 4	NM_002087.2:c.350-1G>T		**IVS4-1G>T**
Exon 5	NM_002087.2:c.559dup:p.(Leu187Profs*11)	p.L187PfsX11	**L187fs (559dup)**
Exon 8	NM_002087.2:c.745C>T:p.(Gln249*)	p.Q249X	**Q249X**
Exon 8	NM_002087.2:c.759_760dup:p.(Asp254Valfs*3)	p.D254VfsX3	**D254fs**
Exon 8	NM_002087.2:c.761_762insTG:p.(Leu255Alafs*2)	p.L255AfsX2	**L255fs**
Exon 10	NM_002087.2:c.988_989dup:p.(Gln331Argfs*31)	p.Q331RfsX31	**Q331fs**
Intron 10	NM_002087.2:c.1179+3A>G		**IVS10+3A>G**
Exon 11	NM_002087.2:c.1196_1197del:p.(D399Afs*14)	p.D399AfsX14	**D399fs**
Exon 11	NM_002087.2:c.1256_1263dup:p.(Ile422Glufs*72)	p.I422EfsX72	**I422fs**
Exon 12	NM_002087.2:c.1428_1431del:p.(Glu476Aspfs*14)	p.E476DfsX14	**E476fs**
Exon 12	NM_002087.2:c.1446C>A:p.(Cys482*)	p.C482X	**C482X**

Supplementary Table 4: Novel *MAPT* mutations reported in this study.

MAPT	Mutation	Predicted protein change	Mutation alias
Exon 9	NM_001123066.3:c.1816G>C:p.(Gly606Arg)	p.G271R (p.G606R)	**G271R**
Intron 9	NM_001123066.3:c.1828-11G>C		**IVS9-11G>C**
Intron 9	NM_001123066.3:c.1828-10G>C		**IVS9-10G>C**
Intron 10	NM_001123066.3:c.1920+12C>A		**IVS10+12C>A**

Of note, the majority of the *GRN* mutations found either via a Pubmed search or newly described here are expected to cause haploinsufficiency. We also included two missense mutations: C105Y has been studied functionally and shown to affect both progranulin secretion and cleavage by elastase suggesting it is pathogenic (ref 6), whilst P373S has been shown to be associated with very low progranulin levels in CSF (ref 24).

In total therefore we report 130 mutations in *GRN* and 67 mutations in *MAPT*, a much larger number than previously described, either in previous reviews or current online databases. The majority of these mutations are reported in 5 or fewer families, with only 50 mutations in *GRN* and 23 mutations in *MAPT* reported in more than 5 families. A complete table of mutations included in the study is shown below in Supplementary Table 5 with number of participants and means for age at onset (AAO), age at death (AAD) and disease duration (DD).

Supplementary Table 5. Individual genetic mutations included within the *GRN* and *MAPT* mutation groups, with mean age at onset (AAO), age at death (AAD) and disease duration (DD). N = number: for AAO, AAD and DD this is the number of participants with available data.

GRN	Mutation	Predicted protein change	Mutation alias	N total	N families	N AAO	Mean AAO	N AAD	Mean AAD	N DD	Mean DD
Complete gene			**delGRN[DR184]**	1	1	1	71.0	1	74.0	1	3.0
Intron 1	NM_002087.2:c.-8+3A>T		**IVS1+3A>T**	1	1	1	58.0	0		0	
Intron 1	NM_002087.2:c.-8+5G>C		**IVS1+5G>C**	35	26	35	61.2	25	67.0	25	5.4
Intron 1-12			**delGRN[London]**	7	1	2	53.0	4	58.3	1	4.0
Intron 1-12			**delGRN[French]**	16	9	14	61.6	7	72.7	5	8.9
Intron 1-12			**delGRN[Tubingen]**	1	1	1	51.0	0		0	
Exon 2	NM_002087.2:c.1A>G	p.M1	**M1 (1A>G)**	8	2	7	54.6	5	63.0	4	7.3
Exon 2	NM_002087.2:c.2T>C	p.M1	**M1 (2T>C)**	4	3	4	56.5	2	66.0	2	11.0
Exon 2	NM_002087.2:c.3G>A	p.M1	**M1 (3G>A)**	2	1	1	62.0	2	68.0	1	10.0
Exon 2	NM_002087.2:c.26C>A:p.(Ala9Asp)	p.A9D	**A9D**	37	4	36	62.1	31	71.7	30	9.3
Exon 2	NM_002087.2:c.58dup:p.(Cys20Leufs*45)	p.C20LfsX45	**C20fs**	0		0		0		0	
Exon 2	NM_002087.2:c.63_64insC:p.(Asp22Argfs*43)	p.D22RfsX43	**D22fs**	9	3	8	62.0	7	68.6	7	7.0
Exon 2	NM_002087.2:c.78C>A:p.(Cys26*)	p.C26X	**C26X**	0		0		0		0	
Exon 2	NM_002087.2:c.87dup:p.(Cys30Leufs*35)	p.C30LfsX35	**C30fs**	3	2	3	59.7	1	68.0	1	8.0
Exon 2	NM_002087.2:c.87_90dup:p.(Cys31Leufs*35)	p.C31LfsX35	**C31fs**	47	10	32	60.3	31	65.0	25	5.9
Exon 2	NM_002087.2:c.102del:p.(Gly35Glufs*19)	p.G35EfsX19	**G35fs**	42	10	40	61.2	31	63.2	30	5.1
Exon 2	NM_002087.2:c.117dup:p.(Ser40Glnfs*25)	p.S40QfsX25	**S40fs**	0		0		0		0	
Intron 2	NM_002087.2:c.138+1G>A		**IVS2+1G>A**	3	1	3	62.0	1	63.0	1	7.0
Intron 2	NM_002087.2:c.139-4C>T		**IVS2-4C>T**	1	1	1	70.0	0		0	
Intron 2	NM_002087.2:c.139del:p.(Asp47Thrfs*7)	p.D47TfsX7	**D47fs**	1	1	1	68.0	1	72.0	1	4.0
Exon 3	NM_002087.2:c.154del:p.(Thr52Hisfs*2)	p.T52HfsX2	**T52fs**	37	9	33	67.8	25	76.7	24	7.0
Exon 3	NM_002087.2:c.232dup:p.(Ser78Phefs*41)	p.S78FfsX41	**S78fs**	2	1	2	53.0	0		0	
Exon 3	NM_002087.2:c.234_235del:p.(Gly79Aspfs*39)	p.G79DfsX39	**G79fs**	2	1	2	56.0	2	67.0	2	11.0
Exon 3	NM_002087.2:c.243del:p.(Ser82Valfs*174)	p.S82VfsX174	**S82fs**	31	1	24	60.1	21	66.2	19	6.9
Exon 3	NM_002087.2:c.255del:p.(Phe86Serfs*170)	p.F86SfsX170	**F86fs**	0		0		0		0	
Intron 3	NM_002087.2:c.264+2T>C		**IVS3+2T>C**	5	4	5	65.8	2	65.0	2	4.0
Intron 3	NM_002087.2:c.265-2del		**IVS3-2delA**	3	1	3	56.0	1	69.0	1	4.0
Exon 4	NM_002087.2:c.280del:p.(Asp94Metfs*162)	p.D94MfsX162	**D94fs**	0		0		0		0	
Exon 4	NM_002087.2:c.295_308del:p.(Cys99Profs*15)	p.Cys99fsX15	**C99fs**	2	1	2	63.5	1	66.0	1	5.0
Exon 4	NM_002087.2:c.299del:p.(Pro100Hisfs*156)	p.P100HfsX156	**P100fs**	1	1	1	60.0	0		0	
Exon 4	NM_002087.2:c.314dup:p.(Cys105Trpfs*14)	p.C105fs	**C105fs**	1	1	1	60.0	1	64.0	1	4.0
Exon 4	NM_002087.2:c.314G>A:p.(Cys105Tyr)	p.C105Y	**C105Y**	4	1	4	65.8	0		0	
Exon 4	NM_002087.2:c.328C>T:p.(Arg110*)	p.R110X	**R110X**	8	5	7	59.6	3	66.3	2	9.0
Exon 4	NM_002087.2:c.347C>A:p.(Ser116*)	p.S116X	**S116X**	1	1	1	57.0	0		0	
Intron 4	NM_002087.2:c.349+1G>C		**IVS4+1G>C**	1	1	1	58.0	0		0	
Intron 4	NM_002087.2:c.350-1G>T		**IVS4-1G>T**	6	2	6	58.7	4	63.0	4	3.5
Exon 5	NM_002087.2:c.350_462del:p.(Asn118Phefs*4)	p.N118FfsX4	**N118fs**	1	1	1	56.0	1	62.0	1	6.0
Exon 5	NM_002087.2:c.361del:p.(Val121Trpfs*135)	p.V121WfsX135	**V121fs**	6	1	4	58.8	3	69.7	2	6.0
Exon 5	NM_002087.2:c.373C>T:p.(Gln125*)	p.Q125X	**Q125X**	10	1	7	59.3	5	71.2	5	7.8
Exon 5	NM_002087.2:c.378C>A:p.(Cys126*)	p.C126X	**C126X**	2	1	2	52.5	2	62.5	2	10.0
Exon 5	NM_002087.2:c.380_381del:p.(Pro127Argfs*2)	p.P127RfsX2	**P127fs**	2	2	2	55.5	0		0	

GRN	Mutation	Predicted protein change	Mutation alias	N total	N families	N AAO	Mean AAO	N AAD	Mean AAD	N DD	Mean DD
Exon 5	NM_002087.2:c.384_387del:p.(Gln130Serfs*125)	p.Q130SfsX125	**Q130fs (384_387delTAGT)**	4	2	2	51.5	3	76.3	1	9.0
Exon 5	NM_002087.2:c.388_391del:p.(Gln130Serfs*125)	p.Q130SfsX125	**Q130fs (388_391delCAGT)**	23	11	20	67.4	11	80.7	10	6.9
Exon 5	NM_002087.2:c.421_422del:p.(Val141Tyrfs*18)	p.V141YfsX18	**V141fs**	3	1	2	57.0	2	62.0	1	7.0
Exon 5	NM_002087.2:c.445_446del:p.(Cys149Leufs*10)	p.C149fsX10	**C149fs**	9	2	8	69.4	5	80.6	4	10.5
Intron 5	NM_002087.2:c.463_598del:p.(Ala155Trpfs*56)	p.A155WfsX56	**A155fs**	3	2	3	64.7	1	60.0	1	5.0
Exon 6	NM_002087.2:c.468_474del:p.(Cys157Lysfs*97)	p.C157KfsX97	**C157fs**	30	10	22	58.4	14	68.2	6	5.5
Exon 6	NM_002087.2:c.481_482del:p.(Arg161Glyfs*36)	p.R161GfsX36	**R161fs**	1	1	1	48.0	0		0	
Exon 6	NM_002087.2:c.559del:p.(Leu187Trpfs*69)	p.L187WfsX69	**L187fs (559del)**	0		0		0		0	
Exon 5	NM_002087.2:c.559dup:p.(Leu187Profs*11)	p.L187PfsX11	**L187fs (559dup)**	3	1	3	52.3	3	60.3	3	8.0
Exon 6	NM_002087.2:c.592_593del:p.(Arg198Glyfs*19)	p.R198GfsX19	**R198fs**	2	2	2	60.5	0		0	
Exon 6	NM_002087.2:c.596C>T:p.(Ala199Val)	p.A199V	**A199V**	11	3	6	60.5	7	63.6	2	8.0
Exon 7	NM_002087.2:c.603dup:p.(Ser203Valfs*15)	p.S203VfsX15	**S203fs (603_604insC)**	3	3	2	49.0	3	62.0	2	6.5
Exon 7	NM_002087.2:c.607del:p.(Ser203Profs*53)	p.S203PfsX53	**S203fs (607delT)**	1	1	1	58.0	0		0	
Exon 7	NM_002087.2:c.675_676del:p.(Ser226Trpfs*28)	p.S226WfsX28	**S226fs**	6	6	6	56.8	6	62.3	6	5.6
Exon 7	NM_002087.2:c.687T>A:p.(Tyr229*)	p.Y229X	**Y229X**	5	1	3	62.7	5	69.2	3	8.7
Intron 7	NM_002087.2:c.708+1G>A		**IVS7+1G>A**	14	7	10	59.9	9	68.6	5	7.3
Intron 7	NM_002087.2:c.708+1G>C		**IVS7+1G>C**	1	1	1	55.0	1	61.0	1	6.0
Intron 7	NM_002087.2:c.708+5_8delGTGA		**IVS7+5_8delGTGA**	8	4	6	62.2	6	72.3	4	10.0
Intron 7	NM_002087.2:c.708+6_9delTGAG		**IVS7+6_9delTGAG**	17	9	12	60.9	15	70.7	10	5.0
Intron 7	NM_002087.2:c.709-2A>G		**IVS7-2A>G**	10	5	8	56.0	6	63.2	6	5.8
Intron 7	NM_002087.2:c.709-2A>T		**IVS7-2A>T**	12	1	12	67.0	8	74.6	8	6.0
Intron 7	NM_002087.2:c.709-1G>A		**IVS7-1G>A**	50	18	38	60.5	26	67.0	23	6.5
Exon 8	NM_002087.2:c.745C>T:p.(Gln249*)	p.Q249X	**Q249X**	6	1	6	60.5	6	66.5	6	6.0
Exon 8	NM_002087.2:c.759_760del:p.(Cys253*)	p.C253X	**C253X**	5	4	5	58.6	3	62.0	3	6.3
Exon 8	NM_002087.2:c.759_760dup:p.(Asp254Valfs*3)	p.D254VfsX3	**D254fs**	3	1	3	57.7	1	82.0	1	22.0
Exon 8	NM_002087.2:c.761_762insTG:p.(Leu255Alafs*2)	p.L255AfsX2	**L255fs**	3	1	3	62.0	3	70.0	3	8.0
Exon 8	NM_002087.2:c.768_769dup:p.(Gln257Profs*27)	p.Q257PfsX27	**Q257fs**	16	6	16	61.3	7	69.0	7	8.8
Exon 8	NM_002087.2:c.775A>T:p.(Lys259*)	p.K259X	**K259X**	4	2	3	62.3	1	90.0	0	
Exon 8	NM_002087.2:c.813_816del:p.(Thr272Serfs*10)	p.T272SfsX10	**T272fs**	201	95	154	62.7	71	71.1	59	7.0
Intron 8	NM_002087.2:c.709_835del:p.(Ala237Trpfs*4)	p.A237WfsX4	**A237fs**	33	4	32	61.0	25	69.0	24	9.2
Intron 8	NM_002087.2:c.833_834del:p.(Thr278Serfs*7)	p.T278SfsX7	**T278fs**	6	1	6	60.5	4	74.3	4	8.0
Intron 8	NM_002087.2:c.836-1G>C		**IVS8-1G>C**	7	4	7	63.1	1	69.0	1	4.0
Intron 8	NM_002087.2:c.836-1G>T		**IVS8-1G>T**	2	1	2	69.5	0		0	
Exon 9	NM_002087.2:c.848_854dup:p.(Asp285Glufs*3)	p.D285EfsX3	**D285fs**	1	1	1	53.0	0		0	
Exon 9	NM_002087.2:c.882T>G:p.(Tyr294*)	p.Y294X	**Y294X**	9	3	4	59.0	3	67.0	3	5.7
Exon 9	NM_002087.2:c.898C>T:p.(Gln300*)	p.Q300X	**Q300X**	18	8	16	61.6	9	63.3	8	6.5
Exon 9	NM_002087.2:c.900_901dup:p.(Ser301Cysfs*61)	p.S301CfsX61	**S301fs**	22	9	20	59.5	13	71.5	11	5.1
Exon 9	NM_002087.2:c.903_904insTG:p.(Gly302Trpfs*60)	p.G302WfsX60	**G302fs**	0		0		0		0	
Exon 9	NM_002087.2:c.907dup:p.(Ala303Glyfs*14)	p.A303GfsX14	**A303fs (907_908insG)**	2	2	1	53.0	0		0	
Exon 9	NM_002087.2:c.907del:p.(Ala303Profs*58)	p.A303PfsX58	**A303fs (907delG)**	1	1	1	63.0	0		0	
Exon 9	NM_002087.2:c.909del:p.(Trp304Glyfs*57)	p.W304GfsX57	**W304fs (909delC)**	4	4	4	56.3	3	64.7	3	6.0
Exon 9	NM_002087.2:c.910_911insTG:p.(Trp304Leufs*58)	p.W304LfsX58	**W304fs (910_911insTG)**	19	4	9	61.1	15	70.7	8	7.3
Exon 9	NM_002087.2:c.911G>A:p.(Trp304*)	p.W304X	**W304X**	9	8	8	62.8	4	69.0	3	7.7
Intron 9	NM_002087.2:c.933+1del		**IVS9+1delG**	5	1	5	58.8	0		0	
Intron 9	NM_002087.2:c.933+1G>A		**IVS9+1G>A**	8	4	8	61.0	3	64.0	3	5.0
Exon 10	NM_002087.2:c.942C>A:p.(Cys314*)	p.C314X	**C314X**	6	4	4	72.8	3	78.3	2	4.0
Exon 10	NM_002087.2:c.975del:p.(Phe326Leufs*35)	p.F326LfsX35	**F326fs**	0		0		0		0	

