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Variants in triggering receptor expressed on myeloid cells 2 are associated with both behavioral variant frontotemporal lobar degeneration and Alzheimer's disease

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ABSTRACT

Recent evidence suggests that rare genetic variants within the *TREM2* gene are associated with increased risk of Alzheimer's disease. *TREM2* mutations are the genetic basis for a condition characterized by polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) and an early-onset dementia syndrome. TREM2 is important in the phagocytosis of apoptotic neuronal cells by microglia in the brain. Loss of function might lead to an impaired clearance and to accumulation of necrotic debris and subsequent neurodegeneration. In this study, we investigated a consanguineous family segregating autosomal recessive behavioral variant FTLD from Antioquia, Colombia. Exome sequencing identified a nonsense mutation in *TREM2* (p.Trp198X) segregating with disease. Next, using a cohort of clinically characterized and neuropathologically verified sporadic AD cases and controls, we report replication of the AD risk association at rs75932628 within *TREM2* and demonstrate that TREM2 is significantly overexpressed in the brain tissue from AD cases. These data suggest that a mutational burden in *TREM2* may serve as a risk factor for neurodegenerative disease in general, and that potentially this class of *TREM2* variant carriers with dementia should be considered as having a molecularly distinct form of neurodegenerative disease.

1. Introduction

Triggering receptor expressed on myeloid cells 2 (*TREM2*) is an immunoreceptor expressed on activated macrophages, osteoclast, immature dendritic cells, and microglia (Colonna, 2003). It is a 26-kDa transmembrane glycoprotein that consists of a single extracellular immunoglobulin-like domain, a transmembrane region with a charged lysine residue, and a short cytoplasmic tail lacking any signaling motifs (Colonna, 2003). TREM2 forms a receptor signaling complex with TYROBP (Paloneva et al., 2002). The charged lysine in the transmembrane domain of TREM2 is needed for its association with TYROBP (Bouchon et al., 2000; Bouchon et al., 2001) and as TREM2 lacks an intracellular signaling tail, it is completely dependent on the presence of the adaptor protein TYROBP (Colonna, 2003). The TREM2/TYROBP complex

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regulates key signaling events involved in immune responses, differentiation of dendritic cells and osteoclasts, and phagocytic activity in microglia (Bouchon et al., 2001; Hsieh et al., 2009; Otero et al., 2012).

After neuronal injury, microglia initiate repair by phagocytizing dead neurons without eliciting inflammation. TREM2 has been shown to play a role in the phagocytosis of apoptotic neuronal cells by microglia and resolution of inflammation (Hsieh et al., 2009). TREM2 can directly bind to neuronal cells, with increased binding to apoptotic neuronal cells. When neuronal cells undergo apoptosis, they increase the expression of TREM2-ligands, which mediate signal transduction by TREM2 on microglia and promote phagocytosis (Hsieh et al., 2009). In osteoclasts, TREM2 has been shown to regulate bone mass by regulating the rate of osteoclast generation (Otero et al., 2012).

Genetic mutations in either *TREM2* or *TYROBP* cause a similar clinical phenotype, the Nasu-Hakola syndrome (or polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy [PLOSL]) (Fig. 1), which is characterized by cystic-like lesions of the bone and brain demyelination that lead to fractures and presenile dementia (Paloneva et al., 2002). The disease is characterized by different stages. The first symptoms present with an osseous stage at the third decade of life with pathological bone fractures. This is followed by the early neuropsychiatric stage in the fourth decade, presenting a frontal lobe syndrome, and the late neuropsychiatric stage, with profound dementia and usually death by the age of 50 years (Bianchin et al., 2004; Numasawa et al., 2011). Neuropathological findings include loss of myelin and axons in the brain, with reactive astrocytosis and microglial activation (Klunemann et al., 2005). Mutations in *TREM2* have also been described in pure early-onset dementia without bone cysts, and frontotemporal dementia (FTD)–like syndrome (Chouery et al., 2008). Recently, a variant in *TREM2* (rs75932628) has also been implicated as a risk factor for both early-onset and late-onset Alzheimer's disease (Jonsson et al., 2012; Pottier et al., 2013; R. Guerreiro et al., 2012).

