Heterozygous *TREM2* mutations in frontotemporal dementia

Barbara Borroni [a,*], Francesca Ferrari [a], Daniela Galimberti [b], Benedetta Nacmias [c], Cinzia Barone [b], Silvia Bagnoli [c], Chiara Fenoglio [b], Irene Piaceri [c], Silvana Archetti [d], Cristian Bonvicini [e], Massimo Gennarelli [e], Marinella Turla [f], Elio Scarpini [b], Sandro Sorbi [c], Alessandro Padovani [a]

[a] *Center of Neurodegenerative Disorders, Neurology Unit, University of Brescia, Brescia, Italy*
[b] *Neurology Unit, Department of Pathophysiology and Transplantation, University of Milan, Fondazione Cà Granda, IRCCS Ospedale Maggiore Policlinico, Milan, Italy*
[c] *Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy*
[d] *III Laboratory of Analysis, Brescia Hospital, Brescia, Italy*
[e] *Istituto di Ricerca e Cura a Carattere Scientifico Fatebenefratelli, Brescia, Italy*
[f] *Neurology Unit, ValleCamonica Hospital, Brescia, Italy*

1. Introduction

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder characterized by behavioral disturbances, language impairment, and deficits in executive functions (Seelaar et al., 2011). On the basis of presenting clinical symptoms, the behavioral variant of FTD (bvFTD), agrammatic variant of primary progressive aphasia, and semantic variant of primary progressive aphasia (svPPA) represent the most common phenotypes (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

FTD has a strong genetic background, as suggested by positive family history in almost 40% of patients, and several monogenic forms of FTD have been identified. Mutations within microtubule-associated protein tau (*MAPT*) and granulin (*GRN*) genes along with repeat expansion of *C9orf72* gene represent the most frequent causes of autosomal dominant inherited disorder (Rademakers et al., 2012; Rohrer et al., 2011). Despite a giant step forward in the knowledge of genetic bases of FTD, several cases even with positive family history remain of unknown pathogenesis. The identification of new genetic predisposing factors, even rare variants, is key to further elucidating the pathogenetic mechanisms leading to frontotemporal brain damage.

Homozygous loss-of-function mutations in *TREM2*, encoding the triggering receptor expressed on myeloid cells 2 protein, have been previously associated with an autosomal recessive form of early-onset dementia presenting with bone cysts and consequent fractures called polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, or Nasu-Hakola disease (Paloneva et al., 2000, 2002). Interestingly, it has been reported that homozygous *TREM2* exon 2 mutations may resemble FTD clinical phenotype without any bone-associated symptoms (Guerreiro et al., 2013a). Nevertheless, heterozygosis of *TREM2* exon 2 mutations also has a role in neurodegenerative disorders because it has recently been associated with increased risk of late-onset Alzheimer's disease (AD) (Guerreiro et al., 2013b; Jonsson et al., 2013).

* Corresponding author at: Department of Neurology, University of Brescia, Piazza Spedali Civili 1-25125 Brescia, Italy. Tel.: +39 030 3995632; fax: +39 030 3995027.
E-mail address: bborroni@inwind.it (B. Borroni).

Table 1
TREM2 exon2 genetic variations in the screened population

TREM2 mutation	SNP	FTD % (n)	HC % (n)	AD % (n)	*p* FTD vs. HC	*p* FTD vs. AD	*p* AD vs. HC	OR (95% CI) FTD vs. HC	OR (95% CI) FTD vs. AD	OR (95% CI) AD vs. HC
Overall	—	4.0 (14)	1.0 (5)	2.6 (5)	0.005	0.393	0.126	3.97 (1.42–11.12)	1.57 (0.56–4.41)	2.53 (0.72–8.85)
Q33X[a]	rs104894002	0.9 (3)	0 (0)	1.5 (3)	0.042	0.457	0.023	NA	0.54 (0.11–2.74)	NA
R47H	rs75932628	0.3 (1)	0 (0)	0 (0)	0.241	0.457	—	NA	NA	NA
R62H	rs143332484	0.9 (3)	0.4 (2)	0.5 (1)	0.221	0.466	0.637	2.77 (0.50–15.21)	2.22 (0.24–20.00)	1.30 (0.11–13.85)
T66M[a]	rs201258663	0.3 (1)	0 (0)	0 (0)	0.241	0.457	—	NA	NA	NA
D87N	rs142232675	0.6 (2)	0.2 (1)	0 (0)	0.388	0.293	0.714	2.76 (0.29–30.56)	NA	NA
T96K	rs2234253	0.9 (3)	0.2 (1)	0 (0)	0.182	0.197	0.714	4.15 (0.43–40.08)	NA	NA
R98W	rs147564421	0 (0)	0.2 (1)	0.5 (1)	0.393	0.178	0.491	NA	NA	2.5 (0.15–40.21)
S116C	—	0.3 (1)	0 (0)	0 (0)	0.241	0.457	—	NA	NA	NA

Key: AD, Alzheimer's disease; CI, confidence interval; FTD, frontotemporal dementia; HC, healthy control subjects; NA, not applicable; OR, odds ratio; SNP, single nucleotide polymorphism.
[a] Mutation causative of Nasu-Hakola disease in homozygous state.

