Progranulin and Frontotemporal Lobar Degeneration

Masato Hosokawa and Tetsuaki Arai

Abstract Granulin (*GRN*) mutations were first found in frontotemporal dementia (FTD) patients with ubiquitin-positive, tau-negative inclusions in 2006. These inclusions were also found to contain a TAR-DNA binding protein of 43 kDa (TDP-43). PGRN protein itself is not a component of ubiquitin-positive inclusion bodies. Since then, more than 190 *GRN* mutations have been reported, including substitutions, insertions, and deletions. The common pathological mechanism observed with these mutations was proposed to arise from haploinsufficiency; the amount of functional PGRN was reduced to half of the normal level. In fact, *GRN* mutation carriers showed significantly reduced expression levels of PGRN in plasma and serum. Immunohistochemical analyses of phosphorylated TDP-43 revealed that cases of FTLD-TDP with a *GRN* mutation invariably display type A pathology, which is characterized by numerous short dystrophic neurites (DNs) and crescentic or oval shaped neuronal cytoplasmic inclusions (NCIs). *GRN* mutations were initially found in FTD patients with tau-negative, TDP-43-positive inclusions, however, recent findings suggested that different clinical phenotypes may be seen in the same *GRN* mutation carriers and additional tau or α-synuclein accumulation may be observed.

Keywords Frontotemporal dementia (FTD) · Frontotemporal lobar degeneration (FTLD) · *GRN* mutation · Nonsense-mediated dacay

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Introduction

Frontotemporal lobar degeneration (FTLD) is a collective term for a disease group characterized by progressive neurodegeneration limited to frontal and temporal lobes. FTLD is clinically divided into three types: frontotemporal dementia (FTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA) (Neary et al. 1998). This classification is based on clinical manifestations that reflect differences in the degenerative brain region. They do not reflect specific neuropathological characteristics. FTLD can be subdivided into three neuropathological groups, depending on the presence of inclusion bodies or a certain protein component (McKhann et al. 2001). The first group, exhibiting "tauopathy", has tau-positive inclusion bodies. This group includes Pick's disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). The second group might be called FTLD-U since it is similar to FTLD but has ubiquitin-positive tau-negative neurocytoplasmic inclusions (Mackenzie et al. 2006a). FTLD is divided into two types, FTLD with motor neuron disease: (FTLD-MND) and FTLD with MND type inclusions but without MND. The third group consist of FTLD without tau- or ubiquitin-positive inclusions, and this group has been considered a dementia lacking distinctive histology (DLDH). However, most cases of the third group consist of FTLD-U with inclusions which are identified using high-sensitivity ubiquitin immunostaining. Rare cases with tau-negative, cytoplasmic and nuclear ubiquitin-positive inclusions have also been found (Mackenzie et al. 2006c).

Some 35–50% of FTLD patients have a family history of dementia and the causative gene loci have been identified on chromosomes 3, 9 and 17. Microtubule-associated protein tau (tau, MAPT), valosin-containing protein (VCP) and charged multivesicular body protein 2b (CHMP2B) have been identified as causative of FTLD. The identification of the tau gene mutation on chromosome 17q21 reminds us of the importance of tau in neurodegenerative disease research (Hutton et al. 1998). However, a considerable number of familial FTLD-U cases linked on chromosome 17q21 with tau-negative, cytoplasmic and nuclear ubiquitin-positive inclusions have been found.

In 2006, Cruts and Baker identified a granulin (*GRN*) mutation in FTLD-U patients (Baker et al. 2006; Cruts et al. 2006). Since then, more than 190 *GRN* mutations have been reported including substitutions, insertions and deletions (Tables 1, 2 and 3 and Alzheimer Disease & Frontotemporal Dementia Mutation Database, http://www.molgen.ua.ac.be/FTDMutations/) (Cruts et al. 2012). The common pathological mechanism in these mutations was proposed to arise from haploinsufficiency. Symptoms of haploinsufficiency appear after inactivation of one allele of the causative gene in a dominantly-inherited disease (Wilkie 1994). With *GRN* mutation, a mutated form of mRNA is degraded by nonsense-mediated decay (NMD) which is likely to create a null (no expression) allele. It is thought that the functional form of the PGRN protein decreases with disease onset.

Table 1 *GRN* mutations (**pathogenic**)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
1	delGRN[DR184]	Genomic deletion of 69.1 to 74.3 kb containing *GRN, RUNDC3A and SLC25A39*		Complete gene deletion	Complete protein	FTD	71.0	74.0	1	Gijselinck et al. (2008)
2	IVS1+3A>T	g.-3828A>T		IVS1	Complete protein	FTD	58.0	n/a	1	Le Ber et al. (2007) and Brouwers et al. (2007)
3	IVS1+5G>C	g.-3826G>C		IVS1	Complete protein	FTD/PD	61.4	68.7	11	Cruts et al. (2006)
4	delGRN[French]	g.-95_3490del		IVS1-IVS12	Complete protein	FTD/PD	72.0	71.8	1	Rovelet-Lecrux et al. (2008)
5	delGRN			EX1-IVS1	Complete protein	FTLD	47.0	n/a	1	Clot et al. (2014)
6	delGRN		c.-7-1121_159delinsGATCA	IVS1-EX3	Complete protein	FTLD	58.0	65.0	1	Clot et al. (2014)
7	Met1?	g.1A>G	c.1A>G	EX2	Signal peptide	FTD/PPA	55.0	55.0	1	Le Ber et al. (2008) and Gomez-Tortosa et al. (2013)
8	Met1?	g.1A>C	c.1A>C	EX2	Signal peptide	FTLD/AD	n/a	n/a	n/a	Hosokawa et al. (2017)
9	Met1?	g.2T>C	c.2T>C	EX2	Signal peptide	FTD	51.0	n/a	2	Baker et al. (2006)
10	Met1?	g.3G>A	c.3G>A	EX2	Signal peptide	FTD	62.0	n/a	1	Cruts et al. (2006)
11	Trp2X	g.6G>A	c.6G>A	EX2	Signal peptide	FTD	61.0	n/a	1	Mendez (2018)

(continued)

Table 1 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
12	Ala9Asp	g.26C>A	c.26C>A	EX2	Signal peptide	FTD/PPA	56.2	63.4	6	Mukherjee et al. (2006), Gass et al. (2006), Spina et al. (2007), Ghetti et al. (2008), Mukherjee et al. (2008), Spina et al. (2008), Kelley et al. (2009), and Yu et al. (2010)
13	Asp22ArgfsX43	g.63_64insC	c.63_64insC	EX2	ParaGran	FTD	64.2	73.0	2	Gass et al. (2006) and Pietroboni et al. (2011)
14	Cys31LeufsX34	g.90_91insCTGC	c.90_91insCTGC	EX2	ParaGran	FTD	57.9	64.5	6	Baker et al. (2006), Gass et al. (2006), Beck et al. (2008), Rohrer et al. (2008, 2009, 2010a, b), and Yu et al. (2010)
15	Gly35GlufsX19	g.102delC	c.102delC	EX2	ParaGran	FTD/PPA	68.5	58.2	3	Gass et al. (2006), Chiang et al. (2008), and Skoglund et al. (2009)
16	IVS2+1G>A	g.139G>A	c.-7_138del	IVS2	Complete protein	FTD	58.1	68.8	2	Gass et al. (2006), Boeve et al. (2006), Pickering-Brown et al. (2006), and Kelley et al. (2009)

