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Confirmation of high frequency of *C9orf72* mutations in patients with frontotemporal dementia from Sweden

Linn Öijerstedt [a,b], Huei-Hsin Chiang [a], Jenny Björkström [b], Charlotte Forsell [a], Lena Lilius [a], Anna-Karin Lindström [a], Håkan Thonberg [a,b], Caroline Graff [a,b,*]

[a] Division for Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[b] Karolinska University Hospital, Theme Aging, Unit for Hereditary Dementias QA12, Stockholm, Sweden

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ABSTRACT

Frontotemporal dementia (FTD) is the second most common early-onset dementia. Up to half of the cases are familial, and several mutations have been identified as pathogenic. Repeat expansion mutations in *C9orf72* are the most common genetic cause of FTD and are particularly frequent in Sweden and Finland. We aimed to determine the mutation frequency in patients with FTD ascertained at a memory clinic in Sweden and assess the inheritance pattern in the families. We screened 132 patients with FTD for mutations in *C9orf72*, *GRN*, and *MAPT*, and the frequency was 34.1%. Two novel variations, not previously published, were found; a pathogenic *GRN* mutation and a *MAPT* variation in intron 9 that we report as VUS. The likelihood of finding a mutation was highest in patients with a clear family history of dementia or motor neuron disease (76%), but mutations were also found in apparent sporadic cases. This confirms that FTD cohorts from Sweden have a relatively higher risk of an underlying mutation in all risk categories compared with other reported cohorts.

1. Introduction

Frontotemporal dementia (FTD) is a heterogeneous group of neurodegenerative diseases and the second most common early-onset dementia. Different clinical phenotypes have been described in FTD: behavioral FTD (bvFTD) and primary progressive aphasia (PPA), which includes progressive nonfluent aphasia (PNFA), semantic dementia (SD), and logopenic variant of aphasia (lvPPA) (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Patients with bvFTD present with personality changes such as apathy and inappropriate and stereotype behavior. Patients with PNFA have difficulties in language output such as phonetic errors and agrammatism, whereas patients with SD have fluent speech but difficulties in comprehending the meaning of words. There is also an overlap to other neurological diseases such as corticobasal syndrome and progressive supranuclear palsy and about 15% of FTD cases have motor neuron disease (MND), most typically amyolateral sclerosis (ALS) (Lashley et al., 2015; Neary et al., 1998). Up to half of the cases have a positive family history of dementia. Several mutations have been found to cause autosomal dominant FTD, and they are most frequently found in 3 genes: chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), and microtubule-associated protein tau (*MAPT*) (Baker et al., 2006; Cruts et al., 2006; DeJesus-Hernandez et al., 2011; Hutton et al., 1998; Renton et al., 2011). In Northern Europe, the *C9orf72* expansion mutation is considerably more common than in other European countries and it has been suggested to have a Scandinavian founder (Englund et al., 2012; van der Zee et al., 2013). In this study, we aimed to determine the mutation frequency in *C9orf72*, *MAPT* and *GRN* in an FTD cohort from Sweden. In addition, we wanted to explore how these mutations are distributed depending on the inheritance pattern in the family and whether the presence of ALS increased the likelihood of finding a mutation.

2. Material and method

2.1. Study cohort

The study included 132 patients (referred to as the "Swedish cohort") diagnosed with FTD or FTD-ALS, recruited at the Memory Clinic, Karolinska University Hospital, Huddinge, Sweden, between 1992 and 2013. The clinical diagnoses were according to the studies by Neary et al. (1998), Gorno-Tempini et al. (2011), and/or El Escorical criteria (Brooks, 1994). In conjunction with the diagnostic

* Corresponding author at: Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Unit Head & Clinical Geneticist, Manager of the Brain Bank at KI, Karolinska Institutet Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital-Solna, Visionsgatan 4, J10:20, 171 64 Solna, Sweden. Tel.: +46 733 839399.
E-mail address: caroline.graff@ki.se (C. Graff).