These observations defined the aim of the present study, and we hypothesized that variations within *TREM2* gene might be associated with a broader clinical spectrum and might predispose to FTD phenotype in heterozygous state. We evaluated genetic variations within *TREM2* exon 2 gene in a large cohort of patients with FTD, compared with healthy control subjects and a group of patients with AD.

2. Methods

2.1. Subjects

Patients fulfilling revised criteria for FTD (Gorno-Tempini et al., 2011; Rascovsky et al., 2011) were consecutively recruited from the Center for Aging Brain and Neurodegenerative Disorders, University of Brescia, the Neurology Unit, University of Florence, and the Neurology Unit, University of Milan, Italy.

All subjects underwent a somatic and neurologic evaluation, routine laboratory examination, and brain structural imaging study. A standardized neuropsychological assessment including global cognitive evaluation and a standardized neuropsychological test battery for investigating the main cognitive domains was performed. The diagnostic assessment included a review of full medical history, a semistructured neurologic examination, and a complete mental status evaluation. Patients considered to have a positive family history were those who had a first-degree relative with dementia, parkinsonism, or motor neuron disease. No patients belonging to the same family were included. A venous blood sample was drawn from each patient for *TREM2* exon 2 sequencing.

Patients with *MAPT* or *GRN* mutations and with repeat expansion of *C9orf72* gene were excluded (Borroni et al., 2011; Galimberti et al., 2013). Moreover, a control group similar in age and gender composition was recruited in the same Italian area from which the patients were drawn and was sequenced for *TREM2* exon 2 genetic variations. Two subgroups were considered for comparisons, that is, subjects found to be cognitively intact, following medical history, presence of comorbidities, and neuropsychological examination (healthy controls [HCs]), and patients fulfilling clinical diagnosis of AD according to current criteria (McKhann et al., 1984).

Informed consent was obtained for blood collection from venous puncture and genetic analysis from each subject. The work conform to the Helsinki Declaration and was approved by the ethics committee of our hospital.

2.2. TREM2 *exon 2 sequencing*

Total genomic DNA was prepared from peripheral blood according to standard procedures. *TREM2* exon 2 and at least 100 base pairs of its flanking introns were evaluated by polymerase chain reaction (PCR), the primers of which were designed to optimize denaturing high-performance liquid chromatography (dHPLC) conditions (forward primer: 5′-CACAGAGCAAGTGTTCAAAGC-3′ and reverse primer: 5′-CACACAGACGCCCAAAAC-3′ with the annealing temperature of 57 °C.

Preliminary dHPLC analysis was performed on the Wave nucleic acid fragment analysis system (Transgenomic, Santa Clara, CA, USA), and samples with an altered dHPLC profile were sequenced. Nucleotide direct sequencing was performed on genomic DNA for both strands by ABI 3130xl DNA analyzer (Applied Biosystems, Foster City, CA, USA) and analyzed using SeqScape Software version 2.6 (Applied Biosystems, Foster City, CA, USA).

2.3. Bioinformatic analyses

A multiple protein alignment was constructed with multiple alignment by Bioedit (http://www.mbio.ncsu.edu/bioedit/bioedit.html) and CLUSTALW (http://clustalw.ddbj.nig.ac.jp/top-e.html) software.

The potential effect of the newly detected mutations on protein structure or function was analyzed with 4 prediction programs: PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/), Pmut: (http://mmb.pcb.ub.es/PMut/), SNAP (http://rostlab.org/services/snap/), and SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html).

2.4. Statistical analysis

Comparisons of each mutation and overall mutation frequencies between patients and HCs were compared by Pearson χ^2 test. Logistic regression analysis was performed to assess odds ratio, and corresponding 95% confidence intervals. Results are expressed as mean ± SD or percentage, as reported. The significant level was established at $p < 0.05$. Data analyses were carried out using SPSS 13.0 software (http://wwwspss.com).

3. Results

One thousand and thirty subjects were included in the present study, 352 patients with a diagnosis of FTD (aged 65.6 ± 8.6 years, 48.8% women), and, as control groups, 484 HCs (aged 72.2 ± 10.1 years, 54.5% women) and 194 patients with AD (aged 65.9 ± 7.2 years, 53.1% women).