GRN	Mutation	Predicted protein change	Mutation alias	N total	N families	N AAO	Mean AAO	N AAD	Mean AAD	N DD	Mean DD
Exon 10	NM_002087.2:c.988_989del:p.(Thr330Alafs*6)	p.T330AfsX6	**T330fs**	1	1	1	62.0	0		0	
Exon 10	NM_002087.2:c.988_989dup:p.(Gln331Argfs*31)	p.Q331RfsX31	**Q331fs**	4	4	2	63.5	2	61.0	0	
Exon 10	NM_002087.2:c.998del:p.(Gly333Valfs*28)	p.G333VfsX28	**G333fs**	3	2	3	63.7	3	70.3	3	6.7
Exon 10	NM_002087.2:c.1009C>T:p.(Gln337*)	p.Q337X	**Q337X**	2	2	2	60.5	1	69.0	1	10.0
Exon 10	NM_002087.2:c.1013_1024del:p.(Gly338_Gln341del)	p.Q337_340del	**Q337_340del**	1	1	1	69.0	0		0	
Exon 10	NM_002087.2:c.1012_1013delinsC:p.(Gly338Argfs*23)	p.G338RfsX23	**G338fs**	1	1	1	54.0	0		0	
Exon 10	NM_002087.2:c.1014del:p.(His340Thrfs*21)	p.H340TfsX21	**H340fs**	2	2	1	54.0	0		0	
Exon 10	NM_002087.2:c.1021C>T:p.(Gln341*)	p.Q341X	**Q341X**	7	4	7	66.4	2	88.0	2	10.5
Exon 10	NM_002087.2:c.1048dup:p.(Ala350Glyfs*18)	p.A350GfsX18	**A350fs**	5	1	2	58.0	4	66.0	1	3.0
Exon 10	NM_002087.2:c.1070del:p.(Pro357Hisfs*4)	p.P357HfsX4	**P357fs**	1	1	1	44.0	1	51.0	1	7.0
Exon 10	NM_002087.2:c.1072C>T:p.(Gln358*)	p.Q358X	**Q358X**	0		0		0		0	
Exon 10	NM_002087.2:c.1095_1096del:p.(Cys366*)	p.C366fsX1	**C366fs**	13	6	13	61.2	4	77.8	4	8.5
Exon 10	NM_002087.2:c.1117C>T:p.(Pro373Ser)	p.P373S	**P373S**	4	1	4	59.8	2	69.5	2	4.5
Exon 10	NM_002087.2:c.1144dup:p.(Thr382Asnfs*32)	p.T382NfsX32	**T382fs (1144_1145insA)**	1	1	1	62.0	0		0	
Exon 10	NM_002087.2:c.1145del:p.(Thr382Serfs*30)	p.T382SfsX30	**T382fs (1145delC)**	9	3	7	54.9	5	59.8	5	6.0
Exon 10	NM_002087.2:c.1157G>A:p.(Trp386*)	p.W386X	**W386X**	11	4	10	64.2	7	74.3	6	5.5
Intron 10	NM_002087.2:c.1179del:p.(Ala394Leufs*18)	p.A394LfsX18	**A394fs**	1	1	1	51.0	0		0	
Intron 10	NM_002087.2:c.1179+2T>C		**IVS10+2T>C**	2	1	1	59.0	1	63.0	1	4.0
Intron 10	NM_002087.2:c.1179+3A>G		**IVS10+3A>G**	3	1	3	60.7	1	64.0	1	9.0
Exon 11	NM_002087.2:c.1196_1197del:p.(D399Afs*14)	p.D399AfsX14	**D399fs**	2	1	1	60.0	1	60.0	0	
Exon 11	NM_002087.2:c.1201C>T:p.(Gln401*)	p.Q401X	**Q401X**	5	3	5	58.2	1	63.0	1	7.0
Exon 11	NM_002087.2:c.1212C>A:p.(Cys404*)	p.C404X	**C404X**	1	1	1	58.0	1	66.0	1	8.0
Exon 11	NM_002087.2:c.1231_1232del:p.(Val411Serfs*2)	p.V411SfsX2	**V411fs**	2	1	1	66.0	2	72.5	1	4.0
Exon 11	NM_002087.2:c.1231_1232dup:p.(Ala412*)	p.A412X	**A412X**	1	1	1	61.0	1	68.0	1	7.0
Exon 11	NM_002087.2:c.1243C>T:p.(Gln415*)	p.Q415X	**Q415X**	6	6	6	58.2	0		0	
Exon 11	NM_002087.2:c.1246dup:p.(Cys416Leufs*30)	p.C416LfsX30	**C416fs**	11	1	9	64.4	9	72.1	8	7.5
Exon 11	NM_002087.2:c.1252C>T:p.(Arg418*)	p.R418X	**R418X**	20	8	13	56.9	14	65.5	11	8.7
Exon 11	NM_002087.2:c.1256_1263dup:p.(Ile422Glufs*72)	p.I422EfsX72	**I422fs**	6	1	5	61.0	3	70.0	2	6.5
Exon 11	NM_002087.2:c.1317_1318del:p.(Asp441Hisfs*4)	p.D441HfsX4	**D441fs**	11	4	8	57.4	7	62.1	5	5.0
Exon 11	NM_002087.2:c.1354del:p.(Val452Trpfs*39)	p.V452WfsX39	**V452fs**	9	4	6	60.0	5	70.2	5	10.8
Exon 11	NM_002087.2:c.1395dup:p.(Cys466Leufs*46)	p.C466LfsX46	**C466fs**	4	2	3	57.0	3	61.3	3	4.3
Exon 11	NM_002087.2:c.1402C>T:p.(Gln468*)	p.Q468X	**Q468X**	3	2	2	59.5	1	66.0	1	6.0
Intron 11	NM_002087.2:c.1415_1645del:p.(Ala472_Gln548del)	p.A472_Q548del	**A472_Q548del**	2	2	2	50.0	0		0	
Exon 12	NM_002087.2:c.1414_1644del:p.(Ala472Valfs*10)	p.A472VfsX10	**A472fs**	4	3	3	65.0	2	74.0	2	8.5
Exon 12	NM_002087.2:c.1420_1421del:p.(Cys474Leufs*37)	p.C474LfsX37	**C474fs**	0		0		0		0	
Exon 12	NM_002087.2:c.1428_1431del:p.(Glu476Aspfs*14)	p.E476DfsX14	**E476fs**	2	1	2	62.0	2	74.0	2	12.0
Exon 12	NM_002087.2:c.1446C>A:p.(Cys482*)	p.C482X	**C482X**	5	1	4	55.8	3	70.7	3	17.3
Exon 12	NM_002087.2:c.1477C>T:p.(Arg493*)	p.R493X	**R493X**	55	22	40	60.2	42	67.5	30	6.3
Exon 12	NM_002087.2:c.1494_1498del:p.(Glu498Aspfs*12)	p.E498DfsX12	**E498fs**	8	5	8	57.6	0		0	
Exon 12	NM_002087.2:c.1507C>T:p.(Gln503*)	p.Q503X	**Q503X**	1	1	1	75.0	0		0	
Exon 12	NM_002087.2:c.1603C>T:p,(Arg535*)	p.R535X	**R535X**	1	1	1	72.0	0		0	
Exon 12	NM_002087.2:c.1612C>T:p.(Arg538*)	p.R538X	**R538X**	0		0		0		0	

MAPT	Mutation	Predicted protein change	Mutation alias	N total	N families	N AAO	Mean AAO	N AAD	Mean AAD	N DD	Mean DD
Exon 1	NM_001123066.3:c.14G>A:p.(Arg5His)	p.R5H (p.R5H)	**R5H**	3	2	3	59.3	3	78.0	3	18.7
Exon 1	NM_001123066.3:c.14G>T:p.(Arg5Leu)	p.R5L (p.R5L)	**R5L**	1	1	1	62.0	1	67.0	1	5.0
Exon 2	NM_001123066.3:c.163G>A:p.(Gly55Arg)	p.G55R (p.G55R)	**G55R**	2	1	2	61.0	1	76.0	1	6.0
Exon 9	NM_001123066.3:c.1775A>C:p.(Lys592Thr)	p.K257T (p.K592T)	**K257T**	5	3	4	46.3	3	54.0	3	6.3
Exon 9	NM_001123066.3:c.1783A>G:p.(Ile595Val)	p.I260V (p.I595V)	**I260V**	1	1	1	68.0	1	77.0	1	9.0
Exon 9	NM_001123066.3:c.1801C>G:p.(Leu601Val)	p.L266V (p.L601V)	**L266V**	8	4	7	32.4	6	36.2	6	4.7
Exon 9	NM_001123066.3:c.1816G>C:p.(Gly606Arg)	p.G271R (p.G606R)	**G271R**	1	1	1	50.0	0		0	
Exon 9	NM_001123066.3:c.1820G>T:p.(Gly607Val)	p.G272V (p.G607V)	**G272V**	10	1	7	44.4	5	55.4	5	10.8
Exon 9	NM_001123066.3:c.1822G>A:p.(Gly608Arg)	p.G273R (p.G608R)	**G273R**	1	1	1	63.0	0		0	
Intron 9	NM_001123066.3:c.1828-15T>C		**IVS9-15T>C**	1	1	1	46.0	1	57.0	1	11.0
Intron 9	NM_001123066.3:c.1828-11G>C		**IVS9-11G>C**	5	1	2	58.5	5	66.0	2	8.0
Intron 9	NM_001123066.3:c.1828-10G>C		**IVS9-10G>C**	3	1	1	50.0	3	59.7	1	13.0
Intron 9	NM_001123066.3:c.1828-10G>T		**IVS9-10G>T**	12	2	11	46.1	8	53.5	7	5.9
Exon 10	NM_001123066.3:c.1842T>G:p.(Asn614Lys)	p.N279K (p.N614K)	**N279K**	44	17	36	43.8	38	52.4	31	6.5
Exon 10	NM_001123066.3:c.1846_1848delAAG:p.(Lys616del)	p.deltaK280 (p.deltaK616)	**deltaK280**	4	4	4	57.0	3	66.3	3	8.0
Exon 10	NM_001123066.3:c.1857T>C:p.(=)	p.L284 (p.L619)	**L284L**	7	2	7	51.7	6	62.0	6	9.6
Exon 10	NM_001123066.3:c.1856T>G:p.(Leu619Arg)	p.L284R (p.L619R)	**L284R**	3	1	3	42.3	3	49.0	3	6.7
Exon 10	NM_001123066.3:c.1858A>C:p.(Ser620Arg)	p.S285R (p.S620R)	**S285R**	1	1	1	46.0	1	49.0	1	3.0
Exon 10	NM_001123066.3:c.1876T>C:p.(Cys626Arg)	p.C291R (p.C626R)	**C291R**	2	1	2	53.5	1	67.0	1	7.0
Exon 10	NM_001123066.3:c.1891A>C:p.(Asn631His)	p.N296H (p.N631H)	**N296H**	4	1	1	57.0	4	65.8	1	5.0
Exon 10	NM_001123066.3:c.1892_1894delATA:p.(Asn631del)	p.N296del (p.N631del)	**delN296**	5	4	5	49.2	1	42.0	1	3.0
Exon 10	NM_001123066.3:c.1893T>C:p.(=)	p.N296 (p.N631)	**N296N**	6	3	3	49.3	3	64.3	1	10.0
Exon 10	NM_001123066.3:c.1897A>G:p.(Lys633Glu)	p.K298E (p.K633E)	**K298E**	2	1	2	62.5	2	67.5	2	5.0
Exon 10	NM_001123066.3:c.1906C>A:p.(Pro636Thr)	p.P301T (p.P636T)	**P301T**	5	1	5	49.8	4	52.3	4	3.8
Exon 10	NM_001123066.3:c.1906C>T:p.(Pro636Ser)	p.P301S (p.P636S)	**P301S**	20	5	15	34.3	10	40.8	7	5.0
Exon 10	NM_001123066.3:c.1907C>T:p.(Pro636Leu)	p.P301L (p.P636L)	**P301L**	234	59	174	53.0	139	60.3	111	8.2
Exon 10	NM_001123066.3:c.1913G>T:p.(Gly638Val)	p.G303V (p.G638V)	**G303V**	6	2	6	38.5	5	43.4	5	4.6
Exon 10	NM_001123066.3:c.1915G>A:p.(Gly639Ser)	p.G304S (p.G639S)	**G304S**	2	1	2	67.5	1	87.0	1	17.0
Exon 10	NM_001123066.3:c.1919G>A:p.(Ser640Asn)	p.S305N (p.S640N)	**S305N**	14	5	13	48.1	4	54.8	4	9.3
Exon 10	NM_001123066.3:c.1919G>T:p.(Ser640Ile)	p.S305I (p.S640I)	**S305I**	3	2	3	41.0	2	47.0	2	3.5
Exon 10	NM_001123066.3:c.1920T>C:p.(=)	p.S305 (p.S640)	**S305S**	9	6	8	48.5	6	55.2	6	4.0
Intron 10	NM_001123066.3:c.1920+3G>A		**IVS10+3G>A**	13	4	8	46.3	6	50.3	5	12.5
Intron 10	NM_001123066.3:c.1920+4A>C		**IVS10+4A>C**	1	1	1	46.0	1	57.0	1	11.0
Intron 10	NM_001123066.3:c.1920+11T>C		**IVS10+11T>C**	2	2	2	52.0	2	59.5	2	6.0
Intron 10	NM_001123066.3:c.1920+12C>T		**IVS10+12C>T**	1	1	1	56.0	1	65.0	1	8.0
Intron 10	NM_001123066.3:c.1920+12C>A		**IVS10+12C>A**	2	1	1	48.0	2	54.0	1	9.0
Intron 10	NM_001123066.3:c.1920+13A>G		**IVS10+13A>G**	2	1	1	64.0	2	69.0	1	6.0
Intron 10	NM_001123066.3:c.1920+14C>T		**IVS10+14C>T**	19	2	17	44.6	13	55.6	12	11.8
Intron 10	NM_001123066.3:c.1920+15A>C		**IVS10+15A>C**	6	1	6	47.7	3	57.3	3	7.7
Intron 10	NM_001123066.3:c.1920+16C>T		**IVS10+16C>T**	149	48	105	50.9	94	60.8	66	10.5
Intron 10	NM_001123066.3:c.1920+19C>G		**IVS10+19C>G**	1	1	1	52.0	0		0	
Exon 11	NM_001123066.3:c.1949T>G:p.(Leu650Arg)	p.L315R (p.L650R)	**L315R**	7	1	7	53.6	7	59.1	7	5.6
Exon 11	NM_001123066.3:c.1950G>A:p.(=)	p.L315 (p.L650)	**L315L**	8	2	8	50.9	3	52.3	3	6.0
Exon 11	NM_001123066.3:c.1955A>T:p.(Lys652Met)	p.K317M (p.K652M)	**K317M**	11	1	11	47.0	9	51.9	9	5.6
Exon 11	NM_001123066.3:c.1964C>T:p.(Ser655Phe)	p.S320F (p.S655F)	**S320F**	3	2	2	47.0	2	57.0	2	10.0
Exon 11	NM_001123066.3:c.1999C>T:p.(Pro667Ser)	p.P332S (p.P667S)	**P332S**	3	1	3	53.0	1	85.0	1	25.0
Exon 12	NM_001123066.3:c.2008G>A:p.(Gly670Ser)	p.G335S (p.G670S)	**G335S**	1	1	1	22.0	1	36.0	1	14.0