In this study, we identified a nonsense mutation in *TREM2* in a consanguineous Colombian family segregating autosomal recessive FTLD. Frontotemporal lobar degeneration (*FTLD*) is the second most common cause of early-onset dementia and the fourth most common cause of late-onset dementia, and is characterized by atrophy of the prefrontal and anterior temporal lobes. FTLD is a clinically and genetically heterogeneous degenerative disorder. Patients usually show prominent behavioral and/or language deficits, which evolve gradually into cognitive impairment and dementia (McKhann et al., 2001; Neary et al., 1998). The most common clinical manifestation of FTLD consists of behavioral or personality changes (behavioral variant frontotemporal dementia or bvFTD) (Neary et al., 1998). Two other prototypic clinical phenotypes that occur in FTLD are language impairment disorders: semantic dementia (SD) and progressive nonfluent aphasia (PNFA) (Neary et al., 1998).

In this article, we report that a nonsense mutation in *TREM2* is the cause of FTLD in a Colombian family from the province Antioquia. In addition, we provide replicative evidence demonstrating a role for the rs75932628 *TREM2* variant in Alzheimer's disease, thereby suggesting *TREM2* mutations as a risk factor for neurodegenerative disease in general.

2. Methods

2.1. Clinical diagnosis

A large consanguineous Colombian family segregating autosomal recessive FTLD was collected through the Grupo Neurosciencias, University of Antioquia, Colombia (Fig. 2). Three patients and 5 unaffected relatives from the family were included. Our patients met published criteria for behavioral variant FTD (Rascovsky et al., 2011). The index case was a female offspring of first cousins who first showed symptoms of sexual disinhibition at age 47. She was excessively familiar with strangers and had abandoned all her responsibilities in the home. A paternal uncle and a brother had similar symptoms before age 60.

2.1.1. Clinical tests

All patients and controls underwent a standard medical and neurological history, physical examination, and office-based clinical cognitive assessment. Patient III:16 (index patient) and her brother (patient III:10) additionally underwent more detailed neuropsychological assessment that included the following: general: mental status examinations (maximum score 30 points); memory: 10-item, 3 learning trials word-list learning with delayed free recall and recognition, and the Rey-Osterrieth Complex Figure Test (copy and recall, 36 points maximum for each); Attention/Psychomotor Speed: Trail Making Test (seconds to complete), Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution Test (raw total score); Language: FAS letter fluency (numbers of words generated in one minute for each letter), Category Fluency (animals named in 1 minute), and sentence writing; executive functions: Wisconsin Card Sorting Test (categories and perseverative responses).

This study was conducted according to the guidelines of the ethical committee at the University of Antioquia. Informed consent

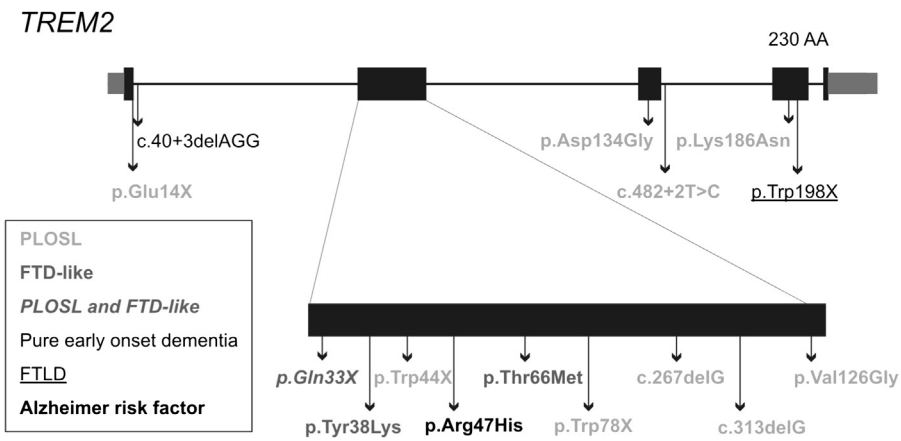

Fig. 1. Overview of the mutations found in *TREM2*. ENST00000373113.3; ENSP00000362205.3.