In the overall sample, we found 8 genetic variations in 24 subjects in 24 subjects: Q33X, R47H, R62H, T66M, D87N, T96K, R98W, and S116C. As reported in Table 1, R47H, T66M, and S116C were found only in patients with FTD; Q33X was found in patients with both FTD and AD, and R62H, D87N, T96K, and R98W were also found in HCs.

Table 2
In silico analyses of the amino acid changes found in the analyzed sample

In silico software	Q33X	R47H	R62H	T66M	D87N	T96K	R98W	S116C
PolyPhen2 (score[a])	Stop gained. NA	Probably damaging (1.0)	Benign (0.016)	Probably damaging (1.0)	Probably damaging (1.0)	Probably damaging (1.0)	Probably damaging (0.995)	Probably damaging (0.987)
SNAP	Stop gained. NA	Nonneutral	Neutral	Nonneutral	Neutral	Nonneutral	Nonneutral	Neutral
P-mut	Stop gained. NA	Pathologic	Pathologic	Pathologic	Neutral	Pathologic	Pathologic	Pathologic
SIFT	Stop gained. NA	Tolerated	Tolerated	Damaging	Tolerated	Damaging	Damaging	Tolerated

Key: NA, not applicable.
[a] The lower the score, the more benign the substitution (range 0–1).

Overall, we found significantly more variants in exon 2 of *TREM2* in patients with FTD than in HCs (4.0% vs. 1.0%, $p = 0.005$). Carriers of *TREM2* exon 2 mutations had an almost 4-fold increased risk to develop FTD than noncarriers (odds ratio: 3.97, 95% confidence intervals: 1.42–11.12). In FTD, 6 of 14 patients carried heterozygous *TREM2* mutations that were not found in HCs. As reported in Table 2, in silico analysis demonstrated that the Q33X variant (cytosine to thymine change in position 6818), previously associated with Nasu-Hakola disease in the homozygous state, resulting in a TAG stop codon with a loss of function of the *TREM2* protein. The R47H mutation was characterized by a single point mutation in the CGC codon, with the substitution of guanine with adenine, and was predicted to be damaging in 3 of 4 in silico analyses. The T66M mutation was characterized by a single point mutation in the ACG codon, resulting in a replacement of threonine at position 66 with methionine; all in silico analyses predicted a pathologic effect of this substitution, and this mutation was previously associated with Nasu-Hakola disease in homozygosity. S116C has not been previously described in the literature and causes a substitution of adenine to thymine; no clear-cut results were obtained by in silico analysis because 2 of 4 prediction analyses suggested neutral effect.

In Table 3, demographic and clinical characteristics of patients with FTD carrying *TREM2* Q33X, R47H, T66M, and S116C are reported. In most of these cases, patients presented an early age of onset (range: 52–68 years), and 66.7% were women. Family history was unremarkable in 5 of 6 patients. Half had a diagnosis of svPPA (2 Q33X, 1 S116C), and the others had a diagnosis of bvFTD (1 Q33X, 1 R47H, and 1 T66M), with a phenotypic variability in patients carrying the same genetic variation.

When the AD control group was considered to elucidate whether FTD and AD may share a common at-risk genetic background, no significant differences in the overall number of *TREM2* exon 2 mutations were found (4.0% vs. 2.6, $p = 0.46$). Notably, in 1.5% of patients with AD (n = 3, 2 women, age range 58–69 years), a heterozygous Q33X mutation was found, whereas 1 patient carried R62H and 1 carried R98W, both of which were also found in HCs.

Finally, when the AD group was compared with the HC group, we found significantly more Q33X variants of *TREM2* in the former group (n = 3, 1.5%) then the latter (0.0%, $p = 0.023$). Patients with AD carrying Q33X mutation showed late-onset disease (aged 65–75 years), 2 of 3 were women, and none carried the apolipoprotein E ε4 allele.

Moreover, in AD, we found R62H and R98W mutations, which were detected in HCs as well. We did not find any difference in overall frequency of mutations in patients with AD versus HCs, presumably because of the small sample of patients with AD.