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workup, a blood sample was collected from each participant and information about family history was obtained orally and through questionnaires to a next of kin. Neuropathological diagnoses were available for 37 index patients, and the frontotemporal lobar degeneration (FTLD) subgroup classification was according to the study by Lee et al. (2017). Throughout the text, FTD is used as a collective term for all clinical subgroups (bvFTD, SD, and PNFA), whereas FTLD is used for the neuropathological subgroups. The study was approved by the Ethics Committee, Stockholm, Sweden. An informed consent for DNA sampling and research was obtained from the patients or their next of kin (proxy).

2.2. Genetic analysis

Genomic DNA from 132 FTD patients was isolated from peripheral blood with Gentra Puregene Blood kit (Qiagen) according to manufacturers' protocol. All 13 exons of *GRN* (RefSeq NM_002087.2) and exons 2 and 9–13 of *MAPT* (RefSeq NM_016835.4) were amplified by polymerase chain reaction (PCR) and Sanger-sequenced using in-house and previously published primers (Chiang et al., 2013; Hutton et al., 1998). The *C9orf72* mutation carriers were identified by repeat primed PCR and by determining the size of the hexanucleotide repeat alleles using a short tandem repeat assay as described by Gijselinck et al. (2012). A modified reaction for repeat primed PCR was used that included the addition of 0.2 mM 7-deaza-dGTP. More than 40 G_4C_2 repeats with a sawtooth pattern were scored as pathogenic (Supplementary Fig. 1). Sequencing reactions and fragment analyses were run on a Prism ABI 3100 Genetic Analyzer, Applied Biosystems (now Thermo Fisher Scientific Inc), Foster City, CA, USA. Primer sequences and PCR conditions are found in Supplementary Table 1. Serum progranulin levels were measured in patients where freshly frozen serum was available (n = 71) using the progranulin (human) ELISA kit, (Adipogen, Incheon, Korea) as described in Chiang et al. (2013). The American College of Medical Genetics and Genomics Guidelines (ACMG) were applied for the interpretation of sequence variants (Richards et al., 2015).

2.3. Assessment of family history

The family history of each patient was investigated without knowledge of mutation status and included a review of the medical records together with available neuropathological autopsy reports. Information on age at onset and clinical and neuropathological diagnoses for all affected individuals in 3 generations was collected if available. Pedigrees were made for each index case (data not shown). The term "affected" was applied to relatives diagnosed with FTD, FTD-MND, MND, Alzheimer's disease, Parkinson's disease, or dementia not otherwise specified. In the absence of required consent for retrieving medical records, diagnoses were obtained via the public Swedish death registry (Sveriges dödbok). Each pedigree was categorized into one of 5 different categories (Supplementary Table 2), described in Wood et al., (2013), by 2 independent co-authors. In case of disagreeing categorization, a third author assessed the pedigree(s) and a consensus meeting was held.

2.4. Statistical analyses

All statistical analyses were made using SPSS 22.0. When assessing potential differences between groups, the Pearson χ^2 test was used. Fischer's exact test was used when the expected values were <5 in more than 20% of the contingency cells. A *p*-value of <0.05 was considered significant except for the analyses of mutation frequency across pedigree categorization (*post hoc* tests, Supplementary Table 3) where a $p < 0.005$ was considered significant because of correction for multiple comparisons (Bonferroni).