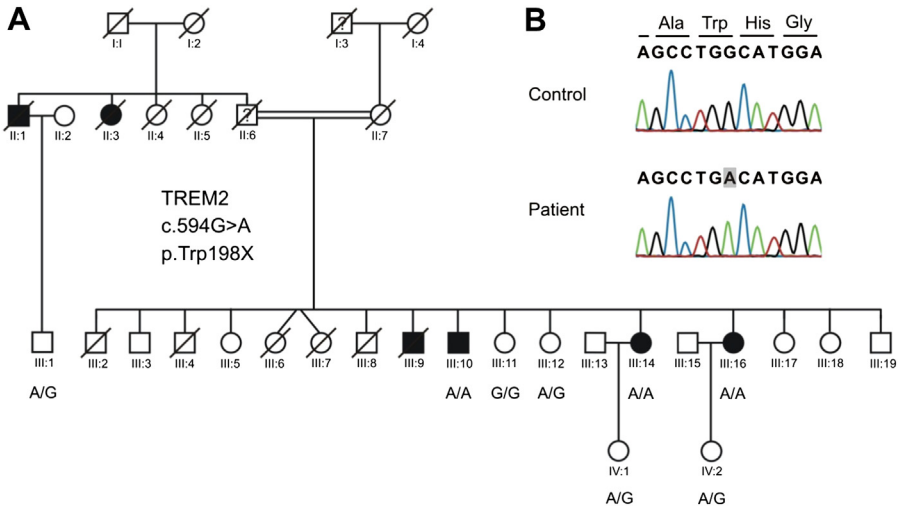

Fig. 2. (A) Inheritance of the nonsense mutation in *TREM2* in the Colombian family. (B) Sanger sequencing results. hg19/GRC37:chr6:41126693T>C ; ENST00000373113.3:c.594G>A; ENSP00000362205.3:p.Trp198X.

was obtained from all individuals or from family members in cases of impaired cognition.

2.2. Exome sequencing

Exome sequencing was performed in 2 affected individuals and 2 unaffected individuals from the family. First, 1.2 μg of DNA was fragmented to 300- to 400-bp fragments with a Covaris E210 instrument (Covaris, Woburn, MA). Next, libraries were prepared with Illumina's Truseq DNA Sample Preparation Kit v2 (Illumina inc, San Diego, CA), following the manufacturer's protocol. All 4 samples were labeled using 4 different indices. Final PCR-enriched fragments were validated on a 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). In addition, samples were quantified with PicoGreen (Molecular Probes, Eugene, OR), and 500 ng of each sample was pooled before entering Truseq 62Mb Exome Enrichment Kit (Illumina, San Diego, CA). The final library was then validated on a 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA), quantified using quantitative polymerase chain reaction (qPCR; 7900 HT, Applied Biosystems, Foster City, CA; Kapa Biosystems, Woburn, MA) and sequenced by 100-bp paired-end sequencing on a HiSeq2000 instrument (Illumina, San Diego, CA).

2.3. Data analysis

Reads were aligned to the Human genome (Hg19/GRC37) using the Burrows-Wheeler transform (BWA v.0.5.9) (Li and Durbin, 2009). PCR duplicates were removed using Picard v1.51(H. Li et al., 2009) and base quality recalibration, indel realignment and SNP, and INDEL discovery were performed using the Genome analysis toolkit (GATK v1.1-31-gdc8398e) (McKenna et al., 2010). Data were filtered against dbSNP135, 1000 genomes, an in-house exome database, and then annotated with snpEff v2.0.2 against ensembl v63 to identify new damaging mutations (nonsense, splice site, frameshift, missense) (Cingolani, 2011). Only homozygous variants present in the 2 affected individuals and either heterozygous or not present in the controls were considered as candidates.

2.4. Sanger DNA sequencing

The c.594G>A mutation in *TREM2* was confirmed with Sanger sequencing in the samples used for exome sequencing along with 3 additional controls and 1 additional case from the family. Primers surrounding the identified variants were designed using Primer3. PCR was carried out under standard conditions. Direct sequencing of the PCR product was performed on an ABI3130XL sequencer (Applied Biosystems, Foster City, CA).

2.5. APOE genotyping

APOE genotyping was performed in all family members by the method of Crook et al (Crook et al., 1994).