MAPT	Mutation	Predicted protein change	Mutation alias	N total	N families	N AAO	Mean AAO	N AAD	Mean AAD	N DD	Mean DD
Exon 12	NM_001123066.3:c.2009G>T:p.(Gly670Val)	p.G335V (p.G670V)	**G335V**	6	1	5	25.4	4	36.5	3	10.0
Exon 12	NM_001123066.3:c.2012A>G:p.(Gln671Arg)	p.Q336R (p.Q671R)	**Q336R**	3	2	2	60.0	1	39.0	0	
Exon 12	NM_001123066.3:c.2013G>C:p.(Gln671His)	p.Q336H (p.Q671H)	**Q336H**	5	3	4	61.8	4	72.8	4	12.0
Exon 12	NM_001123066.3:c.2014G>A:p.(Val672Met)	p.V337M (p.V672M)	**V337M**	20	6	17	48.2	10	71.5	10	14.2
Exon 12	NM_001123066.3:c.2030A>T:p.(Glu677Val)	p.E342V (p.E677V)	**E342V**	2	1	2	43.5	2	55.0	2	11.5
Exon 12	NM_001123066.3:c.2057A>G:p.(Gln686Arg)	p.Q351R (p.Q686R)	**Q351R**	2	1	2	51.5	0		0	
Exon 12	NM_001123066.3:c.2060C>T:p.(Ser687Leu)	p.S352L (p.S687L)	**S352L**	2	1	2	29.5	2	31.5	2	2.0
Exon 12	NM_001123066.3:c.2071T>A:p.(Ser691Thr)	p.S356T (p.S691T)	**S356T**	3	2	3	30.3	1	42.0	1	15.0
Exon 12	NM_001123066.3:c.2092G>A:p.(Val698Ile)	p.V363I (p.V698I)	**V363I**	4	3	4	61.5	1	80.0	1	5.0
Exon 12	NM_001123066.3:c.2093T>C:p.(Val698Ala)	p.V363A (p.V698A)	**V363A**	3	1	3	58.0	1	67.0	1	2.0
Exon 12	NM_001123066.3:c.2095C>T:p.(Pro699Ser)	p.P364S (p.P699S)	**P364S**	3	2	2	52.5	2	57.5	1	2.0
Exon 12	NM_001123066.3:c.2101G>A:p.(Gly701Arg)	p.G366R (p.G701R)	**G366R**	2	1	2	49.5	1	55.0	1	8.0
Exon 12	NM_001123066.3:c.2111A>T:p.(Lys704Ile)	p.K369I (p.K704I)	**K369I**	1	1	1	50.0	1	61.0	1	11.0
Exon 13	NM_001123066.3:c.2120A>G:p.(Glu707Gly)	p.E372G (p.E707G)	**E372G**	1	1	1	40.0	1	58.0	1	18.0
Exon 13	NM_001123066.3:c.2170G>A:p.(Gly724Arg)	p.G389R (p.G724R)	**G389R (2170G>A)**	6	5	5	29.0	2	30.5	2	4.0
Exon 13	NM_001123066.3:c.2170G>C:p.(Gly724Arg)	p.G389R (p.G724R)	**G389R (2170G>C)**	6	6	6	30.8	5	35.0	5	5.8
Exon 13	NM_001123066.3:c.2221C>T:p.(Arg741Trp)	p.R406W (p.R741W)	**R406W**	67	9	39	55.4	28	70.9	21	16.9
Exon 13	NM_001123066.3:c.2233A>C:p.(Asn745His)	p.N410H (p.N745H)	**N410H**	1	1	1	53.0	1	67.0	1	14.0
Exon 13	NM_001123066.3:c.2275C>A:p.(Gln759Lys)	p.Q424K (p.Q759K)	**Q424K**	0		0		0		0	
Exon 13	NM_001123066.3:c.2285C>T:p.(Thr762Met)	p.T427M (p.T762M)	**T427M**	1	1	1	56.0	1	65.0	1	9.0

Data from published studies was included if individual-level data was available rather than group-level data only.

All mutations described in the literature are included here even when no individual clinical data was available for analysis within the study – these mutations are shown here by a 0 in the 'N total' column: 11 *GRN* mutations and 1 *MAPT* mutation.

Of note, data was included from both confirmed mutation carriers and from some family members who were assumed to be mutation carriers based on their clinical phenotype – this was the case for data from sites in the study as well as the data taken from publications. However, there is a potential that some untested family members could be phenocopies and not true mutation carriers.

Data on individual mutations is also affected by the extent to which families have been investigated – it is likely that some families have been studied in more detail than others which may affect the observed frequencies.

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Section 2) Detailed statistical methods

The different statistical methods used in each part of the Results section are detailed below. Age at Onset = AAO, Age at Death = AAD, Disease Duration = DD.

Sex distribution

A chi-squared test was used to compare sex distribution in each of the genetic groups.

Age at Onset, Age at Death and Disease Duration

i) Differences between genetic groups (GRN, MAPT and *C9orf72*), *and ii) within a genetic group (GRN and MAPT)*

We used mixed effects models to examine whether there were differences in AAO, AAD and DD between genetic groups (*C9orf72, MAPT* and *GRN*) and between the common mutations in the *GRN* and *MAPT* groups. Due to the skewed distribution of DD, this was log transformed before analysis. To compare the mean AAO, AAD and DD between the *C9orf72, MAPT* and *GRN* groups we included a fixed effect of group in the model (g = *GRN*, *MAPT,* or *C9orf72*) and used Wald tests for hypothesis testing. The model allowed for relatedness by including a random effect for family membership. The model can be written as:

$y_{ijg} = \alpha_g + \mu_{jg} + \varepsilon_{ijg}$ (Equation 1)

where,

y_{ijg} is the AAO or AAD for the ith participant in the jth family within mutation group g

α_g is the mean for mutation group g

μ_{jg} is the random deviation for the jth family away from the mean in group g

ε_{ijg} is the residual error

The random effects and residual variance were assumed to follow a normal distribution and we assessed this assumption through plots of the residuals from the model. To allow variability in AAO, AAD or DD to differ by genetic group the model included three variance terms for the family random effects and three residual variance terms, one for each of the mutation carrier groups:

$\mu_{jg} \sim N(0, \sigma^2_{\mu,g})$

$\varepsilon_{ijg} \sim N(0, \sigma^2_{\varepsilon,g})$

Within the *GRN* and *MAPT* groups we used a mixed model to examine whether there were differences in mean AAO, AAD or DD between the common mutations. This model included fixed effects for the individual mutation and a random effect for family. Wald tests were used for comparisons between the mutations.

It is important to note that age at death was known for 59% of those with data on age at onset (57% in the *GRN* group, 65% in the *MAPT* group and 57% in the *C9orf72* group). For those with missing data of age at death, no information was available on disease duration or reasons for censoring so it was not possible to take account of this in the analysis (e.g. through survival models). This means the reported disease durations, and extent of variability in disease durations, may be underestimates of the true values.

It is also important to note that we did not account for the particular geographical site where a participant was from within the mixed models as there was no a priori hypothesis about this affecting age at onset or death, but if geography did have an effect then this could have introduced bias.

Lastly, AAO, AAD and DD data were captured in two methods, via a standardized form from the FTD Prevention Initiative sites, and via data taken from Pubmed articles. There is a possibility that AAO, AAD and DD data is differently interpreted when captured via these two methods.

iii) Generational analysis

In order to investigate potential anticipation and differences in AAO between generations we performed a subanalysis investigating families with two generations of AAO data (insufficient data being unavailable to explore three or more generations). Within each genetic group (*GRN*, *MAPT,* and *C9orf72)* we used a mixed effect model in which generation was included as a fixed effect and used a Wald test to examine whether there was evidence of a difference in AAO. Family membership was included as a random effect.

Analysis of differences within group of iv) sex and v) phenotype

We used mixed effects models including random effects for family to examine whether within each mutation carrier group there were differences in AAO, AAD and DD by sex and clinical phenotype. Due to the skewed distribution of DD, this was log transformed before analysis. In each model we included fixed effects for sex or clinical phenotype and used Wald tests for hypothesis testing on these variables.

vi) Disease duration analysis in MAPT mutation carriers

In the *MAPT* group we used the same mixed effect modelling approach to examine whether there were systematic differences in DD between those carrying mutations categorised by their functional consequences and underlying pathology into five groups: group 1 (exons 1,2 and 9); group 2 (exon/intron 10 affecting splicing); group 3 (exon 10 not affecting splicing); group 4 (exons 11-13 with non-PHF-tau pathology) and group 5 (exon 11-13 with PHF-tau pathology group).

Correlation of individual AAO (or AAD) with parental and mean family AAO (or AAD)

The Pearson correlation coefficient was calculated between a) an individual's AAO (or AAD) and the AAO (or AAD) of their affected parent, and b) an individual's AAO (or AAD) and the average AAO (or AAD) of other members of the same family.

Modelling variability in age at onset and age at death

We used mixed effects models to explore the extent to which variability in AAO and AAD were explained by *family membership* and the *specific mutation* carried, and how this differed between the genetic groups.

Firstly, to explore the variability in AAO (and AAD) by *family membership* in all mutation carriers we fitted the two level linear mixed effects model given in equation 1 using the *mixed* command in Stata. This includes a fixed effect for genetic group (g = *GRN*, *MAPT,* or *C9orf72*) and a random effect for family membership. It allows for variability in AAO (and AAD) to differ by genetic group by including three variance terms for the family random effects and three residual variance terms, one for each of the mutation carrier groups (g = *GRN, MAPT,* or *C9orf72*):

$\mu_{jg} \sim N(0, \sigma^2_{\mu,g})$

$\varepsilon_{ijg} \sim N(0, \sigma^2_{\varepsilon,g})$

To test for heterogeneity in the *within* family variability we used a likelihood ratio test to compare the above model to a simpler model that allowed for different distribution of the family random effect for each mutation carrier group but had one common residual variance for all carriers:

$\mu_{jg} \sim N(0, \sigma^2_{\mu,g})$

$\varepsilon_{ijg} \sim N(0, \sigma_{\varepsilon}^2)$

i.e. $\sigma_{\varepsilon,GRN}^2 = \sigma_{\varepsilon,MAPT}^2 = \sigma_{\varepsilon,C9orf72}^2$

To test whether there was heterogeneity in the *between* family variability we used a likelihood ratio test to compare the more complex model to a simpler model that allowed for different residual variance in each mutation carrier group but had one common variance for the family random effect:

$\mu_{jg} \sim N(0, \sigma_{\mu}^2)$

$\varepsilon_{ijg} \sim N(0, \sigma_{\varepsilon,g}^2)$

i.e. $\sigma_{\mu,GRN}^2 = \sigma_{\mu,MAPT}^2 = \sigma_{\mu,C9orf72}^2$

Secondly, for *GRN* and *MAPT* groups only we explored the extent to which variability in AAO (or AAD) was explained by the specific mutation by fitting a three level model with a fixed effect for genetic group (g = *GRN* and *MAPT*), and random effects of family membership nested within mutation carried.

$$y_{ijkg} = \alpha_g + \delta_{kg} + \mu_{jkg} + \varepsilon_{ijkg}$$

Where,

y_{ijkg} is the AAO or AAD for the ith participant in the jth family with specific mutation k, within mutation group g

α_g is the mean for mutation group g

μ_{jkg} is the random deviation for the jth family with specific mutation k away from the mean in group g

δ_{kg} is the random deviation for those carrying specific mutation k away from the mean in group g

ε_{ijkg} is the residual error

As before, to allow variability in AAO (and AAD) to differ by genetic group we allowed for different variance of the family random effect and residual variance for each of the mutation carrier groups (g = *GRN, MAPT*). In addition, we also allowed variability of the specific mutation random effect to differ by carrier group (g = *GRN, MAPT*)

$\delta_{kg} \sim N(0, \sigma_{\delta,g}^2)$

$\mu_{jkg} \sim N(0, \sigma_{\mu,g}^2)$

$\varepsilon_{ijkg} \sim N(0, \sigma_{\varepsilon,g}^2)$

To test whether *GRN* and *MAPT* groups differed in the extent to which the variability in AAO (and AAD) was due to the *specific mutation* we used a likelihood ratio test to compare the above model to a simpler model with one common variance for the specific mutation random effect, but still allowing for different family variance and residual variance terms for each mutation carrier group:

$\delta_{kg} \sim N(0, \sigma_{\delta}^2)$

$\mu_{jkg} \sim N(0, \sigma_{\mu,g}^2)$

$\varepsilon_{ijkg} \sim N(0, \sigma_{\varepsilon,g}^2)$

i.e. $\sigma_{\delta,GRN}^2 = \sigma_{\delta,MAPT}^2 = \sigma_{\delta,C9orf72}^2$

For the best fitting model, the intraclass correlation was used to quantify the degree of variability explained by family and by the specific mutation. Confidence intervals for the ICC were calculated in Stata using the *estat icc* command.