3. Results

3.1. Genetic screening

Mutations were found in 45 of the 132 index patients (34.1%). The most frequent mutation was the repeat expansion in *C9orf72* (26.5%), followed by mutations in *GRN* and *MAPT* (6.8% and 0.8% respectively, Table 1). The detected mutations in *GRN* and *MAPT* are listed in Table 2. The *C9orf72* expansion mutation, the *MAPT* splice site mutation (c.1866T>C), and all but one of the *GRN* mutations have previously been reported (Chiang et al., 2013, 2008; Skoglund et al., 2008; van der Zee et al., 2013). We found a novel frameshift mutation (c.87dupC) in *GRN* that causes a premature stop codon (Supplementary Fig. 2). The mutation was examined for functional impact by measuring progranulin levels in serum from the index case carrying the variation. The analysis confirmed a reduction in progranulin protein levels compared with noncarriers (49.4 ng/mL in carrier vs. mean value 133.6 ng/mL in *GRN* noncarriers). The c.87dupC variation was considered as pathogenic according to the ACMG criteria of Richards et al. (2015). We also found 2 *GRN* missense variations, previously classified as benign, c.1297C>T and c.1294C>T (Chiang et al., 2013), with normal serum progranulin levels (148.7 ng/mL and 119.6 ng/mL respectively). Also, 2 variations in *MAPT* were found, c.1666G>A and IVS9-11G>C. The variant c.1666G>A has previously been reported as likely benign with an MAF(A) of 0.003 (Pickering-Brown et al., 2006). The other *MAPT* variant, IVS9-11G>C (g.44087665G>C), is located in the polypyrimidine region upstream of exon 10 (Supplementary Fig. 3), which might affect the splicing (Malkani et al., 2006). In silico analysis suggests that the variant increases the strength of the wild-type splice site (computations by Alamut (R) Visual). Segregation analysis was not possible because of lack of DNA samples from affected family members. However, neuropathological examination showed FTLD-tau pathology in agreement with other pathogenic *MAPT* mutations. Based on ACMG criteria, the *MAPT* variant was classified as a "variant of uncertain significance" since the criteria for a pathogenic mutation are not fulfilled (Table 2).

3.2. Clinical and neuropathological findings

The mean age at disease onset was 60.0 ±8.9 years, and 82 of the patients were female (62.1%). The most common phenotype was the behavioral variant (43.9%), as shown in Table 1. Twenty-six patients could not be subclassified as bvFTD, PPA, or FTD-ALS and were therefore classified as only FTD. Two patients fulfilled the criteria for corticobasal syndrome and one for progressive supranuclear palsy. Mutations were less frequent in patients with a clinical diagnosis of aphasia compared with other clinical diagnoses (Fisher's exact test 10.49, $p = 0.023$, Table 1). All mutation carriers with an FTD-ALS phenotype had the *C9orf72* expansion, whereas 4 of 5 mutation carriers with aphasia had a *GRN* mutation.

Thirty-six of the clinical diagnoses were neuropathologically confirmed. Most of the autopsied cases (and all with an FTD-ALS phenotype) had cortical, intracellular aggregates of phospho-TDP-43 (i.e., FTLD-TDP, Table 1). Both cases with semantic dementia were FTLD-TDP type C.

3.3. Pedigree categorization and mutation frequency

The family history of all 132 patients was assessed, and the pedigrees were categorized according to the criteria proposed by Wood et al. (2013). The distribution across categories is displayed in

Table 1
Mutation screening results, clinical phenotypes, and neuropathological diagnoses

Characteristics	Total	Type of mutation (n = 45)				Neuropathological diagnoses (n = 36)				
		C9orf72	*GRN*	*MAPT*	Absence of mutation	FTLD-TDP[b]	FTLD-tau[c]	FTLD-MND[d]	FTLD-FUS	FTLD-NOS[e]
Clinical diagnosis, n (%)	132	35 (26.5)	9 (6.8)	1 (0.8)	87 (65.9)					
FTD	26 (19.7)	7 (26.9)	0	1 (3.8)	18 (69.2)	3	1	0	1	0
bvFTD	58 (43.9)	19 (32.8)	5 (8.6)	0	34 (58.6)	12	3	0	1	1
PPA	30 (22.7)	1 (3.3)	4 (13.3)	0	25 (83.3)	4	0	0	0	0
FTD-MND	15 (11.4)	8 (53.3)	0	0	7 (46.7)	0	0	8	0	0
Other[a]	3 (2.3)	0	0	0	3 (100)	0	2	0	0	0