2.6. Clinically characterized and neuropathologically verified subjects

Our U.S. series was obtained from 21 National Alzheimer's Coordinating Center (NACC) brain banks and from the Miami Brain Bank, as previously described (Corneveaux et al., 2010; Myers et al., 2007; Webster et al., 2009). Additional cohorts from the United Kingdom and Europe were obtained in the same manner as the original U.S. series. Our criteria for inclusion were as follows: self-defined ethnicity of European descent (in an attempt to control for the known allele frequency differences between ethnic groups); neuropathologically confirmed AD or no neuropathology present; and age of death greater than 65 years. Neuropathological diagnosis was defined by board-certified neuropathologists according to the standard NACC protocols (Beekly et al., 2004). Samples derived from subjects with a clinical history of stroke, cerebrovascular disease, Lewy bodies, or comorbidity with any other known neurological disease were excluded. AD or control neuropathology was confirmed by plaque and tangle assessment with 45% of the entire series undergoing Braak staging (Braak and Braak, 1995). Samples were de-identified before receipt, and the study met human studies institutional review board (IRB) and HIPPA regulations. This work is declared not human-subjects research and is IRB exempt under regulation 45 CFR 46. (See the Acknowledgements section for a list of individual sites that contributed samples to this effort.)

2.7. Genome-wide SNP genotyping

Genomic DNA samples were analyzed on the Genome-Wide Human SNP 6.0 Array (Affymetrix, Inc. Santa Clara, CA) according

to the manufacturer's protocols (Affymetrix Genome-Wide Human SNP Nsp/Sty 6.0 User Guide;Rev. 1 2007) and as described previously (Corneveaux et al., 2010).

2.8. SNP imputation

Genotypes were imputed using MACH v.1.0.16 (Y. Li et al., 2009) as described previously (Corneveaux et al., 2010).

2.9. Gene expression profiling analysis of donor brain tissue

Total RNA was isolated from the frontal or temporal region of the brain from clinically characterized and neuropathologically confirmed Alzheimer's disease case (n = 185) and control (n = 183) donors using the RNeasy Lipid Tissue Kit (Qiagen, Valencia CA). The gene expression profiles were generated on a HumanHT-12 Expression BeadChip (Illumina, San Diego, CA) according to the manufacturer's instructions. A modified surrogate variable analysis procedure was used with the goal of retaining biological variability while removing as many latent variables due to systematic measurement errors. First, we regressed out all the biological and known technical variables of interest from the observed gene expression that was previously quantile-normalized with the lumi package (Du et al., 2008). These biological variables included disease status, Braak and CERAD scores, and APOE status, whereas the technical/batch variables include hybridization date, chip lot, and site. Then, using the residual matrix produced by this process, we record the percent variance accounted for by all principal components of this matrix. Typically the most significant principal components would be considered to be latent variables and would systematically be removed. However, it is possible that some of these principal components represent true biological sources of variability, such as the co-expression of various gene sets. Therefore, we test for biological enrichment of genes that are highly correlated with each principal component of the residual matrix. If the principal component–correlated genes are not biologically enriched for certain functions, then we remove the corresponding components. Only the first principal component did not have strong biological enrichment associated with it. To create the final expression matrix, we regressed out both known technical variables as well as this first principal component. The remaining matrix contains normalized expression measurements that are predicted to be relatively free of sources of known or suspected technical variation. The expression measurements for the *TREM2* gene within this matrix were used to compare AD cases versus controls using a Welch 2-sample t-test.

3. Results

3.1. Clinical syndrome

Initial symptoms began between ages 45 and 50 involving altered social behavior in all 3 individuals, as well as an oropharyngeal tic in 1 that subsequently developed in the other 2 as well. Two of the 3 developed the new onset of substance use including alcohol and tobacco as well as complex partial seizures characterized by versive head and eye turning and speech arrest. Eventually, all 3 developed a severe pan-frontal syndrome with apathy, disinhibition, and impulsivity, obsessive and perseverative behavior, impaired social behavior, and cognitive decline that included psychomotor slowing and impaired problem solving with increased perseverative errors, as well as constructional apraxia, and memory loss (Table 1). Physical examination revealed frontal release signs but no evidence of motor neuron disease. Magnetic resonance imaging (index patient) showed asymmetric bifrontal atrophy (Fig. 3).