For a model which included only family random effect (e.g. in *C9orf72* carriers) the ICC for family was:

$$ICC(family) = \frac{\sigma_{\mu,g}^2}{\sigma_{\mu,g}^2 + \sigma_{\varepsilon,g}^2}$$

For a model which included random effects for both family and specific mutation random effect the ICC for specific mutation was:

$$ICC(mutation) = \frac{\sigma_{\delta,g}^2}{\sigma_{\delta,g}^2 + \sigma_{\mu,g}^2 + \sigma_{\varepsilon,g}^2}$$

And the ICC for family was:

$$ICC(family) = \frac{\sigma_{\delta,g}^2 + \sigma_{\mu,g}^2}{\sigma_{\delta,g}^2 + \sigma_{\mu,g}^2 + \sigma_{\varepsilon,g}^2}$$

The ICC for family includes both the family and specific mutation variance components in the numerator because members of the same family also share the same mutation.

Section 3) Geographical distribution

Geographical variability in the prevalence of the different genetic groups is shown in the main text and in Figure 1. Data from the following countries was included in the study:

Countries in the FPI	Other countries
Australia	Austria
Belgium	Brazil
Canada	Chile
France	China
Germany	Cyprus
Italy	Czech Republic
Netherlands	Denmark
Portugal	Finland
Spain	Greece
Sweden	India
UK	Ireland
USA	Israel
	Japan
	Malaysia
	Poland
	Slovenia
	Switzerland

Discussion

The study supports previous work suggesting that the most common genetic form of FTD overall across the world is due to pathogenic expansions of the *C9orf72* gene[45,46]. However, there is geographical variability: in Italy, *GRN* mutations are the most common cause of genetic FTD[47], mainly due to a large founder family with the T272fs variant[48], the most common *GRN* mutation in our study. Similarly, there are large *GRN* founder families in Spain (IVS7-1G>A[49,50], in the Basque country) as well as in Belgium (IVS1+5G>C[51,52]). *MAPT* mutations are the least common form of genetic FTD overall, although they are more common in some countries than others: in the Netherlands, this is due to a variety of mutations, whilst in the US, although different mutations contribute, there are a number of large families e.g. the pallido-ponto-nigral-degeneration (PPND) family with the N279K mutation[53-55]; similarly, in the UK, *MAPT* mutations are almost as common as *C9orf72* mutations due to a large founder family from the North Wales area of the UK with the IVS10+16C>T mutation[56]. In contrast, some of the most common mutations are seen across the world in a wider distribution e.g. the *GRN* R493X[57] and *MAPT*

P301L[58-61] mutations. Whilst *C9orf72* expansions are seen across the world, they are more common in North America and Europe (particularly the Nordic countries) than Asia[62-66]. One limitation of this study was our focus on age at onset and death data rather than ascertaining all families reported in the literature (i.e. those without any data were not included), and so the data may be an underrepresentation of some mutations, given the emphasis was not specifically on geographical variability.

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Section 4) Clinical phenotype

Many family members in previous generations did not have a specific diagnosis beyond 'dementia' and here they are categorized as 'Dementia-not otherwise specified' (Table 2 in main text, Supplementary Table 6). *Excluding these cases from a phenotypic analysis*, most patients in each group had a clinical diagnosis within the FTD spectrum (82% in *GRN*, 85% in *MAPT*, 87% in *C9orf72*). The most common phenotype was bvFTD across all three genetic groups: 55% of patients with *GRN* mutations, 66% of those in the *MAPT* mutation group and 42% of those with *C9orf72* expansions. Beyond bvFTD, there was variability across the mutations: PPA was a more common diagnosis in *GRN* mutation carriers (20%) with the specific variant usually being nfvPPA or PPA-NOS, compared with *MAPT* (6%) or *C9orf72* (4%). ALS (or FTD-ALS) was only a very rare occurrence in *GRN* (2%) or *MAPT* mutation carriers (1%) whereas 40% of *C9orf72* expansion carriers had either pure ALS (26%) or an FTD-ALS overlap (15%). CBS was seen not uncommonly in the *GRN* group (6%) and more rarely in the *MAPT* group (3%) but only in 2 patients in the *C9orf72* group. In comparison, a PSP syndrome (Richardson's syndrome) was seen in 6% of *MAPT* mutation carriers but not in the *GRN* group and in only 1 *C9orf72* expansion carrier. In each of the groups, clinical diagnoses outside of the FTD spectrum were seen in a sizeable minority: AD in 12% of *GRN*, 4% of *MAPT* and 8% of *C9orf72*; and Parkinson's disease (PD) had been diagnosed in 2% of *GRN*, 7% of *MAPT* and 1% of *C9orf72*.

Looking at the common mutations individually (Supplementary Table 6), the majority of *GRN* mutations had a similar pattern, with bvFTD being the most common phenotype and a substantial minority having PPA: T272fs 47% bvFTD, 18% PPA; R493X 49% bvFTD, 30% PPA; IVS7-1G>A 61% bvFTD, 18% PPA; C31fs 44% bvFTD, 25% PPA; and G35fs 49% bvFTD, 31% PPA. However, the A9D mutation was predominantly associated with bvFTD, found in 84% of patients. In the common *MAPT* mutations, P301L and R406W were associated mainly with bvFTD: 91% in both mutations. In comparison, the N279K mutation was associated mainly with a primary parkinsonian phenotype (94% with a primary diagnosis of PSP, CBS or PD). The IVS10+16C>T mutation was associated mainly with bvFTD (67%) but with a significant minority having a primary parkinsonian phenotype (17%).

Supplementary Table 6: Individual primary clinical diagnoses in each of the mutations. Diagnoses within the frontotemporal dementia (FTD) spectrum include behavioural variant FTD (bvFTD), the primary progressive aphasia (PPA) subtypes [nfv = nonfluent variant, sv = semantic variant, lv = logopenic variant, PPA-NOS = PPA not otherwise specific i.e. does not meet criteria for a specific subtype], FTD with amyotrophic lateral sclerosis (ALS), ALS, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). Diagnoses outside the FTD spectrum include Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), VaD (vascular dementia) and a dementia diagnosis not otherwise specific (Dementia-NOS).

	bvFTD	nfvPPA	svPPA	lvPPA	PPA-NOS	FTD-ALS	ALS	CBS	PSP	AD	HD	PD	DLB	VaD	Dementia-NOS	Other
All mutations total	**1250**	**147**	**40**	**7**	**42**	**166**	**284**	**63**	**34**	**205**	**5**	**70**	**10**	**17**	**997**	**66**
GRN total	**446**	**107**	**13**	**4**	**36**	**7**	**7**	**47**	**0**	**97**	**0**	**16**	**4**	**9**	**361**	**25**
delGRN[DR184]	1															
IVS1+3A>T															1	
IVS1+5G>C	15	12	2	1						2					2	1
delGRN [London]	1				1										5	
delGRN[French]	5	2				1	1					1			5	1
delGRN[Tubingen]	1															
M1 (1A>G)	2	1			1			1		2					1	
M1 (2T>C)	1														3	
M1 (3G>A)															2	
A9D	31							2		1					3	
C20fs																
D22fs	5	1													3	
C26X																
C30fs	2														1	
C31fs	7	4				2		1		2					31	
G35fs	17	5	1		5	1				2				4	7	
S40fs																
IVS2+1G>A	1														2	
IVS2-4C>T							1									
D47fs															1	
T52fs	8	2	1		1			2		9		1			13	
S78fs	1							1								
G79fs	1														1	
S82fs	22	2													7	
F86fs																
IVS3+2T>C		1						1		1					2	
IVS3-2delA		2													1	

	bvFTD	nfvPPA	svPPA	lvPPA	PPA-NOS	FTD-ALS	ALS	CBS	PSP	AD	HD	PD	DLB	VaD	Dementia-NOS	Other
D94fs																
C99fs	1														1	
P100fs															1	
C105fs	1															
C105Y	2											1			1	
R110X	5	1													2	
S116X															1	
IVS4+1G>C			1													
IVS4-1G>T															6	
N118fs	1															
V121fs	3														3	
Q125X	5	1													4	
C126X															2	
P127fs	1														1	
Q130fs (384_387delTAGT)	2														2	
Q130fs (388_391delCAGT)	9	2						1		4					7	
V141fs	1														2	
C149fs	4									1					4	
A155fs	1									1					1	
C157fs	9	6			1			2				1			9	2
R161fs	1															
L187fs (559del)																
L187fs (559dup)	2							1								
R198fs										1					1	
A199V	4	1	1			1		2							2	
S203fs (603_604insC)	1	1													1	
S203fs (607delT)	1															
S226fs	1	2													3	
Y229X	1							1						1	2	
IVS7+1G>A	7							2							5	
IVS7+1G>C															1	
IVS7+5_8delGTGA		2													6	
IVS7+6_9delTGAG	5	1			1					5					5	
IVS7-2A>G	5			1			3			1						
IVS7-2A>T	9	1													2	
IVS7-1G>A	23	7						1		5		1			12	1
Q249X	6															
C253X	1		1							1			1		1	
D254fs	1									2						
L255fs										1		1			1	
Q257fs	7	1	1		3					1					3	
K259X	2														2	
T272fs	71	18			9	2		11		22		1	2	1	51	13

	bvFTD	nfvPPA	svPPA	lvPPA	PPA-NOS	FTD-ALS	ALS	CBS	PSP	AD	HD	PD	DLB	VaD	Dementia-NOS	Other
A237fs	28				1					2					2	
T278fs	2														4	
IVS8-1G>C	2							2		2						1
IVS8-1G>T	1											1				
D285fs															1	
Y294X	3	1													5	
Q300X	9	2					2								5	
S301fS	11	2			1			1							5	2
G302fs																
A303fs (907_908insG)	1	1														
A303fs (907delG)	1															
W304fs (909delC)	1							2							1	
W304fs (910_911insTG)	1	2								2		5			9	
W304X	2							1							6	
IVS9+1delG	1														4	
IVS9+1G>A	2							1		3					2	
C314X	3														3	
F326fs																
T330fs																1
Q331fs	3														1	
G333fs		1	1												1	
Q337X															2	
Q337_340del								1								
G338fs		1														
H340fs	2															
Q341X	1	1			1					1				1	2	
A350fs	1							1							3	
P357fs	1															
Q358X																
C366fs	1	3			3					4					2	
P373S	2														2	
T382fs (1144_1145insA)															1	
T382fs (1145delC)	2		1					1							5	
W386X	4				1					1					5	
A394fs															1	
IVS10+2T>C	1														1	
IVS10+3A>G	1									1					1	
D399fs	1														1	
Q401X	2	1													1	1
C404X	1															
V411fs	1														1	
A412X													1			
Q415X	5	1														

	bvFTD	nfvPPA	svPPA	lvPPA	PPA-NOS	FTD-ALS	ALS	CBS	PSP	AD	HD	PD	DLB	VaD	Dementia-NOS	Other
C416fs										5				2	4	
R418X	4	2						1							13	
I422fs	1	1								1		1			2	
D441fs	1	3			1			2				1			3	
V452fs	4	2													3	
C466fs	1														3	
Q468X	1														2	
A472_Q548del								2								
A472fs			2	1						1						
C474fs																
E476fs					2											
C482X	1									4						
R493X	18	6		1	4					5		1			18	2
E498fs	3	1	1					3								
Q503X	1															
R535X										1						
R538X																
MAPT total	**354**	**14**	**14**	**0**	**2**	**2**	**1**	**14**	**33**	**24**	**1**	**39**	**1**	**1**	**274**	**17**
R5H	1	1														1
R5L									1							
G55R	1														1	
K257T	4														1	
I260V	1															
L266V	4		1												2	1
G271R		1														
G272V	6														4	
G273R		1														
IVS9-15T>C	1															
IVS9-11G>C	2														3	
IVS9-10G>C	2														1	
IVS9-10G>T	9									1					2	
N279K	2								6	2		22			12	
deltaK280	3									1						
L284L															7	
L284R									3							
S285R									1							
C291R							1	1								
N296H	1														3	
delN296	1								2			2				
N296N	1							1	1						3	
K298E		1								1						
P301T	2														3	
P301S	3							2	1			3			11	

	bvFTD	nfvPPA	svPPA	lvPPA	PPA-NOS	FTD-ALS	ALS	CBS	PSP	AD	HD	PD	DLB	VaD	Dementia-NOS	Other
P301L	134	1	4		1			1		3		1	1		86	2
G303V									6							
G304S		2														
S305N	6									1					6	1
S305I	2	1														
S305S	2								2			2		1	2	
IVS10+3G>A	4									1	1	1			5	1
IVS10+4A>C	1															
IVS10+11T>C															2	
IVS10+12C>T	1															
IVS10+12C>A															2	
IVS10+13A>G	1														1	
IVS10+14C>T	14									1					4	
IVS10+15A>C	4									1					1	
IVS10+16C>T	62	1	2		1			5	4	7		5			56	6
IVS10+19C>G	1															
L315R	6		1													
L315L	3	2	1												2	
K317M	2	1							6			1			1	
S320F	2														1	
P332S			2													1
G335S	1															
G335V	1														5	
Q336R	1		1							1						
Q336H						2		1							2	
V337M	16														4	
E342V															2	
Q351R	2															
S352L																2
S356T	1															2
V363I		1	2					1								
V363A												2			1	
P364S	3															
G366R	2															
K369I										1						
E372G	1															
G389R (2170G>A)	3														3	
G389R (2170G>C)	2	1						1							2	
R406W	31									3					33	
N410H								1								
Q424K																
T427M	1															
C9orf72 total	**450**	**26**	**13**	**3**	**4**	**157**	**276**	**2**	**1**	**84**	**4**	**15**	**5**	**7**	**362**	**24**

Discussion

The study further supports the clinical heterogeneity of genetic FTD, identifying multiple phenotypes both within and outside the FTD spectrum in each of the mutations. Whilst bvFTD is the most common phenotype in all three genetic groups, each group has particular associations with other primary phenotypes: ALS in *C9orf72* expansions, PPA in *GRN* mutations, and parkinsonism in *MAPT* mutations. Expansions in *C9orf72* are the commonest cause of familial ALS, and exemplify the spectrum of disease across FTD/ALS with pure FTD (46% of cases here with bvFTD or PPA) and ALS (26%) at either end, and the overlapping condition of FTD-ALS (15%) in the middle – of note, the frequencies here represent the primary phenotype, and it may well have been that many patients presenting with 'pure' ALS or FTD went on to develop the other condition later in time. The PPA phenotype in *GRN* mutations has not been explored in detail, but this study suggests two major phenotypes, nfvPPA fitting consensus Gorno-Tempini criteria[67], and a PPA syndrome not meeting criteria for any of the three major variants (PPA-NOS) – this 'mixed' aphasia pattern has been previously described as potentially distinctive for those with *GRN* mutations[68]. Whilst parkinsonism is most common in *MAPT* mutations, the phenotype is variable, often being diagnosed as either 'PD'[69] (suggesting the presence of an asymmetrical akinetic-rigid syndrome), or PSP (Richardson's syndrome)[70], more commonly than CBS, a condition that was also seen in a substantial minority of people with *GRN* mutations[71-73]. The phenotypic heterogeneity does not seem to be particularly related to the individual mutation in the *GRN* group (apart from perhaps the A9D variant), but there was a clear distinction between the majority of the common *MAPT* mutations in which bvFTD was the most frequent syndrome, and the N279K variant where a primary parkinsonian disorder predominated.