Key: bvFTD, behavioral variant FTD; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; MND, motor neuron disease; FTLD-FUS, FTLD fused in sarcoma; FTLD-NOS, FTLD not otherwise specified.
[a] Two individuals with corticobasal syndrome and one with progressive supranuclear palsy.
[b] Fourteen cases with TDP type A (2 cases with a *GRN* mutation and 12 cases with the *C9orf72* repeat expansion), 2 cases with TDP type B (one with the *C9orf72* repeat expansion), and 3 cases with TDP type C (one with the *C9orf72* repeat expansion).
[c] One case with the *C9orf72* repeat expansion and one with a *MAPT* mutation.
[d] Three cases with *C9orf72* repeat expansion.
[e] One case had neuronal atrophy consistent with FTLD but could not be further classified: Uncertain ubiquitin, TPD-43 and p62; Tau negative, few tau inclusions in the hippocampus and entorhinal cortex; Alpha synuclein negative, TATA-binding protein-associated factor 15 negative.

Supplementary Table 3. The mutation frequency is different depending on pedigree category. The highest mutation frequency was found in index patients in category "high," followed by "medium."

We compared our results to data from similar studies (Fostinelli et al., 2018; Wood et al., 2013; Supplementary Tables 4 and 5). The ratio of mutation carriers in the categories "apparent sporadic" and "unknown significance" in our cohort is different compared with the US and Italian cohorts. In agreement with previous reports, the frequency of the *C9orf72* expansion was significantly higher in the Swedish cohort compared with the US and Italian cohorts (26.5% vs. 8.2% and 3.5%, respectively).

4. Discussion

In this study, 132 patients with FTD were screened for mutations in *C9orf72*, *GRN*, and *MAPT*. Our results confirm a high mutation frequency (34.1%) in patients with FTD from Sweden. We also confirm that the *C9orf72* repeat expansion mutation has a higher prevalence in Sweden compared with other countries (26.5%) (Supplementary Table 4) (van der Zee et al., 2013). Most of the identified genetic variations have previously been reported (Chiang et al., 2008, 2013; DeJesus-Hernandez et al., 2011; Renton et al., 2011; Skoglund et al., 2008). However, we identified a novel pathogenic *GRN* mutation (c.87dupC) in one family. In addition, a *MAPT* variation (IVS9-11G>C), identified in a patient with bvFTD, associated with FTLD-tau pathology has not been reported previously, and in absence of information about its functionality it was considered as a variant of uncertain significance. Interestingly, this patient had a strong family history of dementia: a father with FTD, a brother and a paternal grandfather with dementia not otherwise specified. Other variations in intron 9 have been linked to FTD, showing that the alternative splicing of exon 10 alters the normal ratio of 4R/3R tau isoforms (D'Souza and Schellenberg, 2002; Malkani et al., 2006). Variations upstream of exon 10 strengthen the polypyrimidine tract, which increases the likelihood of exon 10 being included in the transcript (4R tau). Although Malkani et al. (2006) showed that the intron 9 variation (IVS9-10G>T) segregated with FTD, further studies are needed to determine whether this specific variation is pathogenic.

One aim of the study was to investigate whether an FTD-ALS phenotype was a particularly strong predictor for the presence of a pathogenic mutation. Of all 15 index cases with FTD-ALS, we found 8 mutation carriers and 7 noncarriers indeed indicating a strong risk of being a mutation carrier. Furthermore, the pedigree assessments