Table 1
Demographic characteristics and neuropsychological test scores in 2 *TREM2* carrier members of the Colombian kindred

Characteristic	Patient 1	Patient 2
Age (y)	48	55
Gender	Female	Male
Education (y)	10	14
Handedness	Right	Right
Occupation	Homemaker	Unemployed
Mini-Mental Status Exam	24/30	23/30
Trail Making Test–A (s)	99	154
Trail Making Test–B (s)	278	Na
WAIS-R* Digit Symbol (raw total)	23	11
10-Word list		
3 Learning trials	2—3—3	2—3—3
Spontaneous recall	1	0
True positive recognition	7	1
True negative recognition	9	10
Complex Figure Test —Copy	18.5	16.5
Recall (%)	5 (27%)	0 (0%)
Animal fluency (1 min)	8	3
Wisconsin Cart Sorting Test		
Categories	1	0
Perseverative responses (%)	28 (58.3%)	47 (97.9%)
FAS letter fluency	15	2
Frontal Behavioral Inventory	34/72	54/72

Key: WAIS-R, Wechsler Adult Intelligence Scale–Revised.

Patient III:16 (Index patient) began to express noticeable behavioral and personality changes at age 47 years, starting with sexual and social disinhibition, mood changes, and neglect of personal hygiene. In addition, her abstract reasoning, decision making, planning, and judgment decreased severely. Her brother

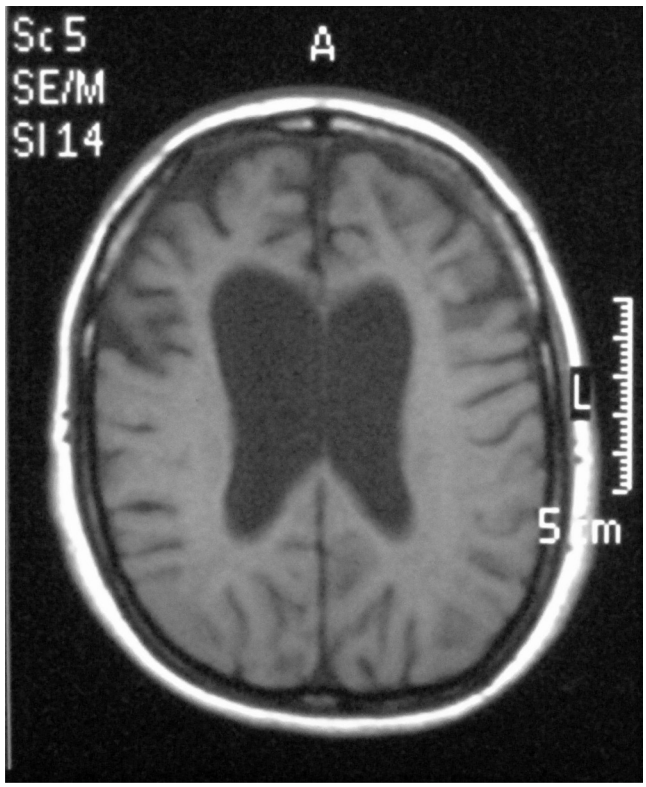

Fig. 3. Magnetic resonance image of the index case patient demonstrating the frontal lobe atrophy.

(patient III:10), presented with behavioral changes at the age of 50. He became apathetic and showed progressive memory loss and obsessive-compulsive behaviors. Later, he suffered from insomnia and presented motor and phonetic tics, and seizures characterized by versive head movement, gaze deviation, and speech arrest. The older sister (patient III:14), started showing personality changes, disinhibition, and progressive memory loss at the age of 45. She emits guttural speech sounds and presents with seizures similar to those of her brother, characterized by a versive head, eye motions, and speech arrest. In all 3 patients, functionality has been reduced to only basic self-caring activities.

3.2. Identification of a nonsense mutation in TREM2

Two patients (III:10 and III:14) and 2 controls (III:11 and III:12) from the Colombian family were sequenced using the Illumina 62Mb Truseq Exome Enrichment Kit. Variants identified by next generation sequencing were filtered by dbSNP135, the 1000 genomes project and an in-house list of exomes. Only variants homozygous in the 2 patients were further prioritized. This led to the identification of a nonsense mutation in exon 4 of the gene *TREM2*, which leads to premature truncation of the protein (c.594G>A;p.Trp198X). We confirmed the presence of the mutation in the patients by Sanger sequencing, and subsequently checked the inheritance of the mutation in the family (Fig. 2).