17	Thr52HisfsX2	g.277delA	c.154delA	EX3	InterParaG	FTD/AD	66.8	81.5	5	Gass et al. (2006), Kelley et al. (2009, 2010), and Lindquist et al. (2009)
18	Gly79AspfsX39	g.357_358delAG	c.234_235delAG	EX3	GranG	FTD	56.0	67.0	2	Gass et al. (2006)
19	Ser82ValfsX174	g.366delC	c.243delC	EX3	GranG	FTD	61.2	70.7	1	Bronner et al. (2007)
20	Phe86SerfsX170	g.378delC	c.255delC	EX3	GranG	FTD	n/a	n/a	1	Gijselinck et al. (2008)
21	Ala89ValfsX41 (IVS3+2T>C)	g.389T>C	c.0 (C.264_265ins34)	IVS3	GranG	FTD	60.0	71.0	2	Gijselinck et al. (2008), Yu et al. (2010) and Gomez-Tortosa et al. (2013)
22	IVS3-2delA	g.385delA		IVS3	GranG	PPA	63.0	n/a	1	Cioffi et al. (2016)
23	Pro100HisfsX156	g.537delC	c.299delC	EX4	GranG	FTD	60.0	n/a	1	Yu et al. (2010)
24	Cys105TrpfsX13	g.552dup	c.314dup	EX4	GranG	CBD	n/a	n/a	1	Dopper et al. (2011)
25	Arg110X	g.566C>T	c.328C>T	EX4	GranG	FTD	54.0	n/a	3	Van Deerlin et al. (2007), Le Ber et al. (2008), and Yu et al. (2010)
26	Ser116X	g.585C>A	c.347C>A	EX4	interGF	FTD	57	n/a	1	Yu et al. (2010)
27	Asn118PhefsX4	g.1064delG	c.350_462del	EX5	interGF	PPA	69.0	n/a	2	Le Ber et al. (2008) and Gijselinck et al. (2008)
28	Val121TrpfsX135	g.1075delG	c.361delG	EX5	InterGF	FTD	54.5	63.0	1	Le Ber et al. (2007, 2008)

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Table 1 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
29	Gln125X	g.1087C>T	c.373C>T	EX5	GranF	FTD	64.9	70.0	1	Baker et al. (2006), Cruts et al. (2006), and Bronner et al. (2007)
30	Pro127ArgfsX2	g.1094_1095delCT	c.380_381delCT	EX5	GranF	FTD	55.5	n/a	2	Cruts et al. (2006) and Le Ber et al. (2008)
31	Gln130SerfsX125	g.1098_1101delTAGT	c.384_387delTAGT	EX5	GranF	FTD	45.0	49.0	1	Le Ber et al. (2007, 2008)
32	Gln130SerfsX125	g.1102_1105delCAGT	c.388_391delCAGT	EX5	GranF	FTD	64.2	68.0	8	Baker et al. (2006), Gass et al. (2006), Beck et al. (2008), Finch et al. (2009), Carecchio et al. (2009), Yu et al. (2010), and Rohrer et al. (2010a, b)
33	Cys149LeufsX10	g.1159_1160delTG	c.445_446delTG	EX5	GranF	FTLD/AD	62.6	n/a	11	Calvi et al. (2015) and Piaceri et al. (2018)
34	Ala155TrpfsX56	g.1277G>A	c.0 (c.463_598del)	IVS5	GranF	FTD	63.3	60.0	2	Gass et al. (2006) and Le Ber et al. (2008)
35	Cys157LysfsX97	g.1283_1289delCTGCTGT	c.468_474delCTGCTGT	EX6	GranF	FTD/CBS	52.0	61.0	1	Le Ber et al. (2007, 2008) and Coppola et al. (2012)

36	Arg161GlyfsX36	g.1296_1297delAG	C.481_482delAG	EX6	GranF	PPA	51.0	n/a	1	Gazzina et al. (2017)
37	Arg198GlyfsX19	g.1407_1408delAG	c.592_593delAG	EX6	InterFB	AD	60.5	n/a	2	Finch et al. (2009) and Yu et al. (2010)
38	Ala199Val	g.1411C>T	c.596C>T	EX6	InterFB	FTLD	n/a	n/a	1	Luzzi et al. (2017)
39	IVS6+2_5delTGAG			IVS6	InterFB	FTD	n/a	58.5	n/a	Mao et al. (2017)
40	IVS6+5_8delGTGA			IVS6	InterFB	FTD/AD	n/a	n/a	1	Marcon et al. (2011)
41	Ser203ValfsX15	g.1531_1532insC	c.603_604insC	EX7	InterFB	FTD	n/a	n/a	1	Beck et al. (2008) and Rohrer et al. (2010a, b)
42	Ser226TrpfsX28	g.1603_1604delCA	c.675_676delCA	EX7	GranB	FTD/PPA	58.0	63.0	7	Gass et al. (2006), Van Deerlin et al. (2007), Davion et al. (2007), Coppola et al. (2008), Yu et al. (2010), and Kim et al. (2016)
43	Tyr229X	g.1615T>A	c.687T>A	EX7	GranB	FTLD	60.0	70.5	1	Kuuluvainen et al. (2017)
44	Val200GlyfsX18 (IVS7+1G>A)	g.1637G>A	c.0 (c.599_708del)	IVS7	InterFB	FTD/CBS	60.0	64.3	3	Masellis et al. (2006) and Le Ber et al. (2007, 2008)
45	Val200GlyfsX18 (IVS7+1G>C)	g.1637G>C	c.0 (c.599_708del)	IVS7	InterFB	FTD	55.0	61.0	1	Gass et al. (2006)
46			c.708+6_+9delTGAG	IVS7	InterFB	FTD/AD	60.1	70.2	n/a	Bit-Ivan et al. (2014)
47			c.709-2A>T	IVS7	InterFB	FTD/PPA	67.0	74.6	1	Sassi et al. (2016)

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Table 1 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
48	Ala237TrpfsX6	g.1871A>G	c.0 (c.709_835del)	IVS7	GranB	FTD/PPA	58.4	67.0	9	Behrens et al. (2007), Spina et al. (2007), Leverenz et al. (2007), Davion et al. (2007), Ghetti et al. (2008), Mukherjee et al. (2008), Yu et al. (2010), and Kim et al. (2016)
49	Ala237TrpfsX4	g.1872G>A	c.0 (c.709_835del)	IVS7	GranB	FTD/ CBS/ MND	59.0	63.0	13	López de Munain et al. (2008) and Moreno et al. (2009)
50	Ala237TrpfsX4	g.1999_2000insCTGA	c.0 (c.709_835del)	IVS7	GranB	FTD	67.0	n/a	1	Cruts et al. (2006)
51	Cys253X	g.1923_1924delTG	c.759_760delTG	EX8	GranB	FTD	59.5	65.0	2	Gass et al. (2006) and Le Ber et al. (2008)
52	Gln257ProfsX27	g.1933_1934insCC	c.769_770insCC	EX8	GranB	AD	54.8	n/a	3	Jin et al. (2012), Pires et al. (2013), and Almeida et al. (2014)
53	Lys259X	g.1939A>T	c.775A>T	EX8	GranB	FTD	54.5	n/a	1	Schlachetzki et al. (2009)

54	Leu271LeufsX10	g.1975_1978delCTCA	c.811_814delCTCA	EX8	InterBA	FTLD/CBS	63.8	69.4	2	Benussi et al. (2008)
55	Thr272SerfsX10	g.1977_1980delCACT	c.813_816delCACT	EX8	InterBA	FTD/PSP	60.1	71.0	35	Le Ber et al. (2008), Borroni et al. (2008), Benussi et al. (2008), Tremolizzo et al. (2009), Carecchio et al. (2009), Yu et al. (2010), and Arosio et al. (2013)
56	Thr278SerfsX7	g.1997_1998delCA	c.0 (c.829_834)	IVS8	InterBA	FTLD	60.5	74.3	1	Rossi et al. (2011)
57	Val279GlyfsX5 (IVS8-1G>C)	g.2198G>C	c.0 (c.836_933del)	IVS8	InterBA	FTD/CBS	56.0	n/a	2	Gass et al. (2006) and Coppola et al. (2008)
58	Asp285GlufsX3	g.2211_2217dupAATGTGA	c.848_854dupAATGTGA	EX9	GranA	FTLD-U	53.0	n/a	1	Yu et al. (2010)
59	Tyr294X	g.2245T>G	c.882T>G	EX9	GranA	FTD	50.0	n/a	1	Alzheimer Disease & Frontotemporal Dementia Mutation Database
60	Gln300X	g.2261C>T	c.898C>T	EX9	GranA	FTD	n/a	n/a	1	Beck et al. (2008) and Rohrer et al. (2009)
61	Ser301CysfsX61	g.2264_2265insGT	c.901_902insGT	EX9	GranA	FTD/CBS	52.7	58.0	3	Guerreiro et al. (2008) and Almeida et al. (2014)
62	Ala303GlyfsX14	g.2270_2271insG	c.907_908insG	EX9	GranA	FTD	n/a	n/a	1	Gijselinck et al. (2008)