Table 2
Detected mutations

Gene	cDNA[a]	gDNA	Predicted protein[b]	No. of cases	SNP ID	Reference
C9orf72	Hexanucleotide repeat GGGGCC	9:27,546,545 −27,573,865		35[c]		DeJesus-Hernandez et al., (2011), Renton et al., (2011)
GRN[e]	c.87dupC	g.42426619dup	p.Cys30Leufs*35	1	rs794729672	
GRN	c.102delC	g.42426634del	p.Gly35Glufs*19	2[d]	rs63751073	Chiang et al., (2008)
GRN	c.462+1G>C	g.42427709G>C	p.Asn118Phefs*4	1	rs794729669	Chiang et al., (2013)
GRN	c.708+1G>A	g.42428169G>A	p.Val200Glyfs*18	1	rs63749817	Chiang et al., (2013)
GRN	c.882T>G	g.42428777T>G	p.Tyr294*	2[g]	rs794729670	Chiang et al., (2013)
GRN	c.1212C>A	g.42429415C>A	p.Cys404*	1	rs193026789	Chiang et al., (2013)
GRN	c.1246dupT	g.42429449dup	p.Cys416Leufs*30	1	rs794729671	Chiang et al., (2013)
MAPT[f]	c.1920T>C	g.44087768 T>C	p.(Ser640=)	1	rs63750568	Skoglund et al., (2008)

[a] *GRN* mutation: The numbering is according to NM_002087.2 starting with A in ATG (start codon) as nucleotide position 1. MAPT mutation: The numbering is according to NM_016835.4 starting with A in ATG (start codon) as nucleotide position 1.
[b] *GRN* mutation: The numbering is according to NP_002078.1 with methionine as amino acid 1. MAPT mutation: The numbering is according to NP_058519.3 with methionine as amino acid 1.
[c] Seventeen of these have previously been reported by van der Zee et al., (2013).
[d] Common founder unlikely as described by Chiang et al., (2008).
[e] Benign variants found in *GRN*: c.1297C>T and c.1294C>T.
[f] Other variants found in *MAPT*: c.1666G>A (likely benign) and IVS9-11G>C (uncertain significance, see Section 3.1 and 4).
[g] Common founder could not be excluded (Chiang et al., 2013).

suggested a strong positive family history in most FTD-ALS also in the cases without mutations in *C9orf72*, *GRN*, and *MAPT* (data not shown). Other genetic causes of FTD-ALS, such as mutations in TANK-binding kinase 1, have not been investigated in this study and could potentially be the underlying cause in these cases.

In FTD, an autosomal dominant inheritance pattern is not always obvious and can be modulated by reduced penetrance and variable age at onset (Murphy et al., 2017). This makes assessments of genetic risk in patients and families as well as prioritization of patients for genetic screening difficult. Hence, a reliable clinical prediction model based on family history would be valuable for genetic counseling. Another aim was thus to assess the likelihood of finding a mutation based on the family history of the index cases (Supplementary Tables 3–5). We chose to apply the criteria proposed by Wood et al. (2013) because they were developed after the discovery of the *C9orf72* repeat expansion. We conclude that although it is not possible to predict the presence of a mutation based solely on the family history of FTD, the categories "high" and "medium" predict the presence of a mutation in more than half of the families (53%–76%). However, we also found a relatively high prevalence of mutations in all other categories, suggesting that absence of a clear family history or missing information about the family history can still hide a substantial risk for a hereditary form of FTD.

A limitation in this study is the low number of cases and that a portion of cases had limited clinical and family history information available. Furthermore, not all subjects were assessed using the recent clinical diagnostic criteria (Rascovsky et al., 2011) and there is always a risk for clinical misdiagnoses as a result of the heterogeneous nature of FTD, which may lead to both underestimation and overestimation of the mutation frequency (Benussi et al., 2015). However, the neuropathologically confirmed cases, 36 of 132 index patients, add strength to the study. The cases with an autopsy-confirmed diagnosis were distributed across all clinical phenotypes, and 21 (58%) cases had a disease-causing mutation (Table 1).

For a patient and/or family to make an informed choice regarding genetic testing, information should be given about the possible outcomes and consequences of such analyses. We suggest, unless the patients and families choose otherwise, that the clinical investigation of patients diagnosed with FTD or FTD-MND should include clinical genetic services in a genetic counseling setting. Pathogenic genetic variations, especially the *C9orf72* expansion mutation, are reported in a significant number of apparent sporadic FTD cases (Majounie et al., 2012; Turner et al., 2017). Thus, even in cases without a family history of dementia, an underlying genetic cause of FTD cannot be excluded.

Disclosure

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.03.009.

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