No possible disease-causing variants were detected in the known FTLD genes (*GRN*, *MAPT*, *VCP, CHMP2B, TARDP* or *C9ORF72* and *TMEM106B*). In addition, all family members were APOE E3/E3 homozygotes.

3.3. TREM2 as a risk factor for Alzheimer's disease

Recent studies show that the p.Arg47His variant (rs75932628) is associated with a significantly increased risk for Alzheimer's disease (Jonsson et al., 2012; Pottier et al., 2013; R. Guerreiro et al., 2012). We saw an enrichment of this variant by a factor of 2.8 in our collection of clinically characterized and neuropathologically confirmed AD cases, which was significant when combined with the data of Guerreiro et al, 2012 (R. Guerreiro et al., 2012) (Table 2). Finally, we examined the expression level of the TREM2 transcript in post mortem tissue from clinically characterized and neuropathologically confired AD cases (n = 185) and controls (n = 183) and observed a significant increase in expression in the AD cases (mean normalized expression level of 7.385 versus 7.337 in cases and controls, respectively, Fig. 4). This difference was significant ($p = 1.29 \times 10^{-9}$) when examined using a Welch 2-sample t test (t = 6.2331, df = 357.19).

4. Discussion

TREM2 is a membrane protein that forms a receptor-signaling complex with TYROBP that triggers activation of the immune response, differentiation of dendritic cells and osteoclasts and phagocytosis in microglia. We identified a mutation in exon 4 of the *TREM2* gene (p.Trp198X) in a consanguineous Colombian family segregating autosomal recessive FTLD (Fig. 2). The clinical phenotype of our family seems very similar to PLOSL, except for the complete absence of a bone phenotype in our family. Chouery et al also reported a mutation in *TREM2* (c.40+3delAGG) in a Lebanese family segregating pure early-onset dementia without bone cysts (Fig. 1) (Chouery et al., 2008). The affected individuals presented with personality and behavioral changes at the age of 30 to 35 years, culminating in severe dementia. Brain MRI showed either a diffuse brain atrophy or cortical atrophy in the temporal lobes (Chouery et al., 2008). Similar to our patients, a subsequent report in Turkish patients (R.J. Guerreiro et al., 2012), also described a frontotemporal dementia (FTD)–like syndrome without bone cysts. Neither prior report described the tics that we observed in our patients, but 2 of the 3 Turkish patients described had generalized seizures.

Also, recently, a rare missense mutation in *TREM2* (p.Arg47His; rs75932628), was found to significantly increase the risk of late-onset Alzheimer's disease (Jonsson et al., 2012; R. Guerreiro et al., 2012) and early-onset Alzheimer's disease (Pottier et al., 2013). The mutation may lead to a decreased affinity of *TREM2* for its natural ligand or affect its signaling. Although this variant is less frequent than APOE E4, it confers risk for Alzheimer's disease with an effect similar to that of APOE E4 (Jonsson et al., 2012). The clinical phenotype in all TREM2-associated dementia cases reported to date have striking panfrontal syndromes quite distinct from the typical AD phenotype. How different genetic variants result in topographically altered patterns of pathology is not yet known, but it has been previously shown that presenilin 1 mutations, unlike sporadic AD or APOE e4 carrier cases, are associated with early striatal deposition of amyloid (Klunk et al., 2007).

We saw an enrichment of this variant in *TREM2* (p.Arg47His) in our cohort of clinically characterized and neuropathologically verified Alzheimer's disease cases and control (Table 2) (Corneveaux et al., 2010), which is in line with the data of Guerreiro et al. (R. Guerreiro et al., 2012). Because *TREM2* has been shown to be involved in PLOSL, FTD-like disease, Alzheimer's disease and now also FTLD, we hypothesize that *TREM2* might be a risk factor for for this *TREM2* variant to better understand its role in the pathophysiology of neurodegeneration.

It is also important to note that the rarity of the p.Arg47His variant results in most carriers existing in the heterozygous state in the general population. This is important, as they likely express a wild-type version of TREM2 in addition to the mutant version. Under the assumption that the TREM2 mutant does not function as a dominant negative molecule, this may represent a therapeutic avenue for treatment or prevention of the neurodegenerative disease in the p.Arg47His heterozygotes. Chemical or biological agonists of TREM2 could be explored for use in these individuals.