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Table 1 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
63	Ala303AlafsX57	g.2271delC		EX9	GranA	FTLD	n/a	n/a	n/a	Gomez-Tortosa et al. (2013)
64	Trp304GlyfsX57	g.2272delC	c.909delC	EX9	GranA	FTD/PD	59.5	74.0	2	Lladó et al. (2007) and Almeida et al. (2014)
65	Trp304LeufsX58	g.2273_2274insTG	c.910_911insTG	EX9	GranA	FTD	58.0	65.0	2	Gass et al. (2006), Kelley et al. (2009), and Kim et al. (2016)
66	Trp304X	g.2274G>A	c.911G>A	EX9	GranA	FTD	61.7	65.0	4	Gass et al. (2006), Van Deerlin et al. (2007), and Yu et al. (2010)
67	Trp304Cys	g.2275G>C	c.912G>C	EX9	GranA	FTD/AD	56.7	n/a	1	Piaceri et al. (2018)
68	Val279GlyfsX5	g.2297G>A	c.0 (c.836_933del)	IVS9	GranA	FTD	61.0	n/a	1	Baker et al. (2006) and Gass et al. (2006)
69	Cys314X	g.2394C>A	c.942C>A	EX10	GranA	FTD	70.5	78.0	2	Le Ber et al. (2007, 2008)
70	Gly333ValfsX28	g.2450delG	c.998delG	EX10	GranA	PPA	62.0	72.0	1	Gass et al. (2006), Mesulam et al. (2007) and Kelley et al. (2009)
71	Gln337X	g.2461C>T	c.1009C>T	EX10	InterAC	FTD	62.0	n/a	2	Van Deerlin et al. (2007) and Yu et al. (2010)

72	Gly338GlyfsX22	n/a	n/a	EX10	InterAC	FTLD	n/a	n/a	n/a	Cupidi et al. (2009, abst)
73	His340ThrfsX21	g.2466delG	c.1014delG	EX10	InterAC	FTD	n/a	n/a	1	Benussi et al. (2008)
74	Gln341X	g.2473C>T	c.1021C>T	EX10	InterAC	PPA	63.0	72.0	1	Benussi et al. (2008)
75	Pro357HisfsX4	g.2522delC	c.1070delC	EX10	InterAC	FTD	44.0	51.0	1	López de Munain et al. (2008)
76	Gln358X	g.2524C>T	c.1072C>T	EX10	InterAC	FTD	n/a	n/a	1	Spina et al. (2008)
77	Cys366fsX1	g.2547_2548delCT	c.1095_1096delCT	EX10	GranC	FTD	74.0	85.0	1	Le Ber et al. (2007, 2008)
78	Pro373ArgfsX37	g.2570_2571delCCinsG	c.1118_1119delCCinsG	EX10	GranC	PPA	n/a	n/a	n/a	Hosaka et al. (2017)
79	Thr382GlnfsX32	g.2596_2597insA	c.1144_1145insA	EX10	GranC	FTD	63.4	70.0	1	Bruni et al. (2007) Frangipane et al. (2008)
80	Thr382SerfsX30	g.2597delC	c.1145delC	EX10	GranC	FTD/CBS	54.0	n/a	1	Baker et al. (2006), Gass et al. (2006), and Kelley et al. (2009)
81	Trp386X	g.2609G>A	c.1157G>A	EX10	GranC	FTD	62.7	71.0	3	Baker et al. (2006), Gass et al. (2006), Lindquist et al. (2009), and Yu et al. (2010)
82	Gly387fsX25	n/a	n/a	EX10	GranC	PD	51.0	n/a	1	Carecchio et al. (2014)
83	Ala394LeufsX18	g.2632delG	c.1179delG	IVS10	GranC	FTD	38.0	n/a	2	Almeida et al. (2014)

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Table 1 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
84	Glu316_Cys397del	g.2633T>C	c.939_1184del	IVS10	GranA; InterAC; GranC	FTD	59.0	n/a	1	Yu et al. (2010)
85	Asp399Val	n/a	n/a	EX11	GranC	FTLD	n/a	n/a	n/a	Cupidi et al. (2009, abst)
86	Gln401X	g.2872C>T	c.1201C>T	EX11	GranC	FTD	58.3	60.5	2	Le Ber et al. (2007, 2008)
87	Thr409Met	g.2897C>T	c.1226G>A	EX11	GranC	PPA	n/a	n/a	1	Cerami et al. (2013)
88	Val411SerfsX2	g.2902_2903delGT	c.1231_1232delGT	EX11	GranC	FTD	66.0	n/a	1	Bronner et al. (2007)
89	Ala412fsX1	g.2903_2904insGT	c.1232_1233insGT	EX11	GranC	FTD	57.5	68.0	2	Le Ber et al. (2007, 2008)
90	Gln415X	g.2914C>T	c.1243C>T	EX11	GranC	FTD	n/a	n/a	4	Pickering-Brown et al. (2008)
91	Arg418X	g.2923C>T	c.1252C>T	EX11	InterCD	FTD	56.3	60.3	5	Baker et al. (2006), Gass et al. (2006), Van Deerlin et al. (2007), Schlachetzki et al. (2009), and Yu et al. (2010)
92	Asp441HisfsX4	g.2988_2989delCA	c.1317_1318delCA	EX11	InterCD	CBS	55.0	n/a	1	Yu et al. (2010)
93	Cys466LeufsX46	g.3066_3067insC	c.1395_1396insC	EX11	GranD	FTD	52.0	56.0	1	Gass et al. (2006) and Kelley et al. (2009)

94	Gln468X	g.3073C>T	c.1402C>T	EX11	GranD	FTD/PPA	60.3	68.8	2	Baker et al. (2006) and Yu et al. (2010)
95	Ala472ValfsX10 (IVS11-15_ EX12+177del)	g.3162_3354del	c.1413_1414ins92; 1644_1645ins89	EX12	GranD; InterDE; GranE	FTD	64.5	86.0	3	Pickering-Brown et al. (2006), Finch et al. (2009), and Yu et al. (2010)
96	Ala472_Gln548del	g.3175A>G	c.1415_1645del	IVS11	GranD; InterDE; GranE	FTD	39.0	n/a	1	Yu et al. (2010)
97	Cys474LeufsX37	g.3183_3184delTG	c.1420_1421delTG	EX12	GranD	FTD	n/a	n/a	1	Spina et al. (2008)
98	Thr487Ile	g.3223C>T	c.1460C>T	EX12	GranD	PD	n/a	n/a	n/a	Chang et al. (2018)
99	Arg493X	g.3240C>T	c.1477C>T	EX12	GranD	FTLD	57.0	63.6	44	Huey et al. (2006), Gass et al. (2006), Pickering-Brown et al. (2006), Mesulam et al. (2007), Spina et al. (2007), Van Deerlin et al. (2007), Davion et al. (2007), Rademakers et al. (2007), Ghetti et al. (2008), Spina et al. (2008), Kelley et al. (2009), Rohrer et al. (2010a, b), Yu et al. (2010), and Kim et al. (2016)