Outside of the FTD spectrum, a number of patients were given the clinical diagnosis of Alzheimer's disease, a diagnosis more commonly given when the AAO was older in each genetic group – this is likely to represent a number of factors including misdiagnosis (particularly in prior generations), a true amnestic presentation, which has been described in all three genetic groups[74-77], and potentially in older patients, a number of 'true' cases of neuropathological Alzheimer's disease occurring coincidentally. Less common phenotypes were also seen: Huntington's disease (HD) in 4 people with *C9orf72* expansions[78], Dementia with Lewy Bodies (DLB) in 4 people with *GRN* mutations and 5 people with *C9orf72* expansions (likely related to the combination of visual hallucinations and parkinsonism that can be seen in these conditions), and vascular dementia (VaD) in 9 people with *GRN* mutations (potentially related to the presence of white matter hyperintensities in a subset of people in this group[79]) and 7 people with *C9orf72* expansions.

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Section 5) Sex distribution

Sex distribution is shown in the text and in Table 1. Comparisons are shown in Supplementary Table 7.

Supplementary Table 7: Chi-squared tests comparing sex distribution across the genetic groups

Comparison of genetic groups	Chi-squared statistic	p-value
MAPT vs *GRN*	10.0442	0.0015
C9orf72 vs *GRN*	27.1048	<0.0001
MAPT vs *C9orf72*	1.8114	0.1783

Discussion

In terms of sex distribution we replicate the results of a recent meta-analysis which found an increased female:male ratio in *GRN* mutations[80]. One suggestion has been that this increase is due to the fact that in most populations women live longer than men and given the known age-related penetrance in *GRN*[81], female mutation carriers are therefore more likely to reach an age where they develop symptoms than men. Supportive of this theory is the finding that the mean age at onset (and age at death) was significantly older in the female *GRN* group, suggesting the presence of more women developing symptoms at an older age [See Section 9 below]. Survival does not seem to be a major factor in the increased female:male ratio as there was no significant difference between men and women in disease duration in the *GRN* group. There is also age-related penetrance in *C9orf72* mutation carriers[82], and this may account for the significantly older age at onset (and older age at death) in females in this group (although, unlike in *GRN* mutation carriers, we did not find any difference in frequency between the sexes). These findings in the *C9orf72* group replicate those of recent studies which showed an earlier onset in males[82,83]. One of these studies highlighted that bulbar onset ALS (which is more common in women) had an older AAO compared with spinal onset ALS[83]; however, we did not have data on the specific ALS type to investigate that further in this study.

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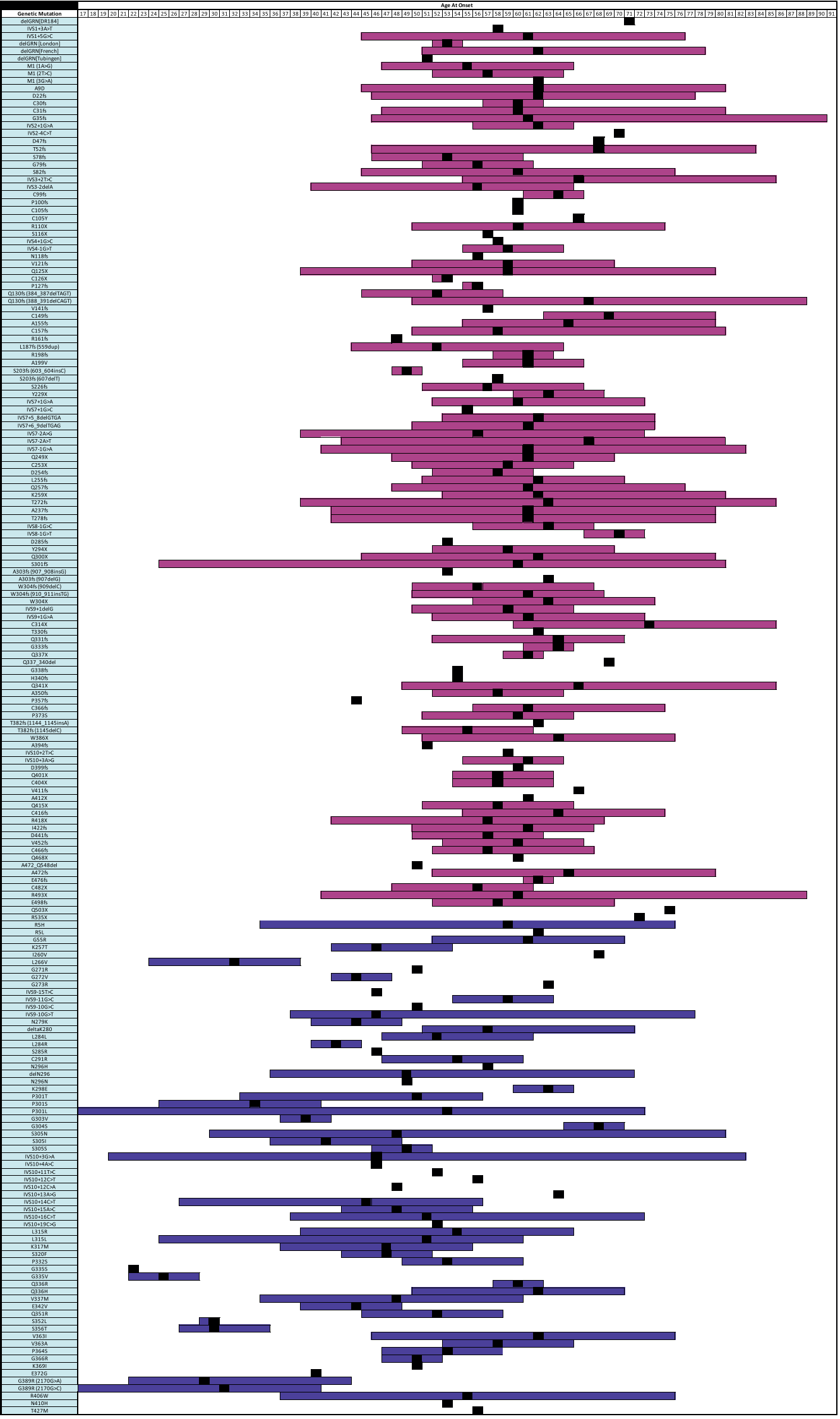
Section 6) Ranges of age at onset, age at death and disease duration in each genetic group and in the individual mutations

The mean AAO, AAD and DD in each individual mutation is shown in Supplementary Table 5 above. Supplementary Figure 2 shows the mean (black rectangle) and ranges for each of ages at onset and death, and disease duration i.e. the left-hand end of the bar is the youngest AAO and AAD, and the shortest DD, whilst the right-hand end of the bar is the oldest AAO and AAD, and the longest DD in each mutation.

Supplementary Figure 2: Mean and range of a) ages at onset, b) ages at death, and c) disease durations for the individual *GRN* and *MAPT* mutations. Means are shown as whole numbers, either rounded up if >.5 or rounded down if <.5.


Age At Onset
Genetic Mutation
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91
delGRN[DR184]
IVS1+3A>T
IVS1+5G>C
delGRN [London]
delGRN[French]
delGRN[Tubingen]
M1 (1A>G]
M1 (2T>C)
M1 (3G>A]
A9D
D22fs
C30fs
C31fs
G35fs
IVS2+1G>A
IVS2-4C>T
D47fs
T52fs
S78fs
G79fs
S82fs
IVS3+2T>C
IVS3-2delA
C99fs
P100fs
C105fs
C105Y
R110X
S116X
IVS4+1G>C
IVS4-1G>T
N118fs
V121fs
Q125X
C126X
P127fs
Q130fs (384_387delTAGT)
Q130fs (388_391delCAGT)
V141fs
C149fs
A155fs
C157fs
R161fs
L187fs (559dup)
R198fs
A199V
S203fs (603_604insC)
S203fs (607delT)
S226fs
Y229X
IVS7+1G>A
IVS7+1G>C
IVS7+5_8delGTGA
IVS7+6_9delTGAG
IVS7-2A>G
IVS7-2A>T
IVS7-1G>A
Q249X
C253X
D254fs
L255fs
Q257fs
K259X
T272fs
A237fs
T278fs
IVS8-1G>C
IVS8-1G>T
D285fs
Y294X
Q300X
S301fS
A303fs (907_908insG)
A303fs (907delG)
W304fs (909delC)
W304fs (910_911insTG)
W304X
IVS9+1delG
IVS9+1G>A
C314X
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G333fs
Q337X
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G338fs
H340fs
Q341X
A350fs
P357fs
C366fs
P373S
T382fs (1144_1145insA)
T382fs (1145delC)
W386X
A394fs
IVS10+2T>C
IVS10+3A>G
D399fs
Q401X
C404X
V411fs
A412X
Q415X
C416fs
R418X
I422fs
D441fs
V452fs
C466fs
Q468X
A472_Q548del
A472fs
E476fs
C482X
R493X
E498fs
Q503X
R535X
R5H
R5L
G55R
K257T
I260V
L266V
G271R
G272V
G273R
IVS9-15T>C
IVS9-11G>C
IVS9-10G>C
IVS9-10G>T
N279K
deltaK280
L284L
L284R
S285R
C291R
N296H
delN296
N296N
K298E
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P301S
P301L
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S305I
S305S
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IVS10+19C>G
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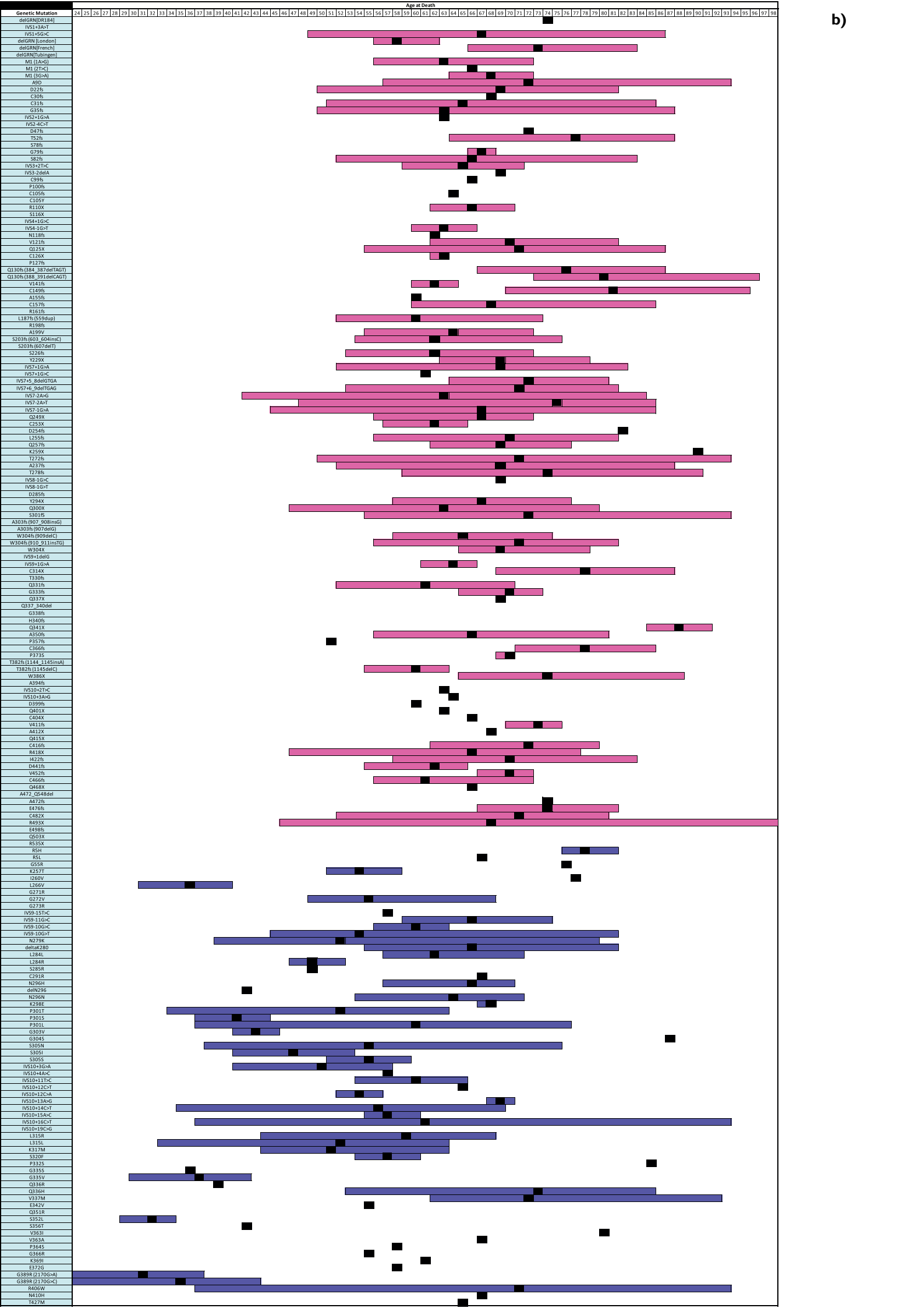
L315L
K317M
S320F
P332S
G335S
G335V
Q336R
Q336H
V337M
E342V
Q351R
S352L
S356T
V363I
V363A
P364S
G366R
K369I
E372G
G389R (2170G>A)
G389R (2170G>C)
R406W
N410H
T427M

a)