Additional evidence that reflects the potential importance of TREM2 antagonism in the context of AD is found in the gene expression results illustrated in Fig. 4. Our transcriptional findings support the immunohistochemistry work of R. Guerreiro et al. (Guerreiro et al., 2012) whereby they demonstrated an increased expression of the TREM2 protein in the transgenic mouse model of AD, and we extend that observation further into well-characterized human donor tissue. This more general link between increased expression of TREM2 in AD warrants further investigation, as our human brain samples are largely derived from donors who have lived with AD for many years; therefore, any potential cause-and-effect relationship of TREM2 to AD is difficult to fully differentiate.

Table 2
Association of p.Arg47His in a cohort of clinically characterized and neuropathologically verified Alzheimer's disease cases and controls ("TGenII")

Group	MAF case	MAF control	Allele case	Allele control	Enrichment	*p* Value	OR (95% CI)
TGen II AD	0.0025	0.0009	5 | 1990	1 | 1158	2.8	0.4242	2.9 (0.3–137.7)
AD meta-analysis	0.0088	0.0027	27 | 3081	6 | 2263	3.3	0.0044	3.3 (1.3–9.8)

Key: AD Meta-Analysis, combination of TGenII Cohort results and Guerreiro et al., 2012; CI, confidence interval; OR, odds ratio; MAF, minor allele frequency.

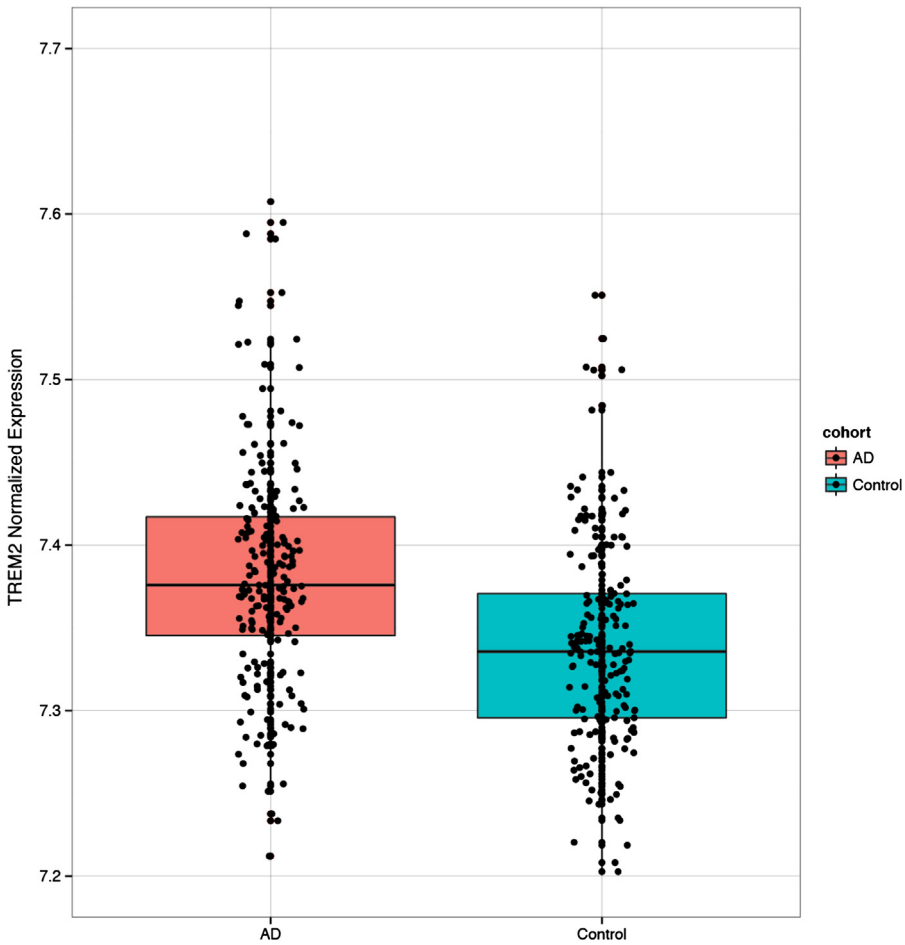

Fig. 4. *TREM2* gene expression is increased in the AD brain. *TREM2* expression was measured in post mortem tissue from clinically characterized and neuropathologically confirmed AD case (n = 185) and control (n = 183) donors. The differential expression of *TREM2* was significant between the groups (Welch 2-sample t-test, $p = 1.29 \times 10^{-9}$).