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Table 1 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
100	Cys495Cys	g.3248C>T	c.1485C>T	EX12	GranD	FTD	n/a	n/a	n/a	van der Zee et al. (2007)
101	Glu498AspfsX12	g.3257_3261delAGTGG	c.1494_1498delAGTGG	EX12	InterDE	FTD	57.2	n/a	4	Beck et al. (2008), Le Ber et al. (2008), and Rohrer et al. (2010a, b)
102	Gln503X	g.3270C>T	c.1507C>T	EX12	InterDE	FTD	75.0	n/a	1	Aswathy et al. (2016)
103	Val516GlyfsX31	n/a	n/a	EX12	InterDE	FTLD	n/a	n/a	n/a	Cupidi et al. (2009, Abst)
104	Cys521Tyr	g.3325G>A	c.1562G>A	EX12	GranE	FTD	60.5	71.8	1	Cruchaga et al. (2009)
105	Arg535X	g.3366C>T	c.1603C>T	EX12	GranE	AD	72.0	n/a	1	Brouwers et al. (2007)

n/a not applicable, *EX* exon, *IVS* intervening sequence, *Gran* Granulin. Phenotype: *AD* Alzheimer's disease, *CBS* corticobasal syndrome, *FTD* frontotemporal dementia, *FTLD* frontotemporal lobar degeneration, *FTLD-U* frontotemporal lobar degeneration with ubiquitin-positive inclusions, *MND* motor neuron disease, *PD* Parkinson's disease, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy

Table 2 *GRN* mutations (**pathogenic nature unknown**)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
1	Val5Leu	g.13G>C	c.13G>C	EX2	Signal peptide	FTD-MND	63.0	65.0	1	López de Munain et al. (2008)
2	Trp7Arg	g.19T>C	c.19T>C	EX2	Signal peptide	FTD	51.0	n/a	1	Le Ber et al. (2008)
3	Asp33Glu	g.99C>A	c.99C>A	EX2	ParaGran	AD/PD	68.5	85.0	2	Brouwers et al. (2008) and Nuytemans et al. (2008)
4	Pro34Ser	g.100C>T	c.100C>T	EX2	ParaGran	FTD	n/a	n/a	n/a	Almeida et al. (2014)
5	Pro34Pro	g.102C>T	c.102C>T	EX2	ParaGran	FTD	n/a	n/a	1	van der Zee et al. (2007) and Le Ber et al. (2007)
6	Gly35Arg	g.103G>A	c.103G>A	EX2	ParaGran	AD	n/a	n/a	1	Galimberti et al. (2008) and Cortini et al. (2008)
7	Leu53Pro	g.281T>C	c.158T>C	EX3	InterParaG	FTD	n/a	n/a	n/a	Skoglund et al. (2007)
8	Gly70Ser	g.331G>A	c.208G>A	EX3	GranG	FTD	55.0	n/a	1	Yu et al. (2010)
9	Val77Ile	g.352G>A	c.229G>A	EX3	GranG	At risk	n/a	n/a	1	Yu et al. (2010)
10	Glu88Glu	g.387G>A	c.264G>A	EX3	GranG	FTLD	n/a	n/a	n/a	Gass et al. (2006)
11	Cys105Arg	g.551T>C	c.313T>C	EX4	GranG	FTD	39.0	n/a	1	Gass et al. (2006) and Yu et al. (2010)
12	Cys105Tyr	g.552G>A	c.314G>A	EX4	GranG	FTD	61.5	n/a	1	Karch et al. (2016)
13	Arg110Gln	g.567G>A	c.329G>A	EX4	GranG	ALS	n/a	n/a	n/a	Sleegers et al. (2008)
14	Ile124Thr	g.1085T>C	c.371T>C	EX5	GranF	ALS	n/a	n/a	n/a	Sleegers et al. (2008)
15	Thr138Thr	g.1128G>A	c.414G>A	EX5	GranF	ALS	n/a	n/a	n/a	Sleegers et al. (2008)
16	Cys139Arg	g.1129T>C	c.415T>C	EX5	GranF	FTD/PPA/AD	72.3	89.0	3	Brouwers et al. (2008), Finch et al. (2009), Bernardi et al. (2009), and Redaelli et al. (2018)

(continued)

Table 2 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
17	Gly168Ser	g.1317G>A	c.502G>A	EX6	GranF	FTLD/ MND	n/a	n/a	1	Pickering-Brown et al. (2008)
18	Arg177His	g.1345G>A	c.530G>A	EX6	GranF	FTD	70.0	78.0	1	López de Munain et al. (2008), Schymick et al. (2007), Guerreiro et al. (2008), Guerreiro et al. (2010), and Yu et al. (2010)
19	Ala199Val	g.1411C>T	c.596C>T	EX6	interFB	CBS	62.0	n/a	2	Beck et al. (2008), Rohrer et al. (2010a, b), and Karch et al. (2016)
20	Arg212Trp	g.1562C>T	c.634C>T	EX7	GranB	FTD	n/a	n/a	1	Yu et al. (2010)
21	Cys222Tyr	g.1593G>A	c.665G>A	EX7	GranB	AD	n/a	n/a	n/a	Lee et al. (2014)
22	Pro233His	g.1626C>A	c.698C>A	EX7	GranB	FTLD	n/a	n/a	1	Bronner et al. (2007)
23	Asn236Asn	g.1636C>T	c.708C>T	EX7	GranB	FTLD	n/a	n/a	n/a	Gass et al. (2006)
24	IVS7-3C>G	g.1870C>G	c.709_835del	IVS7	GranB	FTD	45.0	n/a	1	Benussi et al. (2008)
25	IVS7-1G>A	g.1872G>A	c.709-1G>A	IVS7	GranB	UI	n/a	n/a	n/a	Barandiaran et al. (2012)
26	Pro248Leu	g.1907C>T	c.743C>T	EX8	GranB	FTD	n/a	n/a	n/a	van der Zee et al. (2007) and Le Ber et al. (2007)
27	Thr251Ser	g.1916C>G	c.752C>G	EX8	GranB	FTD	44.0	n/a	1	Yu et al. (2010)
28	Ser258Asn	g.1937G>A	c.773G>A	EX8	GranB	FTD	n/a	n/a	n/a	van der Zee et al. (2007) and Le Ber et al. (2007)
29	Ala276Val	g.1991C>T	c.827C>T	EX8	InterBA	Dep	50.0	n/a	1	Yu et al. (2010)
30	Glu287Asp	g.2224G>C	c.861G>C	EX9	GranA	FTLD	n/a	n/a	n/a	Gass et al. (2006)
31	Arg298His	g.2256G>A	c.893G>A	EX9	GranA	FTD	67.0	n/a	1	Yu et al. (2010) and Karch et al. (2016)
32	Ser353Asn	g.2510G>A	c.1058G>A	EX10	InterAC	FTD	65.0	n/a	1	Yu et al. (2010)
33	Pro357Arg	g.2522C>G	c.1070C>G	EX10	InterAC	FTD	62.0	n/a	1	Yu et al. (2010)
34	G387fsX25	n/a	n/a	EX10	GranC	PD	n/a	n/a	n/a	Carecchio et al. (2014)

35	Pro392Pro	g.2628A>C	c.1176A>C	EX10	GranC	ALS	n/a	n/a	1	Schymick et al. (2007)
36	Arg432Cys	g.2965C>T	c.1294C>T	EX11	InterCD	FTD	75.0	n/a	3	van der Zee et al. (2007), Le Ber et al. (2007), and Sassi et al. (2014)
37	His447His	g.3012C>T	c.1341C>T	EX11	GranD	FTD/ALS	n/a	n/a	n/a	Bronner et al. (2007), Sleegers et al. (2008), and Finch et al. (2009)
38	Pro451Leu	g.3023C>T	c.1352C>T	EX11	GranD	AD	74.0	78.0	1	Brouwers et al. (2008)
39	Leu469Phe	g.3078G>T	c.1407G>T	EX11	GranD	PA	n/a	n/a	1	Beck et al. (2008) and Rohrer et al. (2009)
40	Cys474Cys	g.3185C>T	c.1422C>T	EX12	GranD	FTD	n/a	n/a	n/a	Gass et al. (2006)
41	Val514Met	g.3303G>A	c.1540G>A	EX12	InterDE	AD/PD	71.5	82.0	n/a	Brouwers et al. (2008) and Nuytemans et al. (2008)
42	Val519Met	g.3318G>A	c.1555G>A	EX12	GranE	AD	n/a	n/a	4	Lee et al. (2014)
43	Trp541Cys	g.3386G>C	c.1623G>C	EX12	GranE	FTLD	n/a	n/a	1	Bronner et al. (2007)
44	Arg547Cys	g.3402C>T	c.1639C>T	EX12	GranE	PD	54.0	n/a	1	Wong et al. (2008, per. Comm, 2009)
45	Arg564Cys	g.3542C>T	c.1690C>T	EX13	GranE	AD	70.0	n/a	1	Brouwers et al. (2008)
46	Pro578Pro	g.3586G>A	c.1734G>A	EX13	C-Term	PPA	55.0	n/a	1	Finch et al. (2009)

n/a not applicable, *EX* exon, *IVS* intervening sequence, *Gran* Granulin. Phenotype: *ALS* amyotrophic lateral sclerosis, *AD* Alzheimer's disease, *CBS* corticobasal syndrome, *Dep* depression, *FTD* frontotemporal dementia, *FTLD* frontotemporal lobar degeneration, *FTLD-U* frontotemporal lobar degeneration with ubiquitin-positive inclusions, *MND* motor neuron disease, *PD* Parkinson's disease, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy

Table 3 *GRN* mutations (**not pathogenic**)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
1	Leu14Leu	g.42G>A	c.42G>A	EX2	Signal peptide	FTD/CTRL	n/a	n/a	n/a	Guerreiro et al. (2008, 2010)
2	Arg19Trp	g.55C>T	c.55C>T	EX2	ParaGran	CTRL	n/a	n/a	n/a	Gass et al. (2006), Schymick et al. (2007), Guerreiro et al. (2010), and Del Bo et al. (2011)
3	Asp33Asp	g.99C>T	c.99C>T	EX2	ParaGran	CTRL	n/a	n/a	n/a	Gass et al. (2006), van der Zee et al. (2007), Schymick et al. (2007), Le Ber et al. (2007), Mukherjee et al. (2008), Sleegers et al. (2008), Cortini et al. (2008), Chiang et al. (2008), Guerreiro et al. (2010), Yu et al. (2010), and Del Bo et al. (2011)
4	Leu53Leu	g.282G>A	c.159G>A	EX3	InterParaG	FTD	55.0	n/a	n/a	Yu et al. (2010)
5	Arg55Trp	g.286A>T	c.163A>T	EX3	InterParaG	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
6	Ala69Thr	g.328G>A	c.205G>A	EX3	GranG	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
7	Thr76Thr	g.351C>T	c.228C>T	EX3	GranG	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
8	Ala89Ala	g.505C>T	c.267C>T	EX4	GranG	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
9	Gly93Gly	g.517G>A	c.279G>A	EX4	GranG	FTD/UI	n/a	n/a	n/a	Bronner et al. (2007)
10	Ser106Asn	g.555G>A	c.317G>A	EX4	GranG	UI	n/a	n/a	n/a	van der Zee et al. (2007)
11	Asp108Asp	g.562C>T	c.324C>T	EX4	GranG	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
12	Asn119del	g.1069_1071delAAC	c.355_357delAAC	EX5	InterGF	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
13	Ser120Tyr	g.1073C>A	c.359C>A	EX5	InterGF	ALS-FTD/ FTD/CTRL	63.0	63.0	n/a	Schymick et al. (2007), Guerreiro et al. (2010), and Del Bo et al. (2011)

14	Asp128Asp	g.1098T>C	c.384T>C	EX5	GranF	CTRL	n/a	n/a	n/a	Gass et al. (2006), van der Zee et al. (2007), Guerreiro et al. (2008), Sleegers et al. (2008), Tremolizzo et al. (2009), Guerreiro et al. (2010), and Del Bo et al. (2011)
15	Pro134Pro	g.1116G>A	c.402G>A	EX5	GranF	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
16	Val141Ile	g.1135G>A	c.421G>A	EX5	GranF	CTRL	n/a	n/a	n/a	Schymick et al. (2007)
17	Cys158Tyr	g.1288G>A	c.473G>A	EX6	GranF	UI	n/a	n/a	n/a	van der Zee et al. (2007)
18	Ala169Ala	g.1322C>G	c.507C>G	EX6	GranF	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
19	Thr182Met	g.1360C>T	c.545C>T	EX6	InterFB	FTD/ALS/ MSA/CTRL	52.0	n/a	n/a	Bronner et al. (2007), Schymick et al. (2007), Guerreiro et al. (2008, 2010), and Yu et al. (2010)
20	Thr182Thr	g.1361G>A	c.546G>A	EX6	InterFB	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
21	Arg212Gln	g.1563G>A	c.635G>A	EX7	GranB	UI	n/a	n/a	n/a	van der Zee et al. (2007) and Brouwers et al. (2008)
22	Thr220Ser	g.1586A>T	c.658A>T	EX7	GranB	UI	n/a	n/a	n/a	van der Zee et al. (2007)
23	Cys221Ser	g.1590G>C	c.662G>C	EX7	GranB	UI	n/a	n/a	n/a	Guerreiro et al. (2010)
24	Leu261Ile	g.1945C>A	c.781C>A	EX8	InterBA	AD/UI	n/a	n/a	n/a	van der Zee et al. (2007) and Brouwers et al. (2008)
25	Ser262Ser	g.1950C>T	c.786C>T	EX8	InterBA	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
26	Thr268Thr	g.1968G>A	c.804G>A	EX8	InterBA	ALS/UI	n/a	n/a	n/a	van der Zee et al. (2007) and Sleegers et al. (2008)
27	Ser301Ser	g.2266G>A	c.903G>A	EX9	GranA	FTD/ALS/ UI	n/a	n/a	n/a	Gass et al. (2006), van der Zee et al. (2007), Sleegers et al. (2008), and Yu et al. (2010)

(continued)

Table 3 (continued)

	Mutation (protein)	Mutation (genomic DNA)	Mutation (cDNA)	Exon	Domain	Phenotype	Mean onset ages	Mean age at death	Frequency (family)	Citations
28	Ala324Thr	g.2422G>A	c.970G>A	EX10	GranA	CTRL	n/a	n/a	n/a	Gass et al. (2006), Schymick et al. (2007), Beck et al. (2008), Pickering-Brown et al. (2008), Sleegers et al. (2008), Brouwers et al. (2008), Nuytemans et al. (2008), Finch et al. (2009), Yu et al. (2010), and Sassi et al. (2014)
29	Lys332Lys	g.2448G>A	c.996G>A	EX10	GranA	UI	n/a	n/a	n/a	van der Zee et al. (2007)
30	Asp376Asn	g.2578G>A	c.1126G>A	EX10	GranC	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
31	Ser398Leu	g.2864C>T	c.1193C>T	EX11	GranC	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
32	Thr409Thr	g.2898G>A	c.1227G>A	EX11	GranC	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
33	Gly414Val	g.2912G>T	c.1241G>T	EX11	GranC	FTLD/ CTRL	n/a	n/a	n/a	Bronner et al. (2007)
34	Arg418Gln	g.2924G>A	c.1253G>A	EX11	InterCD	CTRL	n/a	n/a	n/a	Gass et al. (2006), Bronner et al. (2007), van der Zee et al. (2007), Le Ber et al. (2007), Sleegers et al. (2008), and Yu et al. (2010)
35	Arg433Trp	g.2968C>T	c.1297C>T	EX11	InterCD	CTRL	n/a	n/a	n/a	Gass et al. (2006), Spina et al. (2007), van der Zee et al. (2007), Schymick et al. (2007), Beck et al. (2008), Brouwers et al. (2008), Nuytemans et al. (2008), Finch et al. (2009), Yu et al. (2010), and Sassi et al. (2014)
36	Arg433Gln	g.2969G>A	c.1298G>A	EX11	InterCD	FTD/CTRL	73.0	n/a	n/a	Mukherjee et al. (2008)
37	Pro458Leu	g.3044C>T	c.1373C>T	EX11	GranD	CTRL	n/a	n/a	n/a	Schymick et al. (2007)
38	Pro470Leu	g.3080C>T	c.1409C>T	EX11	GranD	UI	n/a	n/a	n/a	van der Zee et al. (2007)
39	Cys475Cys	g.3188C>T	c.1425C>T	EX12	GranD	UI	n/a	n/a	n/a	van der Zee et al. (2007)