Age at Death
Genetic Mutation
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delGRN[DR184]
IVS1+3A>T
IVS1+5G>C
delGRN [London]
delGRN[French]
delGRN[Tubingen]
M1 (1A>G)
M1 (2T>C)
M1 (3G>A)
A9D
D22fs
C30fs
C31fs
G35fs
IVS2+1G>A
IVS2-4C>T
D47fs
T52fs
S78fs
G79fs
S82fs
IVS3+2T>C
IVS3-2delA
C99fs
P100fs
C105fs
C105Y
R110X
S116X
IVS4+1G>C
IVS4-1G>T
N118fs
V121fs
Q125X
C126X
P127fs
Q130fs (384_387delTAGT)
Q130fs (388_391delCAGT)
V141fs
C149fs
A155fs
C157fs
R161fs
L187fs (559dup)
R198fs
A199V
S203fs (603_604insC)
S203fs (607delT)
S226fs
Y229X
IVS7+1G>A
IVS7+1G>C
IVS7+5_8delGTGA
IVS7+6_9delTGAG
IVS7-2A>G
IVS7-2A>T
IVS7-1G>A
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IVS8-1G>T
D285fs
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S301fS
A303fs (907_908insG)
A303fs (907delG)
W304fs (909delC)
W304fs (910_911insTG)
W304X
IVS9+1delG
IVS9+1G>A
C314X
T330fs
Q331fs
G333fs
Q337X
Q337_340del
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IVS10+3A>G
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R418X
I422fs
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V452fs
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R535X
R5H
R5L
G55R
K257T
I260V
L266V
G271R
G272V
G273R
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IVS9-11G>C
IVS9-10G>C
IVS9-10G>T
N279K
deltaK280
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L284R
S285R
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P332S
G335S
G335V
Q336R
Q336H
V337M
E342V
Q351R
S352L
S356T
V363I
V363A
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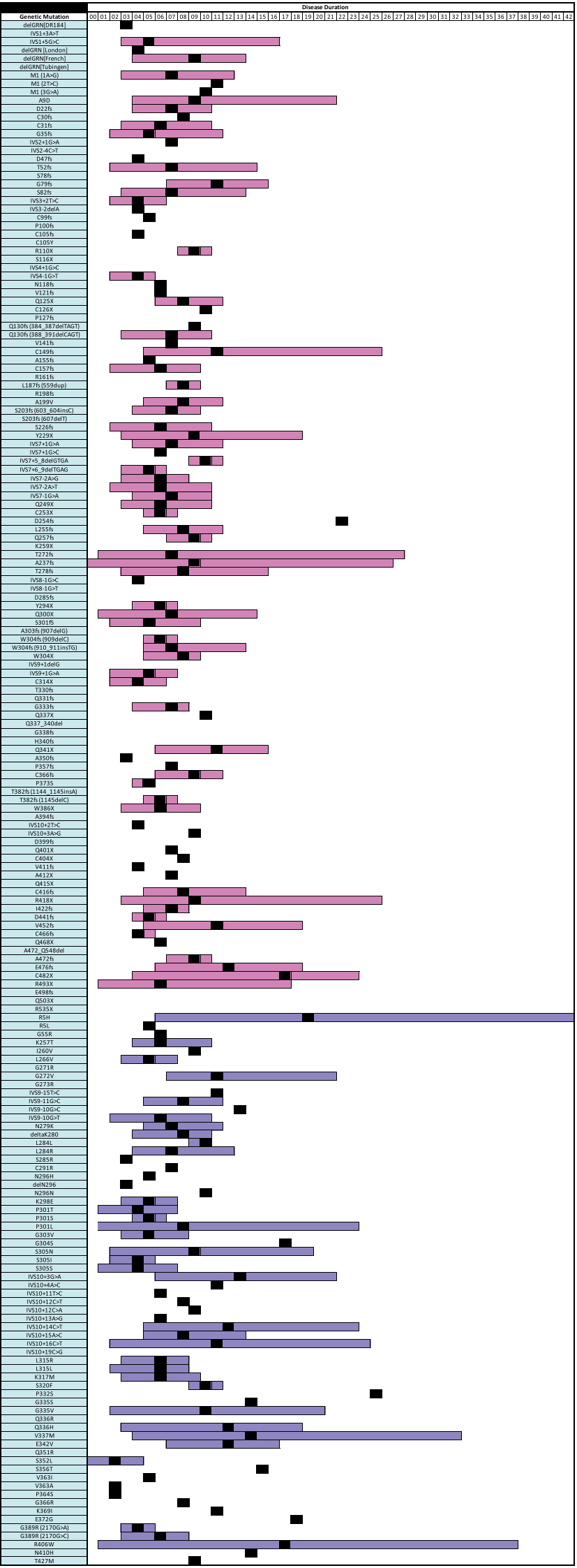
T427M

b)


Disease Duration
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Genetic Mutation
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IVS1+3A>T
IVS1+5G>C
delGRN [London]
delGRN[French]
delGRN[Tubingen]
M1 (1A>G)
M1 (2T>C)
M1 (3G>A)
A9D
D22fs
C30fs
C31fs
G35fs
IVS2+1G>A
IVS2-4C>T
D47fs
T52fs
S78fs
G79fs
S82fs
IVS3+2T>C
IVS3-2delA
C99fs
P100fs
C105fs
C105Y
R110X
S116X
IVS4+1G>C
IVS4-1G>T
N118fs
V121fs
Q125X
C126X
P127fs
Q130fs (384_387delTAGT)
Q130fs (388_391delCAGT)
V141fs
C149fs
A155fs
C157fs
R161fs
L187fs (559dup)
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S203fs (607delT)
S226fs
Y229X
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IVS7+1G>C
IVS7+5_8delGTGA
IVS7+6_9delTGAG
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IVS7-2A>T
IVS7-1G>A
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E498fs
Q503X
R535X
R5H
R5L
G55R
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G272V
G273R
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IVS9-11G>C
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IVS10+16C>T
IVS10+19C>G
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L315L
K317M
S320F
P332S
G335S
G335V
Q336R
Q336H
V337M
E342V
Q351R
S352L
S356T
V363I
V363A
P364S
G366R
K369I
E372G
G389R (2170G>A)
G389R (2170G>C)
R406W
N410H
T427M

c)

Section 7) Cumulative percentage probability of symptom onset in the genetic groups.

Data is shown within the main text and in Figure 3 showing the cumulative proportion of people with symptom onset by each year of age within each genetic group (*GRN, MAPT* and *C9orf72*) and in the common mutations (for *GRN* and *MAPT*). Data is shown in Supplementary Table 8. Comparisons of AAO as well as AAD and DD across the common mutations are shown in Supplementary Table 9.

Supplementary Table 8: Cumulative percentage probability of symptom onset in *GRN, MAPT* and *C9orf72* groups overall and the common *GRN* and *MAPT* mutations [in 5 year intervals]. Mean (standard deviation) AAO for the common mutations is shown in the last row of the table.

	GRN	***MAPT***	***C9orf72***	***GRN***						***MAPT***			
Age				**A9D**	**C31fs**	**G35fs**	**IVS7-1G>A**	**T272fs**	**R493X**	**IVS10+16C>T**	**N279K**	**P301L**	**R406W**
15		0.0	0.0									0.0	
20	0.0	0.7	0.2									1.1	
25	0.1	2.1	0.3									1.1	
30	0.1	4.9	0.5								0.0	1.1	
35	0.1	7.7	1.1					0.0		0.0	2.8	2.3	0.0
40	0.6	17.2	4.1	0.0			0.0	1.3	0.0	4.8	19.4	4.0	5.1
45	2.5	30.5	9.9	5.6	0.0	0.0	2.6	2.6	2.5	20.0	80.6	10.3	7.7
50	10.4	50.7	22.2	13.9	9.4	10.0	5.3	8.4	15.0	53.3	91.7	29.9	17.9
55	25.6	74.4	39.7	33.3	25.0	30.0	26.3	18.2	30.0	80.0	94.4	62.1	64.1
60	50.8	90.3	59.7	61.1	62.5	65.0	47.4	39.0	65.0	96.2	94.4	89.1	82.1
65	72.0	96.4	78.3	61.1	75.0	80.0	78.9	64.9	75.0	99.0	97.2	98.3	92.3
70	86.3	98.2	90.7	66.7	90.6	80.0	92.1	83.1	92.5	99.0	100.0	99.4	94.9
75	93.2	99.5	96.0	86.1	93.8	85.0	97.4	90.3	95.0	100.0		100.0	100.0
80	97.9	99.8	98.9	100.0	100.0	90.0	97.4	96.1	97.5				
85	99.7	100.0	99.5			97.5	100.0	100.0	97.5				
90	100.0		99.9			100.0			100.0				
95			100.0										
Mean (standard deviation)				**62.1 (10.6)**	**60.3 (8.2)**	**61.2 (10.9)**	**60.5 (7.9)**	**62.7 (8.9)**	**60.2 (8.9)**	**50.9 (6.1)**	**43.8 (6.7)**	**53.0 (7.4)**	**55.4 (7.5)**

Supplementary Table 9: Adjusted mean differences (with 95% confidence intervals) in age at onset (AAO), age at death (AAD) and disease duration (DD – natural log differences) comparing the common individual *GRN* and *MAPT* mutations.

	GRN	***MAPT***
AAO	A9D vs C31fs: 1.7 (-5.1, 8.6), p = 0.6151 A9D vs G35fs: 4.7 (-2.1, 11.5), p = 0.1750 A9D vs IVS7-1G>A: 1.8 (-4.8, 8.4), p = 0.5970 A9D vs T272fs: 4.0 (-1.9, 9.9), p = 0.1860 A9D vs R493X: 0.6 (-5.9, 7.2), p = 0.8525 C31fs vs G35fs: 2.9 (-2.3, 8.2), p = 0.2700 C31fs vs IVS7-1G>A: 0.03 (-4.9, 5.0), p = 0.9914 C31fs vs T272fs: 2.2 (-1.8, 6.3), p = 0.2770 C31fs vs R493X: -1.1 (-6.0, 3.8), p = 0.6522 G35fs vs IVS7-1G>A: -2.9 (-7.8, 2.0), p = 0.2458 G35fs vs T272fs: -0.7 (-4.7, 3.3), p = 0.7284 G35fs vs R493X: -4.1 (-8.9, 0.8), p = 0.1005 IVS7-1G>A vs T272fs: 2.2 (-1.4, 5.8), p = 0.2327 IVS7-1G>A vs R493X: -1.2 (-5.7, 3.4), p = 0.6210 T272fs vs R493X: -3.4 (-6.9, 0.2), p = 0.0625	IVS10+16C>T vs N279K: -5.9 (-9.7, -2.1), p = 0.0026 IVS10+16C>T vs P301L: 0.9 (-1.5, 3.3), p = 0.4736 IVS10+16C>T vs R406W: 3.7 (-0.6, 8.0), p = 0.0943 N279K vs P301L: 6.8 (3.0. 10.5), p = 0.0004 N279K vs R406W: 9.6 (4.4, 14.8), p = 0.0003 P301L vs R406W: 2.8 (-1.4, 7.1), p = 0.1934
AAD	A9D vs C31fs: -5.4 (-12.0, 1.2), p =0.1109 A9D vs G35fs: -7.0 (-13.6, -0.3), p = 0.0414 A9D vs IVS7-1G>A: -4.0 (-10.7, 2.8), p = 0.2489 A9D vs T272fs: 0.3 (-5.6, 6.2), p = 0.9136 A9D vs R493X: -3.8 (-10.0, 2.5), p = 0.2428 C31fs vs G35fs: -1.6 (-7.0, 3.9), p = 0.5750 C31fs vs IVS7-1G>A: 1.3 (-4.1, 7.0), p = 0.6099 C31fs vs T272fs: 5.7 (1.2, 10.1), p = 0.0123 C31fs vs R493X: 1.6 (-3.4, 6.6), p = 0.5203 G35fs vs IVS7-1G>A: 3.0 (-2.6, 8.6), p = 0.2923 G35fs vs T272fs: 7.3 (2.7, 11.8), p = 0.0018 G35fs vs R493X: 3.2 (-1.9, 8.3), p = 0.2157 IVS7-1G>A vs T272fs: 4.3 (-0.3, 8.9), p = 0.0690 IVS7-1G>A vs R493X: 0.2 (-4.9, 5.3), p = 0.9386 T272fs vs R493X: -4.1 (-8.0, -0.1), p = 0.0440	IVS10+16C>T vs N279K: -7.3 (-11.5, -3.2), p = 0.0005 IVS10+16C>T vs P301L: -1.2 (-4.1, 1.6), p = 0.3955 IVS10+16C>T vs R406W: 9.2 (4.2, 14.1), p = 0.0003 N279K vs P301L: 6.1 (2.0, 10.1), p = 0.0031 N279K vs R406W: 16.5 (10.8, 22.1), p = <0.0001 P301L vs R406W: 10.4 (5.6, 15.2), p = <0.0001
DD	A9D vs C31fs: -0.38 (-0.77, 0.01), p = 0.0543 A9D vs G35fs: -0.55 (-0.94, -0.16), p = 0.0056 A9D vs IVS7-1G>A: -0.29 (-0.69, 0.10), p = 0.1493 A9D vs T272fs: -0.38 (-0.73, - 0.03), p = 0.0328 A9D vs R493X: -0.46 (-0.84, -0.08), p = 0.0180 C31fs vs G35fs: -0.17 (-0.48, 0.15), p = 0.3037 C31fs vs IVS7-1G>A: 0.10 (-0.22, 0.41), p = 0.5568 C31fs vs T272fs: 0.004 (-0.26, 0.27), p = 0.9739 C31fs vs R493X: -0.07 (-0.38, 0.23), p = 0.6301 G35fs vs IVS7-1G>A: 0.26 (-0.05, 0.58), p = 0.1054 G35fs vs T272fs: 0.17 (-0.09, 0.43), p = 0.2016 G35fs vs R493X: 0.09 (-0.21, 0.39), p = 0.5567 IVS7-1G>A vs T272fs: -0.09 (-0.36, 0.17), p = 0.5004 IVS7-1G>A vs R493X: -0.17 (-0.48, 0.14), p = 0.2743 T272fs vs R493X: -0.08 (-0.33, 0.17), p = 0.5309	IVS10+16C>T vs N279K: -0.20 (-0.51, 0.10), p = 0.1933 IVS10+16C>T vs P301L: -0.25 (-0.46, -0.03), p = 0.0223 IVS10+16C>T vs R406W: 0.33 (-0.02, 0.69), p = 0.0633 N279K vs P301L: -0.04 (-0.34, 0.25), p = 0.7694 N279K vs R406W: 0.54 (0.13, 0.94), p = 0.0198 P301L vs R406W: 0.58 (0.24, 0.92), p = 0.0009