4. Discussion

TREM2 gene has recently gained great interest in the dementia field, as the identification of homozygous mutations in cases of FTD-like phenotype (Guerreiro et al., 2013a, 2013c), and the demonstration that *TREM2* exon 2 genetic variations are risk factors for AD in heterozygosis (Guerreiro et al., 2013b; Jonsson et al., 2013). With these premises, we hypothesized that heterozygous *TREM2* mutations might be related to FTD risk as well. In the present work, we screened a large sample of patients and HCs for *TREM2* exon 2 genetic variations and found that FTD patients showed increased frequency of heterozygous *TREM2* mutations compared with HCs. Interestingly, we confirmed that Q33X, R47H, and T66M mutations were significantly associated with the disease and absent in healthy subjects. Q33X and T66M mutations have previously been demonstrated to cause Nasu-Hakola disease in the homozygous state (Paloneva et al., 2000, 2002), and the heterozygous R47H mutation has been associated with AD risk (Guerreiro et al., 2013b; Jonsson et al., 2013). Accordingly, in silico analysis of these mutations suggested a loss of function in *TREM2*; this might suggest that these variants are causal mutations, even in heterozygosis, rather than risk factors.

Notably, different clinical phenotypes were observed in FTD patients carrying these *TREM2* genetic variations with variable age at disease onset and inconsistent family history for neurodegenerative disorders. Interestingly, patients presented either bvFTD or svPPA, and this is the first association study suggesting a genetic risk factor for svPPA phenotype.

Recently studies on *TREM2* genetic variations have been published in France (Lattante et al., 2013), the United States (Rayaprolu et al., 2013), and Colombia (Giraldo et al., 2013) with different mutation frequencies. No work exploring the role of *TREM2* in the Italian population is available yet.

TREM2 encodes a single-pass type I membrane protein that forms a receptor-signaling complex with the TYRO protein tyrosine kinase-binding protein (TYROBP) that is involved in the activation of immune responses in immune cells, as macrophages and dendritic cells. It is involved in chronic inflammation by triggering the production of constitutive rather than inflammatory chemokines and cytokines and has a critical role in microglia clearance (Neumann et al., 2013; Paloneva et al., 2003; Takahashi et al., 2005).

Interestingly, we also found *TREM2* mutations in our AD patients, confirming previous data (Guerreito et al., 2013b; Jonsson et al., 2013) and suggesting a common pathway in these 2 neurologic disorders, likely associated to inflammation processes. Indeed, emerging evidence has underlined a greater interest in mechanisms targeting inflammation in both diseases (Galimberti and Scarpini, 2011; Piguet, 2013). Furthermore, in human control brain, *TREM2* was expressed at higher levels in the hippocampus and neocortex (Guerreiro et al., 2013a), and this pattern of

Table 3
Demographic and clinical characteristics of FTD patients carrying *TREM2* exon 2 mutations

	Age at onset	Gender	Family history	Phenotype
ID1 Q33X	68	F	No	svPPA
ID2 Q33X	52	F	No	svPPA
ID3 Q33X	53	F	Yes	bvFTD
ID4 R47H	NA	M	No	bvFTD
ID5 T66M	55	M	No	bvFTD
ID6 S116C	59	F	No	svPPA

Key: bvFTD, behavioral variant of primary progressive aphasia; NA, not available; svPPA, semantic variant of primary progressive aphasia.

expression is partly consistent with pathologic features observed in both FTD and AD.

The effect of *TREM2* genetic variations in FTD cases and the possible interaction with protein involved in the known pathogenetic mechanisms of the disease remains to be elucidated. Functional activity assays will be required to determine how these identified mutations might compromise *TREM2* function, providing new clues to the mechanisms underlying the pathogenesis of FTD. Unfortunately, we were not able to assess the effect of *TREM2* genetic variation in our patients because it is expressed only in microglia and not in circulating monocytes.

This is a preliminary study, and we do not exclude the possibility that the frequency of heterozygous mutations we found is partially due to the relatively high number of cases (n = 3) with Nasu-Hakola disease (i.e., homozygous Q33X mutation) that we diagnosed in our geographic area (Bock et al., 2013). Moreover, it is reasonable to suppose that other mutations in *TREM2*, beyond exon 2, may be identified. However, as previously suggested (Guerreiro et al., 2013b), it may be that rare variants in the heterozygous state may be risk factors for late-onset complex disorders, determining defined early-onset disease when in homozygosis.

In conclusion, we report that *TREM2* variants might be considered risk variants in FTD not only in homozygosis as previously demonstrated but in heterozygosis as well. Moreover, the absence of certain variants, in both our control population and others previously published (Guerreiro et al., 2013b; Jonsson et al., 2013; Paloeva et al., 2001), raises the question of whether such variants are mutations leading to dementia and Nasu-Hakola disease rather than polymorphisms influencing the risk of developing FTD. Whether *TREM2* is a major gene or a modifier gene for FTD and AD remains to be determined. Future confirmatory clinical and experimental studies are needed to elucidate the role of this gene in FTD.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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