40	Ala505Ala	g.3278C>T	c.1515C>T	EX12	InterDE	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
41	Gly515Ala	g.3307G>C	c.1544G>C	EX12	InterDE	CTRL	n/a	n/a	n/a	Gass et al. (2006), van der Zee et al. (2007), Brouwers et al. (2008), Guerreiro et al. (2010), and Yu et al. (2010)
42	Asp518Asp	g.3317C>T	c.1554C>T	EX12	GranE	ALS/CTRL	n/a	n/a	n/a	Guerreiro et al. (2010) and Del Bo et al. (2011)
43	Val550Ile	g.3500G>A	c.1648G>A	EX13	GranE	UI	n/a	n/a	n/a	van der Zee et al. (2007)
44	Arg556Cys	g.3518C>T	c.1666C>T	EX13	GranE	CTRL	n/a	n/a	n/a	Schymick et al. (2007)
45	Arg564His	g.3543G>A	c.1691G>A	EX13	GranE	CTRL	n/a	n/a	n/a	Guerreiro et al. (2010)
46	Cys565Cys	g.3547C>T	c.1695C>T	EX13	GranE	FTD/CTRL	n/a	n/a	n/a	van der Zee et al. (2007), Le Ber et al. (2007) and Guerreiro et al. (2010)
47	Ala582Thr	g.3596G>A	c.1744G>A	EX13	C-Term	CTRL	n/a	n/a	n/a	Sassi et al. (2014)

n/a not applicable, *EX* exon, *IVS* intervening sequence, *Gran* Granulin. Phenotype: *ALS* amyotrophic lateral sclerosis, *AD* Alzheimer's disease, *CTRL* control, *FTD* frontotemporal dementia, *FTLD* frontotemporal lobar degeneration, *MND* motor neuron disease, *UI* unaffected individual

A TAR-DNA binding protein of 43 kDa (TDP-43), the main component of ubiquitin-positive inclusions, was observed in FTLD and ALS patients and was identified in 2006 by Arai et al. and Neumann et al. (Arai et al. 2006; Neumann et al. 2006). The tau-negative, ubiquitin-positive inclusions that were seen in *GRN* mutation brains were also identified as containing TDP-43.

GRN Mutations and Pathological Mechanisms

Baker and colleagues examined more than 80 candidate genes within the 3.53-cM (6.19-Mb) critical region clarified by haplotype analysis of Canadian tau-negative FTD families (Baker et al. 2006). They identified an insertion mutation of four base pairs (CTGC) in exon 1 of the *GRN* gene (g.90_91insCTGC) [g: genomic DNA, ins: insertion]. The numbering is relative to the reverse complement of GenBank accession number AC003043.1, starting at adenine (A) of Met 1. This mutation causes a frame shift at codon 31 that induces a premature termination codon after a read through of 34 amino acids (p.Cys31LeufsX34) [p: protein, fs: frame shifts, X: termination codon]. The p.Cys31LeufsX34 mutation was absent in 550 North American control individuals. They sequenced the *GRN* gene in affected families in Canada, the USA, UK, Netherlands and Scandinavia and identified an additional eight *GRN* mutations in nine families. These mutations were as follows: four nonsense mutations: g.1087C>T (p.Gln125X), g.2609G>A (p.Trp386X), g.2923C>T (p.Arg418X), g.3073C>T (p.Gln468X); two flame shift mutations: g.1102_1105delCAGT (p.Gln130SerfsX124), g.2597delC (pThr382SerfsX29); one splicing site mutation: IVS8-1G (p.Val279GlyfsX4); and mutation in start codon: g.2T>C (p.Met1?). Next, they extracted RNA from the lymphoblasts of cases with mutations g.90_91insCTGC (p.Cys31LeufsX34) and c.2923C>T (p.Arg418X), performed quantitative RT-PCR analysis and found that the expression of *GRN* mRNA was reduced by approximately 50%. They performed sequencing of *GRN* mRNAs and found that most of them encoded wild type *GRN*, whereas the mutated type of *GRN* was rarely detected. These results suggested that the mutated mRNA was degraded by NMD. NMD degrades mRNA with a premature termination codon (PTC) which arise from a splicing error or mutation, and thereby prevent production of an abnormal protein (Maquat 2004).

When the lymphoblasts from patients were treated with the NMD inhibitor, cycloheximide, the mutated mRNA was increased. Immunoblotting analysis revealed that the amount of wild type PGRN protein had decreased compared with the controls and mutated PGRN protein was barely detected. They also detected a significant reduction in the amount of mutated mRNA in the brains of patients with the g.2T>C mutation. They suggested that translation of the protein did not occur because the Kozak sequence was disrupted by the g.2T>C mutation.

Cruts and colleagues also identified five novel *GRN* mutations, IVS0+5G>C (now termed IVS1+5G>C), g.3G>A (p.Met1?), g.1094_1095delCT (p.Pro127ArgfsX2), g.1872G>A (p.Ala237TrpfsX4), and g.1087C>T (p.Gln125X).

IVS1+5G>C indicates a point mutation in the intron 1 splice donor site causing intron 1 retention, resulting in nuclear mRNA degradation (Cruts et al. 2006). Sequence analysis of *GRN* in 103 Belgian FTD patients identified this mutation in the eight probands belonging to different branches of the Belgian founder family. An in silico analysis of the IVS1+5G>C mutation predicted an intense decline in the binding efficiency of the U1 snRNP complex.

Next, they analyzed full length *GRN* cDNA from the brains and lymphoblasts of two probands, abnormal transcripts. According to the polymorphism (rs5848) in the 3′ untranslated region of the *GRN* gene, probands were judged C/T heterogeneous (the T-allele is the disease haplotype). However, on sequence analysis of cDNA from their lymphoblasts or brain tissue, only the C allele was observed. These results suggested a complete disappearance of mutated *GRN* mRNA. Immunoblot analysis using an extract from the lymphoblasts of a proband showed PGRN protein reduction. They confirmed loss of mRNA and wild type PGRN protein reduction in the cases of the g.1087C>T (p.Gln125X) mutation. Subsequently, Gass and colleagues performed systematic screening for the *GRN* gene in 378 FTLD and 48 ALS cases at the Mayo Clinic and identified 23 *GRN* mutations in 39 FTLD cases.

Twenty of these twenty-three mutations (4 nonsense mutations, 12 frame shift mutations and 4 splicing donor site mutations) predicted production of PTC and mutated mRNA degradation by NMD. They also identified novel mutations in the splicing donor site of exon 1 (IVS1+1G>A) as well as a missense mutation (g.26C>A (p.Ala9Asp)). In this study, no mutation was identified in ALS cases. RT-PCR analysis of a brain with an IVS1+1G>A mutation revealed two bands corresponding to mutated *GRN* mRNA and wild type *GRN* mRNA, respectively. These results suggested that the IVS1+1G>A mutation did not cause degradation of mutated mRNA by NMD. Initiation of NMD first required a translation process, so that it has been speculated that any IVS1+G>A mutation would escape NMD because no translation would start without the Kozak sequence. The g.26C>A (p.Ala9Asp) mutation was identified as singular missense mutation in this study, the 9th alanine in exon 1 of *GRN* being replaced by aspartic acid. The 9th alanine corresponds to the hydrophobic core of the signal peptide. Mutated mRNA was reduced in the g.26C>A (p.Ala9Asp) brain by an unknown mechanism. If a mutated allele was translated in this case, it would produce a mutated PGRN protein lacking binding capability to the signal recognition motif and could not be transported to the endoplasmic reticulum. Since 2006, many novel *GRN* mutations have been found and are listed in Tables 1, 2 and 3.

PGRN Protein Is Not a Component of Ubiquitin-Positive Inclusion Bodies

Immunohistochemical staining using antibodies for all regions of PGRN protein showed that some of the neurons and activated microglia were positive. Ubiquitin-positive neuronal cytoplasmic inclusions (NCI) and neuronal intranuclear

inclusions (NII) were negative with PGRN antibodies (Baker et al. 2006; Cruts et al. 2006). These results indicated that PGRN accumulation did not occur during development of the FTD pathology caused by the *GRN* mutation. PGRN-positive neuron and activated microglia were also observed in the brains of normal elderly individuals and Alzheimer's disease (AD) cases.