Mutations in *TREM2* leading to PLOSL are mainly loss of function mutations caused by premature truncation of the protein, lacking the complete transmembrane and cytoplasmic domains (Fig. 1) (Klunemann et al., 2005). Although the effect of some of the non-synonymous mutations might be unclear, the p.Lys186Asn mutation changes the positively charged lysine in the transmembrane part of the protein to an asparagine, which disrupts the association with and expression of *TYROBP,* also resulting in a loss of function (Bouchon et al., 2000; Klunemann et al., 2005; Paloneva et al., 2002). The c.40+3delAGG mutation, which leads to pure early-onset dementia without bone cysts, weakens the splice site at the 5′donor site of intron 1. Quantitative reverse transcription–PCR showed a more than 2-fold down-regulation of wild-type *TREM2* transcripts because of this mutation (Chouery et al., 2008). The presence of functional wild-type protein in these patients, although reduced, might explain why these patients present only with a neurodegenerative phenotype and lack a bone phenotype.

A genotype–phenotype correlation is much less clear in our family. The p.Trp198X mutation truncates only the last 33 AA of the protein (Fig. 1), leaving the extracellular and transmembrane part of the protein almost intact, but missing the short cytoplasmic domain (Bouchon et al., 2000). Because the transmembrane region mediates the formation of a complex with TYROBP, the protein might therefore still be expressed and be able to form a partly functional complex with TYROBP on the cell surface, leading to a less severe phenotype in our family. However a genotype–phenotype correlation is less clear for the p.Gln33X mutation, which has been described to cause both FTD-like syndrome and PLOSL. This suggests that environmental factors of modifier genes also influence the phenotype associated with *TREM2* mutations. In addition, heterozygote carriers of p.Gln33X were reported to show memory deficits and might have a higher risk for developing late-onset Alzheimer disease (R. Guerreiro et al., 2012).

The Colombian family in this study originates from Antioquia, which is a young admixture that was founded in the 16th to 17th century by only a few hundred American natives and immigrants mainly from Spain (Carvajal-Carmona et al., 2003). The people in the region have remained relatively isolated since its origin (Carvajal-Carmona et al., 2003). Young genetic isolates confer an advantage to gene mapping, and are usually enriched for specific Mendelian traits that often occur in the population because of a founder effect (Sheffield et al., 1998). In addition to the founder effect, small effective population size and bottlenecks increase consanguinity, and therefore increase the opportunity to map recessive diseases. Rare Mendelian disease in isolated populations is almost always attributable to a single mutation that is shared identically by descent among affected individuals in the population. In the Antioquia population, founder mutations have been identified previously, for example, the c.G736A mutation in the *PARK2* gene that causes early-onset Parkinson's disease (Pineda-Trujillo et al., 2006). It is unclear, however, when the p.Trp198X *TREM2* mutation arose in Antioquia. If the mutation originated before or close to the founding of the population, the carrier frequency could be very high in Antioquia. However, an analysis of the 1,000

Genomes Project dataset revealed no carriers of this variant in 60 individuals from Medellin, Colombia (referred to as "CLM"), suggesting a frequency of less than 1 in 120 chromosomes.

In conclusion, we identified a mutation in *TREM2* that leads to FTLD in a consanguineous family from Colombia. The mechanisms of *TREM2* mutations leading to FTLD and neurodegeneration in PLOSL and are unknown, but we can hypothesize that lack of *TREM2* impairs the clearance of apoptotic neurons in microglia, leading to the accumulation of necrotic debris. We also replicate the association of the *TREM2* p.Arg47His variant and Alzheimer's disease risk. The involvement of *TREM2* genetic variants in PLOSL, FTD-like syndrome, Alzheimer's disease, and now also FTLD suggests that the *TREM2* locus may be associated with neurodegenerative disease in general, and raises the possibility that this variant in the context of other genetic variants or environmental factors are the determinants of the form of neurodegenerative disease with which a carrier patient presents.

Disclosure statement

The authors declare no actual or potential conflicts of interest.

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