Section 8) Generational analysis

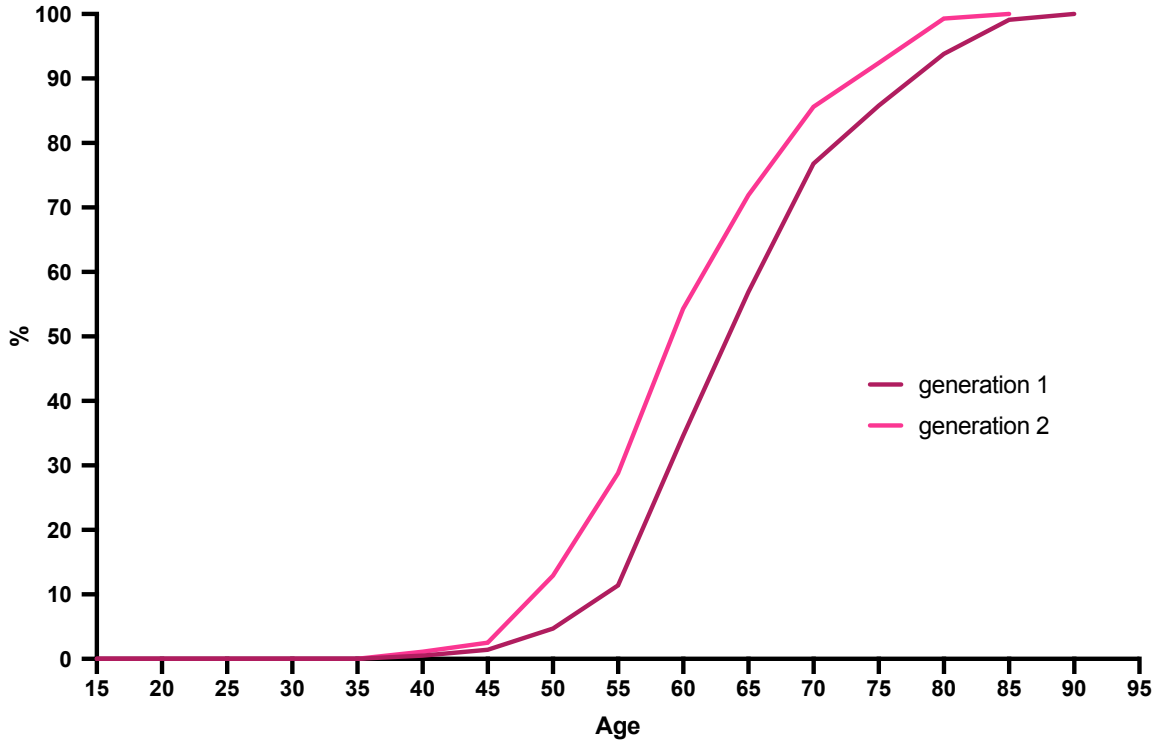
In order to investigate potential anticipation and differences in AAO between generations, we used a mixed effect model to perform a subanalysis investigating families with two generations of AAO data (insufficient data being unavailable to explore three or more generations). Results are shown in the main text, in Supplementary Table 10 and in Supplementary Figure 3.

Supplementary Table 10: Cumulative percentage probability of symptom onset in *GRN, MAPT* and *C9orf72* group generational analysis – generation 1 (earlier), generation 2 (later). N is the number of people in each group. In the bottom row adjusted mean differences between generation 1 and 2 are shown with 95% confidence intervals.

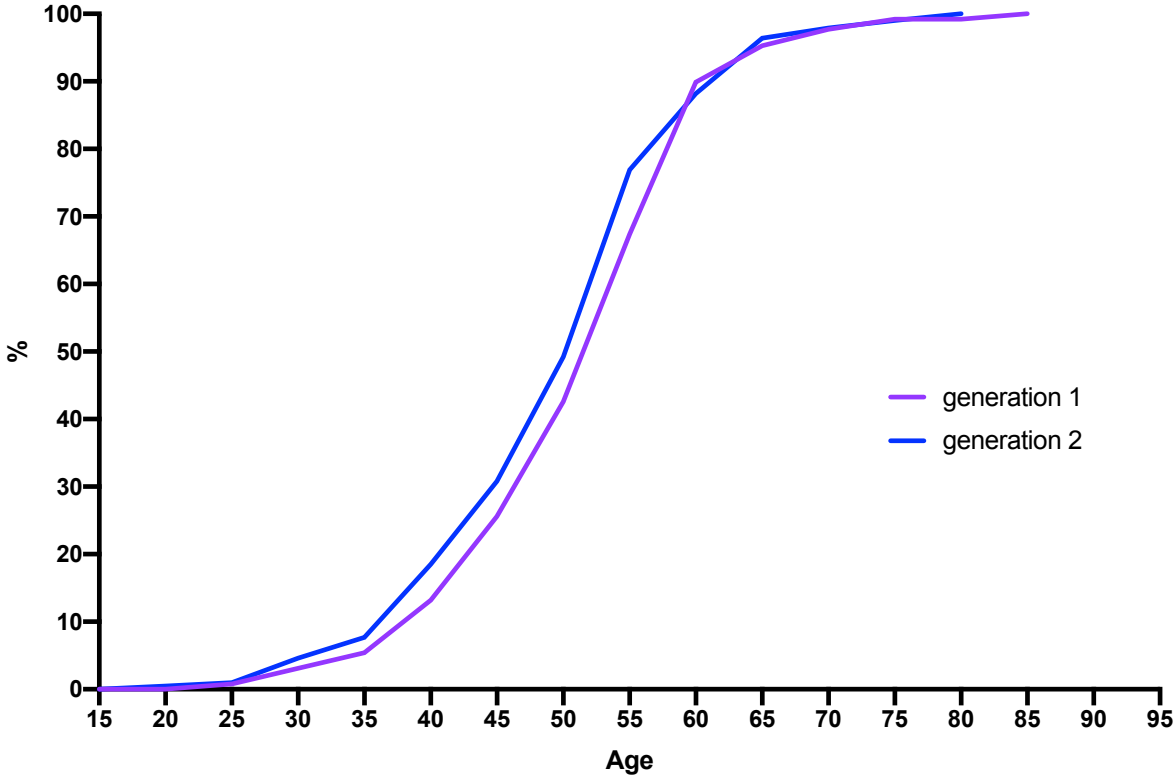
	GRN		***MAPT***		***C9orf72***	
Age	***Generation 1***	***Generation 2***	***Generation 1***	***Generation 2***	***Generation 1***	***Generation 2***
N	211	278	129	195	216	225
15				0.0		
20			0.0	0.5		
25			0.8	1.0		0.0
30			3.1	4.6	0.0	0.4
35	0.0	0.0	5.4	7.7	0.5	1.8
40	0.5	1.1	13.2	18.5	3.7	7.1
45	1.4	2.5	25.6	30.8	6.0	14.2
50	4.7	12.9	42.6	49.2	16.7	28.0
55	11.4	28.8	67.4	76.9	25.9	45.8
60	34.6	54.3	89.9	88.2	47.2	65.3
65	56.9	71.9	95.3	96.4	63.9	82.2
70	76.8	85.6	97.7	97.9	81.0	92.9
75	85.8	92.4	99.2	99.0	87.0	97.3
80	93.8	99.3	99.2	100.0	95.8	99.1
85	99.1	100.0	100.0		98.1	100.0
90	100.0				99.5	
95					100.0	
Adjusted mean difference (95% confidence intervals), p-value	-4.9 (-6.4, -3.5), p = <0.0001		-2.2 (-3.8, -0.5), p = 0.0106		-5.7 (-7.5, -4.0). p = <0.0001	

Supplementary Figure 3: Generational analysis of age at onset in a) *GRN*, b) *MAPT* and c) *C9orf72* groups – generation 1 (earlier), generation 2 (later).

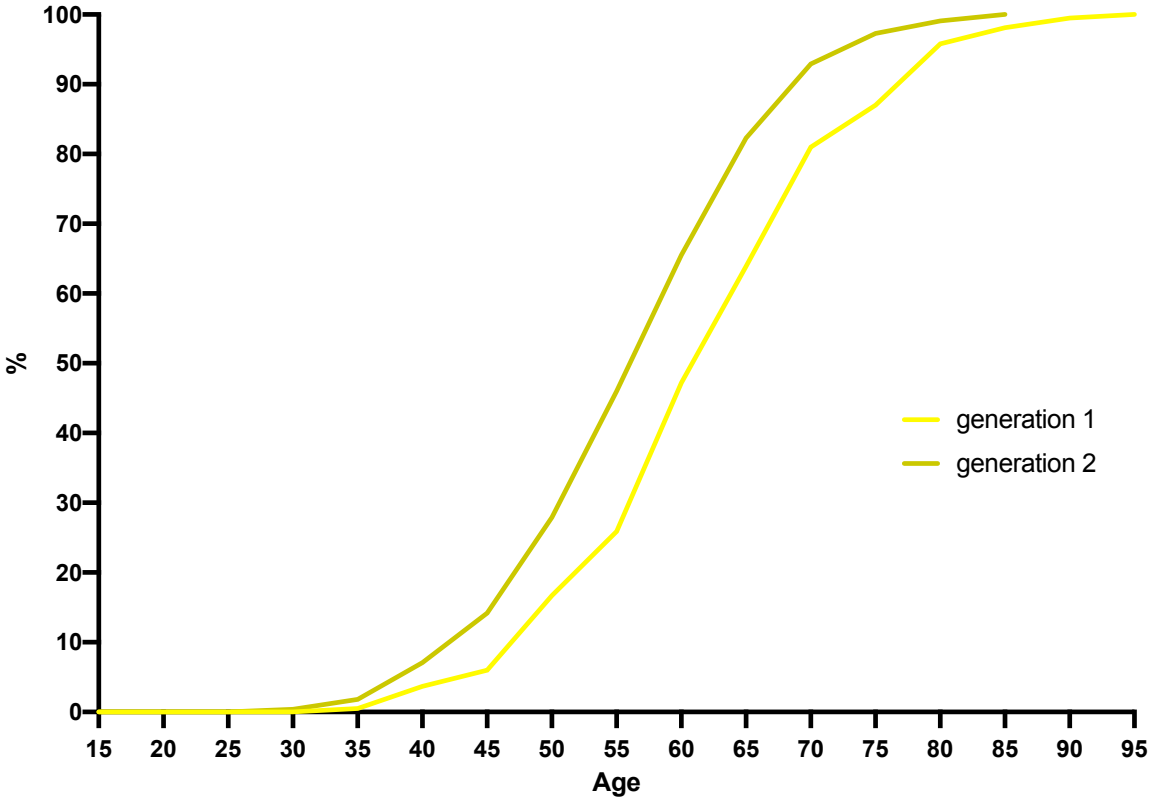
a) *GRN* mutation carriers



b) *MAPT* expansion carriers



c) *C9orf72* mutation carriers



Section 9) Sex analysis

Analyses were performed *within* genetic groups comparing male and female sex. Data is shown in the main text and in Supplementary Table 11.

Supplementary Table 11: Age at onset (AAO), age at death (AAD) and disease duration (DD) in each genetic group by sex. In the bottom row adjusted mean differences (natural log differences for DD) between female and male sex are shown with 95% confidence intervals.

		GRN	***MAPT***	***C9orf72***
Male	AAO	60.5 (8.3)	49.1 (10.2)	57.7 (10.0)
	AAD	67.8 (8.8)	58.1 (10.5)	64.6 (10.8)
	DD	7.0 (3.6)	8.8 (5.9)	6.5 (5.1)
Female	AAO	61.8 (9.2)	49.9 (9.8)	58.9 (9.6)
	AAD	69.4 (10.2)	59.0 (12.0)	66.1 (11.0)
	DD	7.1 (4.1)	9.7 (6.9)	6.4 (4.5)
Adjusted mean difference (95% confidence intervals), p-value	AAO	-1.3 (-2.4, -0.2), p =0.0190	-0.8 (-2.1, 0.5), p = 0.2539	-1.2 (-2.4, -0.1), p = 0.0406
	AAD	-1.6 (-3.1, -0.2), p = 0.0290	-1.1 (-2.5, 0.4), p = 0.1642	-1.6 (-3.0, -0.1), p = 0.0338
	DD	-0.02 (-0.10, 0.07), p = 0.7162	-0.08 (-0.21, 0.04), p = 0.1870	-0.04 (-0.17, 0.09), p = 0.5240

Section 10) Phenotype analysis

Analyses were performed *within* groups comparing the main phenotypes. Data is shown in the main text and in Supplementary Table 12.

Supplementary Table 12: Age at onset (AAO), age at death (AAD) and disease duration (DD) in each genetic group by phenotype [where sufficient data was available; N/A = not applicable, when not enough data]. Atypical parkinsonism (AP) = CBS for *GRN* mutation carriers and a combined CBS/PSP cohort for *MAPT* mutation carriers. In the bottom row adjusted mean differences between phenotypes are shown with 95% confidence intervals.