Clinico-Pathological Characterization of *GRN* Mutation Carriers

Incidence Rate

In the Belgian study, Cruts and colleagues found *GRN* mutations in 10.7% (11 out of 103) of the FTD cases overall and in 25.6% (11 out of 43) of familial FTD cases (Cruts et al. 2006). MAPT mutation frequencies were 2.9% (3 out of 103) in the non-familial FTD and 7% (3 out of 43) in the familial FTD cases. These results indicated that *GRN* mutations are approximately a 3.5 times more frequent cause of FTD in Belgian patients. *GRN* mutation data of Gass and colleagues showed mutations in 10.5% (39 out of 378) of FTD and 25.6% (32 out of 144) of familial FTD cases. However, they pointed out that there was some bias in their cases because the Mayo Clinic treated many familial FTLD patients or FTLD patients with a definitive pathological diagnosis.

To exclude this kind of clinical bias, 167 non-selective FTLD cases were collected between 1990 and 2006 in five different Alzheimer's disease research centers and analyzed. The frequency of the *GRN* mutation was 48%. It was noted that the frequencies of the *GRN* and *MAPT* mutations were almost the same; the frequency of the *MAPT* mutation was 44% in the same series of brains. Further investigation of this similarity will be needed. Of 649 dementia cases collected in Minnesota between 1987 and 2006 as part of a dementia research project, 15 were diagnosed with FTLD. Three patients were identified with the *GRN* mutation. The frequency of the *GRN* mutation in the dementia patients overall was calculated to be 0.5%.

Pickering-Brown and colleagues reported that the frequency of the *GRN* mutation was 7.3% (14 out of 192 FTLD patients) (Pickering-Brown et al. 2008) whereas Le Ber and colleagues reported the frequency to be 6.4% (32 out of 502 FTD patients) (Le Ber et al. 2008). The frequency of *GRN* mutations in probands was 5.7% (20 of 352) in fvFTD, 4.4% (3 of 68) in primary progressive aphasia (PPA) and 3.3% (1 of 30) in corticobasal syndrome (CBS). The authors also mentioned that no mutations were found in the 52 probands with FTD-MND. Yu et al. found the frequency of the *GRN* mutation to be 6.9% (30 of 434) (Yu et al. 2010).

Age of Onset

The age of onset of FTLD in Belgian patients with the IVS1+5G>C mutation was 45–70 years (average 63.4 ± 6.8) (Cruts et al. 2006). This mutation was identified in a few asymptomatic individuals; one who had died at 41 years of age, two who had died within the normal age of onset at ages (44 and 54 years) and the one who died at 81. Gass et al. found that the age of onset was 48–83 years (average 59.0 ± 7.0) among *GRN* mutation carriers over all (Gass et al. 2006). Other studies demonstrated that the average age of FTLD onset was 59.0 ± 5 (Pickering-Brown et al. 2008); 59.4 ± 9.4 in FTD, 62.0 ± 7.9 in FTD-MND, 63.8 ± 8.5 in PPA and 61.8 ± 9.7 in CBS (Le Ber et al. 2008). In another study, the average age of onset was 57.7 years, which was calculated from the onset age of 31 *GRN* mutation-positive patients from 28 different families (Yu et al. 2010). Leverenz et al. investigated two families with the *GRN* c.709-2A>G mutation (now termed g.1871A>G (p.Ala237TrpfsX6)) (Leverenz et al. 2007). In family 1, the mean age of onset was 55.6 ± 8.9 years (range = 35–69), the mean age at death was 65.5 ± 6.8 years (range = 56–78) and the mean duration was 9.8 ± 5.5 years (range = 4–22). In family 2, the mean age of onset was 61.0 ± 6.6 years (range = 50–67), the mean age at death was 68.6 ± 6.0 years (range = 57–73) and the mean duration was 6.8 ± 0.4 years (range = 6–7) (Leverenz et al. 2007).

Clinicopathological Images of FTLD

Patients with the *GRN* IVS1+5G>C mutation show non-fluent aphasia (Cruts et al. 2006). Gass et al. indicated that FTLD patients with the *GRN* mutation often exhibited dysphasia and this was rarely accompanied by motor neuron dysfunction (Gass et al. 2006). Pathological analysis of *GRN* IVS1+5G>C patients revealed the presence of neuronal cytoplasmic inclusions (NCIs). Neuronal intranuclear inclusions (NIIs) were also observed in all cases. These observations corresponded with previous reports in which NIIs were commonly detected in familial FTLD patients without motor neuron dysfunction (Mackenzie and Feldman 2003; Woulfe et al. 2001). These results suggested that NIIs would be a pathological marker of PGRN mutation cases. However, NIIs were also found in sporadic FTLD cases or FTLD patients with motor neuron dysfunction, indicating that more investigation will be needed (Mackenzie et al. 2006a). Investigating the clinical response to the *GRN* mutation, Gass et al. found that the most common diagnosis was FTD followed by PA. Other diagnoses were CBD, AD with convulsions and motor dysfunction (PD, parkinsonism and FTD-MND) (Gass et al. 2006). Snowden and colleagues reported that in a single pedigree of the g.3073C>T (p.Gln468X) mutation, patients showed

symptoms of FTD and PA (Snowden et al. 2006). Masellis et al. reported that a patient with the *GRN* IVS7+1G>A (p.Val200GlyfsX18) mutation exhibited CBD-like symptoms (Masellis et al. 2006). Pickering-Brown et al. reported that in patients with the *GRN* mutation, 57% were diagnosed as FTD, 36% as PNFA and 7% as apraxia and parkinsonism (Pickering-Brown et al. 2008). Le Ber et al. reported that 63% of patients with the GRN mutation were diagnosed as fvFTD with other clinical patterns being PPA (16%), CBS (6%) and Lewy body disease (LBD) (6%) (Le Ber et al. 2008). They also found that 9% of patients had other diagnoses including AD and parkinsonism (Le Ber et al. 2008). The most common diagnosis was FTD including PPA and CBS. Other clinical phenotypes such as AD, AD+PD and LBD were observed (Yu et al. 2010).

Immunohistochemical analyses for phosphorylated TDP-43 revealed a considerable number of neuronal cytoplasmic inclusions and dystrophic neurites in *GRN* mutation cases (Fig. 1). In FTLD-TDP, TDP-43 pathology falls within four histological subtypes (types A-D) based on the predominant type of TDP-43-positive structures exhibited (Mackenzie et al. 2011). Type A is characterized by numerous short dystrophic neurites (DNs) and crescentic or oval shaped neuronal cytoplasmic inclusions (NCIs). Cases of FTLD-TDP with a *GRN* mutation invariably display type A pathology (Cairns et al. 2007; Josephs et al. 2007; Mackenzie et al. 2006b).

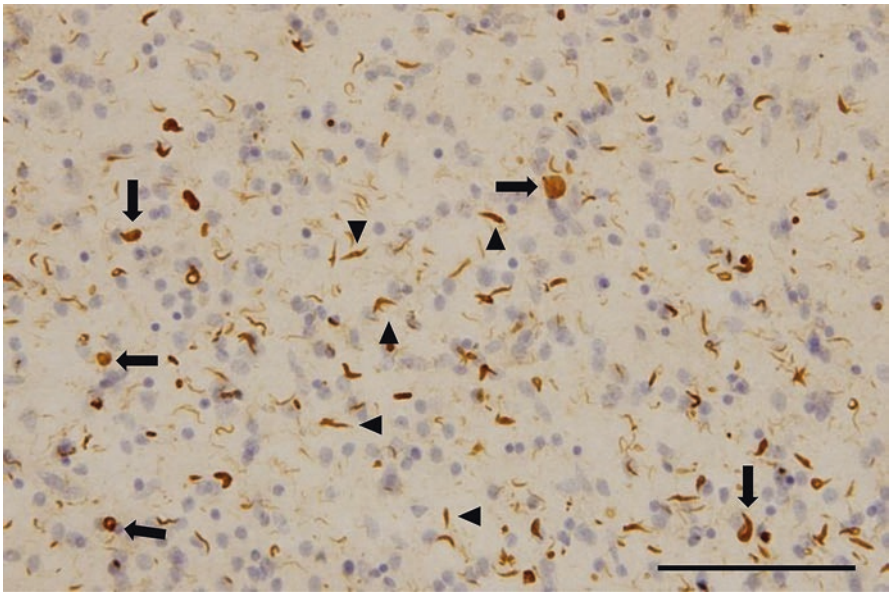

Fig. 1 Immunohistochemical staining of the temporal lobe of a *GRN* mutation case with antibody to phosphorylated TDP-43. Numerous neuronal cytoplasmic inclusions (arrows) and dystrophic neurites (arrowheads) were stained with anti-TDP-43-pS409/410 antibody and the section was counterstained with hematoxylin. Scale bar = 100 μm