		GRN	***MAPT***	***C9orf72***
bvFTD	AAO	59.6 (8.1)	50.5 (9.0)	56.7 (9.0)
	AAD	66.3 (9.3)	60.6 (9.9)	64.6 (9.0)
	DD	7.1 (3.7)	10.2 (6.2)	7.8 (4.4)
PPA	AAO	60.2 (7.7)	52.4 (12.0)	59.7 (7.4)
	AAD	66.6 (7.8)	60.9 (15.2)	65.5 (6.5)
	DD	6.5 (2.8)	9.1 (4.1)	7.5 (4.8)
FTD-ALS	AAO	N/A	N/A	57.8 (8.3)
	AAD	N/A	N/A	62.1 (8.9)
	DD	N/A	N/A	5.0 (4.2)
ALS	AAO	N/A	N/A	57.0 (9.0)
	AAD	N/A	N/A	59.2 (9.7)
	DD	N/A	N/A	2.9 (2.8)
AP	AAO	57.7 (7.3)	44.9 (7.8)	N/A
	AAD	66.3 (7.5)	52.8 (8.9)	N/A
	DD	8.2 (5.7)	7.2 (4.0)	N/A
AD	AAO	66.4 (8.1)	56.7 (11.1)	65.1 (10.6)
	AAD	73.6 (8.2)	66.4 (9.5)	73.9 (9.3)
	DD	7.8 (4.9)	10.2 (6.2)	10.4 (4.9)
Adjusted mean difference (95% confidence intervals), p-value	AAO	PPA vs bvFTD: 1.1 (-0.4, 2.6), p = 0.1502 bvFTD vs AP: 1.3 (-1.1, 3.8), p = 0.2916 bvFTD vs AD: -7.7 (-9.7, -5.7), p = <0.0001 PPA vs AP: 2.4 (-0.2, 5.1), p = 0.0729 PPA vs AD: -6.6 (-8.8, -4.4), p = <0.0001 AP vs AD: -9.0 (-12.0, -6.1), p = <0.0001	PPA vs bvFTD: 0.6 (-2.9, 4.0), p = 0.7416 bvFTD vs AP: 4.1 (0.9, 7.4), p = 0.0132 bvFTD vs AD: -7.0 (-11.0, -3.0), p = 0.0006 PPA vs AP: 4.7 (0.3, 9.1), p = 0.0365 PPA vs AD: -6.4 (-11.5, -1.4), p = 0.0127 AP vs AD: -11.1 (-16.1, -6.2), p = <0.0001	PPA vs bvFTD: 3.1 (0.3, 5.8), p = 0.0277 FTD-ALS vs bvFTD: 1.0 (-0.7, 2.7), p = 0.2370 ALS vs bvFTD: 0.3 (-1.2, 1.8), p = 0.7096 bvFTD vs AD: -7.8 (-10.4, -5.2), p = <0.0001 PPA vs FTD-ALS: 2.1 (-0.9, 5.1), p = 0.1721 PPA vs ALS: 2.8 (-0.1, 5.7), p = 0.0575 PPA vs AD: -4.7 (-8.3, -1.1), p = 0.0098 ALS vs FTD-ALS: -0.7, (-2.6, 1.2), p = 0.4490 FTD-ALS vs AD: -6.8 (-9.6, -4.0), p = <0.0001 ALS vs AD: -7.5 (-10.4, -5.2), p = <0.0001

	AAD	PPA vs bvFTD: 1.1 (-1.3, 3.4), p = 0.3766 bvFTD vs AP: -0.7 (-4.4, 3.1), p = 0.7166 bvFTD vs AD: -8.2 (-10.8, -5.5), p = <0.0001 PPA vs AP: 0.4 (-3.7, 4.4), p = 0.8607 PPA vs AD: -7.1 (-10.1, -4.1), p = <0.0001 AP vs AD: -7.5 (-11.7, -3.2), p = 0.0006	PPA vs bvFTD: 1.8 (-3.5, 7.2), p = 0.4962 bvFTD vs AP: 4.8 (0.5, 9.1), p = 0.0300 bvFTD vs AD: -8.9 (-14.0, -3.9), p = 0.0005 PPA vs AP: 6.6 (0.4, 12.9), p = 0.0363 PPA vs AD: -7.1 (-14.0, -0.1), p = 0.0457 AP vs AD: -13.7 (-20.1, -7.4), p = <0.0001	PPA vs bvFTD: 0.8 (-3.2, 4.8), p = 0.6933 FTD-ALS vs bvFTD: -2.8 (-5.0, -0.6), p = 0.0137 ALS vs bvFTD: -5.6 (-7.4, -3.8), p = <0.0001 bvFTD vs AD: -8.8 (-11.8, -5.9), p = <0.0001 PPA vs FTD-ALS: 3.6 (-0.6, 7.8), p = 0.0964 PPA vs ALS: 6.4 (2.4, 10.5), p = 0.0019 PPA vs AD: -8.0 (-12.7, -3.4), p = 0.0007 ALS vs FTD-ALS: -2.8, (-5.1, -0.6), p = 0.0141 FTD-ALS vs AD: -11.6 (-14.9, -8.4), p = <0.0001 ALS vs AD: -14.5 (-17.4, -11.5), p = <0.0001
	DD	PPA vs bvFTD: -0.03, (-0.17, 0.11), p = 0.6621 bvFTD vs AP: -0.04 (-0.28, 0.19), p = 0.7083 bvFTD vs AD: -0.06 (-0.22, 0.10), p = 0.4693 PPA vs AP: -0.08 (-0.33, 0.18), p = 0.5553 PPA vs AD: -0.09 (-0.28, 0.09), p = 0.3384 AP vs AD: -0.01 (-0.28, 0.25), p = 0.9152	PPA vs bvFTD: 0.06 (-0.28, 0.41), p = 0.7157 bvFTD vs AP: 0.24 (-0.22, 0.50), p = 0.0723 bvFTD vs AD: -0.16 (-0.54, 0.22), p = 0.4126 PPA vs AP: 0.30 (-0.10, 0.71), p = 0.1397 PPA vs AD: -0.95 (-0.59, 0.40), p = 0.7056 AP vs AD: -0.40 (-0.84, 0.04), p = 0.0775	PPA vs bvFTD: -0.04 (-0.33, 0.25), p = 0.7904 FTD-ALS vs bvFTD: -0.53 (-0.69, -0.37), p = <0.0001 ALS vs bvFTD: -1.04 (-1.18, -0.90), p = <0.0001 bvFTD vs AD: -0.34 (-0.58, -0.10), p = 0.0052 PPA vs FTD-ALS: 0.49 (0.19, 0.79), p = 0.0016 PPA vs ALS: 1.00 (0.71, 1.30), p = <0.0001 PPA vs AD: -0.38 (-0.73, -0.03), p = 0.0334 ALS vs FTD-ALS: -0.51, (-0.69, -0.34), p = <0.0001 FTD-ALS vs AD: -0.87 (-1.13, -0.61), p = <0.0001 ALS vs AD: -1.38 (-1.63, -1.14), p = <0.0001

Age at symptom onset subanalysis in C9orf72 expansions carriers

A further AAO analysis was performed within the *C9orf72* group comparing those with a 'cognitive' presentation (combining clinical phenotypes of bvFTD, PPA, AD as well as DLB, VaD, and Dementia-NOS) with those with an ALS presentation:

- Mean (standard deviation) AAO in cognitive *C9orf72* group = 58.6 (10.2)
- Mean (standard deviation) AAO in cognitive *C9orf72* group = 57.0 (9.0)
- Using a mixed models analysis as described above, adjusted mean difference = -1.81 (95% confidence intervals -3.38, -0.24), p=0.0241

In other words, the cognitive *C9orf72* group had a significantly older AAO than the ALS group.

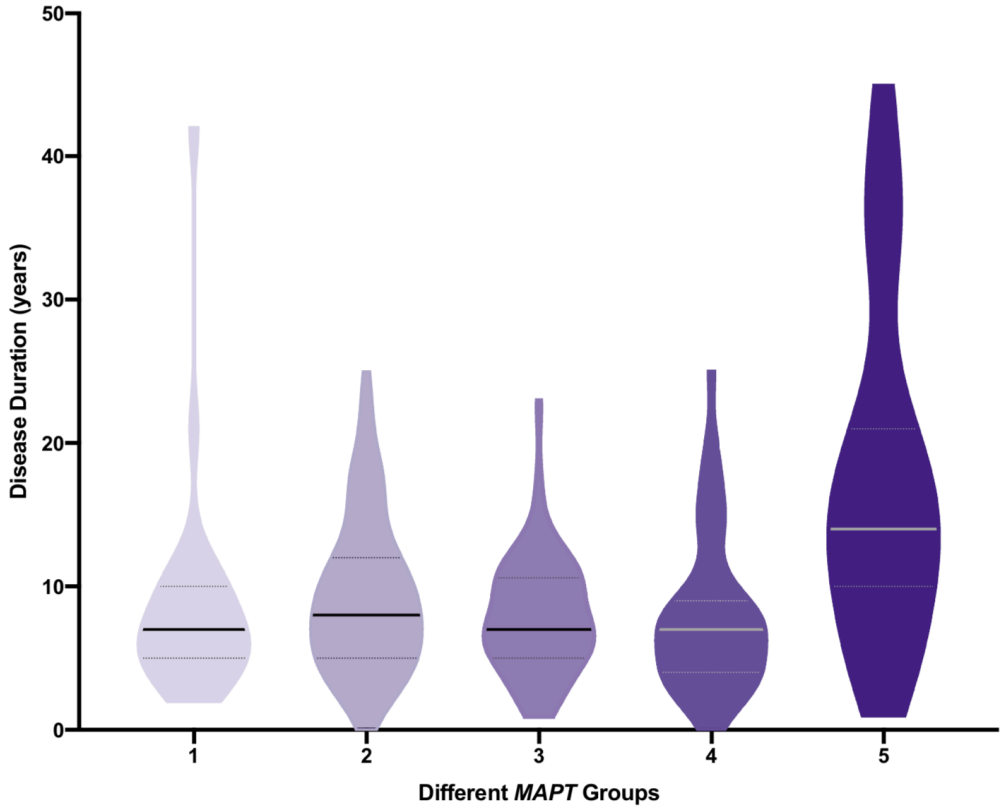
Section 11: Disease duration analysis in MAPT mutation carriers

A mixed effect modelling approach was used to examine whether there were systematic differences in DD between those carrying *MAPT* mutations categorised by their functional consequences and underlying pathology into five groups:

- group 1 – mutations in exons 1,2 and 9;
- group 2 – mutations in exon/intron 10 affecting splicing;
- group 3 – mutations in exon 10 not affecting splicing;
- group 4 – mutations in exons 11-13 with non-paired helical filament (PHF)-tau pathology;
- group 5 – mutations in exon 11-13 with PHF-tau pathology group.

Results are shown in Supplementary Figure 4 and Supplementary Table 13.

Supplementary Figure 4: Disease duration in patients with *MAPT* mutations grouped by type of mutation and pathology (median and interquartile range).



Group 1: ***R5H, R5L, G55R, K257T, I260V, L226V, G272V, IVS9-5T>C, IVS9-11G>C, IVS9-10G>C, IVS9-10G>T;*** **Group 2:** ***N279K, deltaK280, L284L, L284R, S285R, C291R, N296N, K298E, IVS10+3G>A, IVS10+4A>C, IVS10+11T>C, IVS10+12C>T, IVS10+12C>A, IVS10+13A>G, IVS10+14C>T, IVS10+15A>C, IVS10+16C>T, G303V, G304S, S305N, S305I, S305S;*** **Group 3:** ***P301T, P301S, P301L;*** **Group 4:** ***L315R, L315L, K317M, S320F, P332S, G335S, G335V, Q336H, E342V, S352L, S356T, V363A, P364S, G336R, K369I, E372G, G389R (2170G>A), G389R (2170G>C), T427M;*** **Group 5:** ***V337M, R406W.***

Supplementary Table 13: Adjusted mean (natural log) differences with 95% confidence intervals in disease duration between the *MAPT* groups.

Group comparison	Adjusted mean difference (95% confidence intervals), p-value
2 vs 1	0.02 (-0.30, 0.33), p = 0.9250
3 vs 1	-0.15 (-0.54, 0.25), p = 0.4688
4 vs 1	-0.01 (-0.36, 0.33), p = 0.9537
5 vs 1	0.64 (0.19, 1.08), p = 0.0049
3 vs 2	-0.16 (-0.49, 0.17), p = 0.3366
4 vs 2	-0.03 (-0.29, 0.24), p = 0.8525
5 vs 2	0.62 (0.24, 1.00), p = 0.0016
4 vs 3	0.14 (-0.22, 0.49), p = 0.4581
5 vs 3	0.78 (0.33, 1.24), p = 0.0007
5 vs 4	0.65 (0.24, 1.06), p = 0.0021

In summary, group 5 (i.e. the exon 11-13 with PHF-tau pathology group incorporating V337M and R406W mutations) had a significantly longer disease duration compared with all the other groups.

Section 12: Modelling variability in age at onset and age at death

Supplementary Table 14: Variability in age at onset associated with family membership and with presence of a specific mutation. AAO: age at onset (years); CI: confidence interval; SD: standard deviation; N/A: not applicable (for *C9orf72* as only a single mutation).

	GRN	***MAPT***	***C9orf72***
Adjusted mean (95%CI) AAO	60.7 (60.0, 61.4)	48.6 (46.2, 50.9)	58.1 (57.4, 58.7)
Between family SD	3.1	4.9	4.0
Within family SD	8.1	6.7	8.9
% of variability (95%CI) accounted for by family	14 (9, 22)	66 (56, 75)	17 (11, 26)
Between mutation SD	1.2	8.0	N/A
% of variability (95%CI) accounted for by mutation	2 (0, 10)	48 (35, 62)	N/A

Supplementary Table 15: Variability in age at death associated with family membership and with presence of a specific mutation. AAD: age at death (years); CI: confidence interval; SD: standard deviation; N/A: not applicable (for *C9orf72* as only a single mutation).

	GRN	***MAPT***	***C9orf72***
Adjusted mean (95%CI) AAD	68.5 (67.4, 69.7)	57.1 (53.9, 60.2)	65.3 (64.5, 66.2)
Between family SD	3.3	5.0	4.8
Within family SD	8.8	7.0	9.8
% of variability (95%CI) accounted for by family	20 (12, 30)	74 (65, 82)	19 (12, 29)
Between mutation SD	2.9	10.7	N/A
% of variability (95%CI) accounted for by mutation	9 (3, 21)	61 (47, 73)	N/A

Discussion

Little is known about either genetic or environmental factors modifying AAO, AAD or DD in people with *MAPT*, *GRN* or *C9orf72* mutations.

MAPT

One recent study identified that the presence of the *APOE* ε4 genotype lowered AAO in those with FTD and tau pathology, including those with *MAPT* mutations[84] (although it did not look at *MAPT* mutation carriers separately to other tauopathies). However studies have yet to identify other modifying factors.

GRN

Genetic factors affecting AAO in *GRN* mutation carriers include a polymorphism in *TMEM106B*[85], with a lower AAO related to carrying the risk allele, and homozygous carriers of the protective allele rarely found in symptomatic *GRN* mutation carriers[86]. In the Basque IVS7-1G>A families one study has shown an earlier AAO in MM homozygous carriers at *PRNP* codon 129 compared with MV or VV carriers[87]. A number of studies have now identified inflammation as a key player in *GRN*-associated FTD pathogenesis[88,89], and symptomatic patients with *GRN* mutations have a higher risk of also having a co-existent autoimmune disease[90]. It may be therefore that there are environmental factors related to an altered neuroinflammatory response (e.g. traumatic brain injury[91] or systemic inflammation) that modify AAO, that are currently poorly understood.

C9orf72

A number of factors have now been studied as modifiers of AAO in *C9orf72* expansion carriers. There is contradictory evidence in terms of the relationship of expansion length to AAO[92-95], with one recent study suggesting that the association was driven by age at blood sample collection[94] (implying that expansion length in blood may increase with age, although there is no evidence for this at present). Other studies have found that hypermethylation of the *C9orf72* 5'CpG island is a modifier[95,96], with longer DD and later AAD[96]. Another study showed that DNA methylation age-acceleration is associated with a decrease in AAO and a shorter DD[97]. More recently, a study of *C9orf72* expansion carriers identified a locus on chromosome 6 containing two overlapping genes (LOC101929163 and *C6orf10*) in which a polymorphism at rs9357140 was associated with a median AAO six years earlier in GG compared with AA carriers[98]. Lastly, a study of parental-offspring relationships in *C9orf72* revealed a significant correlation in AAO only in the mother-son relationship[99], which they suggest may be related to unknown X-linked genetic modifiers. Environmental or lifestyle factors affecting AAO in *C9orf72* expansion carriers are currently unknown but may be revealed by large prospective cohort studies such as those underway in the FTD Prevention Initiative.

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