PGRN Protein Levels in *GRN* Mutation Carriers

Plasma PGRN protein levels were measured in FTLD patients with the g.1975_1978delCTCA (p.Leu271LeufsX10) mutation or the g.2473 C>T (p.Gln341Arg) mutation and in unaffected individuals with the g.1975_1978del CTCA (p.Leu271LeufsX10) mutation, and in all cases were found to have significantly reduced expression of PGRN (Ghidoni et al. 2008). Plasma PGRN was proposed as a useful biomarker. Sleegers et al. reported that serum PGRN levels were reduced in both affected and unaffected carriers of the PGRN null mutation (IVS1+5G>C) compared with their noncarrier relatives (Sleegers et al. 2009). The authors also measured serum PGRN levels in carriers of the g.1129T>C (p.Cys139Arg) and g.3542C>T (p.Arg564Cys) mutations, and found them to be significantly lower than in controls, but greater than in null mutation carriers. They concluded that the serum PGRN level is a reliable biomarker for diagnosis of FTLD caused by a PGRN null mutation (Sleegers et al. 2009).

Plasma PGRN levels were measured in PGRN loss-of-function mutation carriers, FTLD patients without *GRN* mutations or symptomatic/asymptomatic *GRN* mutation carriers (Finch et al. 2009). Pathogenic *GRN* loss-of-function mutations such as g.26C>A (p.Ala9Asp), g.1098_1101delTAGT (p.Gln130SfsX125), g.2273_2274insTG (p.Trp304LeufsX58fs), g.2450delC (p.Gly333ValfsX28), g.3240C>T (p.Arg493X) and g.3175A>G (p.Ala472_Gln584del) resulted in significantly reduced plasma PGRN levels. Missense mutations (g.2422G>A (p.Ala324Thr)), g.2968C>T (p.Arg433Trp), g.3012C>T (p.His447His) and g.3586G>A (p.Pro578Pro) were associated with plasma PGRN levels equal to those of the controls, but g.55C>T (p.Arg19Trp) and g.1129T>C (p.Cys139Arg) cases showed plasma PGRN levels below the level of detection in controls. These results suggested that g.55C>T (p.Arg19Trp) and g.1129T>C (p.Cys139Arg) mutations might induce a partial loss of PGRN function (Finch et al. 2009). Plasma PGRN levels were also lower than those in carriers of the PGRN g.1A>G (p.Met1), g.1129T>C (p.Cys139Arg), p.Ala89ValfsX41 and p.Ala303AlafsX57 mutations (Gomez-Tortosa et al. 2013).

Mean plasma PGRN levels within the FTLD group were significantly lower in patients with *GRN* mutations than in those with *C9ORF72* expansions, or those without mutation (Gibbons et al. 2015). Meeter and colleagues recently reported that PGRN levels in the plasma and CSF of patients with a loss-of-function *GRN* mutation (g.366delC (p.Ser82ValfsX174), g.1087C>T (p.Gln125X), g.1102_1105delCAGT (p.Gln130SerfsX125) and g.2902_2903delGT (p.Val411SerfsX2)) and presymptomatic loss-of-function *GRN* mutation carriers were lower than those of healthy controls (Meeter et al. 2016).

It has been reported that the homozygous carriers of the T-allele of rs5848 have an elevated risk of developing FTD. TT genotype carriers had lower serum PGRN levels than CT or CC carriers (Hsiung et al. 2011). The rs5848 T-allele is known to be a miRNA-659 binding site and rs5848 may enhance translational inhibition of *GRN* and alter the risk of FTD and other dementias (Hsiung et al. 2011).

The Effect of *GRN* Mutation and Its Influence on PGRN

The effects of *GRN* mutation and its influence on PGRN function are as follows.

1. Mutations that introduce a premature termination codon (PTC) induce nonsense-mediated mRNA decay machinery.
2. Mutations in the intron 1 splice-donor site such as IVS1+3A>T and IVS1+5G>C may generate intron 1 read-through mRNA. Such aberrant mRNAs may not be capable of normal transport through the nuclear pore complex, so that they may remain in the nuclear area where they are then liable to be degraded by the nuclear mRNA degradation system.
3. Complete gene deletion such as found in del*GRN* (Gijselinck et al. 2008) or g.-95_3490del in French patients (Rovelet-Lecrux et al. 2008) may lead to no PGRN at all.
4. Missense mutations in the signal peptide may induce mislocalization of PGRN and insufficient translocation to the endoplasmic reticulum (ER).
5. Missense mutations in other areas may also cause problems. If the mutations exist in the consensus sequence of PGRN, they may be pathological because aberrant protein folding may occur in the ER and reduce PGRN secretion to the extracellular lumen. However, the pathological nature of almost all of them is unknown. The other missense mutations are considered to be benign.

GRN Mutation: Multiple Proteinopathy?

GRN mutations were initially found in tau-negative patients (Baker et al. 2006) (Cruts et al. 2006), but recent findings indicate that these mutations are associated with other neurodegenerative disorders with tau pathology, including AD and CBD. Leverenz et al. found that families with the *GRN* g.1871A>G (p.Ala237TrpfsX6) mutation had variable clinical presentations such as PD, AD, HD, depression and schizophrenia (Leverenz et al. 2007). Immunohistochemical analyses revealed that six of seven cases had evidence of distinctive tau pathology and two of the seven cases also had α-synuclein pathology (Leverenz et al. 2007).

A reduction in progranulin in tau transgenic mice was associated with an increasing tau accumulation (Hosokawa et al. 2015). A reduction in progranulin in APP transgenic mice was associated with a decrease in Aβ accumulation (Takahashi et al. 2017; Hosokawa et al. 2018).

Human *GRN* mutation cases were investigated histochemically and biochemically by Hosokawa and colleagues. Results showed a neuronal and glial tau accumulation in 12 of 13 *GRN* mutation cases (Hosokawa et al. 2017). Tau staining revealed neuronal pretangle forms and glial tau in both astrocytes and oligodendrocytes. Furthermore, phosphorylated α-synuclein-positive structures were also found in oligodendrocytes as well as in the neuropil. Immunoblot analysis of fresh frozen brain tissues revealed that tau and α-synuclein were present in the sarkosyl-insoluble

fraction and were composed of three- and four-repeat tau isoforms, resembling those found in AD. These data suggested that PGRN reduction might be the cause of multiple proteinopathies due to the accelerating accumulation of abnormal proteins. These might include TDP-43 proteinopathy, tauopathy and α-synucleinopathy (Hosokawa et al. 2017).

Very recently, Sieben and their colleagues reported that a family with a *GRN* loss-of-function mutation (IVS1+5G>C) had tau and α-synuclein pathology (Sieben et al. 2018). Of nine members of this family, all were tau-positive and one case had extensive Lewy body pathology. No Aβ pathology or mild accumulation was observed (Sieben et al. 2018).

Recent findings have suggested that different clinical phenotypes may occur in carries of the same *GRN* mutation and additional tau or α-synuclein accumulation may be observed. It has been also reported that PGRN deficiency causes lysosomal dysfunction (Tanaka et al. 2017). Lysosomal dysfunction may reduce protein degradation in brain cells, allowing aggregation-prone neurodegenerative disease-related proteins to deposit more easily (Hosokawa et al. 2017).

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