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Original research

Frontotemporal dementia presentation in patients with heterozygous p.H157Y variant of *TREM2*

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ABSTRACT

Background The triggering receptor expressed on myeloid cell 2 (*TREM2*) is a major regulator of neuroinflammatory processes in neurodegeneration. To date, the p.H157Y variant of *TREM2* has been reported only in patients with Alzheimer's disease. Here, we report three patients with frontotemporal dementia (FTD) from three unrelated families with heterozygous p.H157Y variant of *TREM2*: two patients from Colombian families (study 1) and a third Mexican origin case from the USA (study 2).

Methods To determine if the p.H157Y variant might be associated with a specific FTD presentation, we compared in each study the cases with age-matched, sex-matched and education-matched groups—a healthy control group (HC) and a group with FTD with neither *TREM2* mutations nor family antecedents (Ng-FTD and Ng-FTD-MND).

Results The two Colombian cases presented with early behavioural changes, greater impairments in general cognition and executive function compared with both HC and Ng-FTD groups. These patients also exhibited brain atrophy in areas characteristic of FTD. Furthermore, *TREM2* cases showed increased atrophy compared with Ng-FTD in frontal, temporal, parietal, precuneus, basal ganglia, parahippocampal/hippocampal and cerebellar regions. The Mexican case presented with FTD and motor neuron disease (MND), showing grey matter reduction in basal ganglia and thalamus, and extensive TDP-43 type B pathology.

Conclusion In all *TREM2* cases, multiple atrophy peaks overlapped with the maximum peaks of *TREM2* gene expression in crucial brain regions including frontal, temporal, thalamic and basal ganglia areas. These results provide the first report of an FTD presentation potentially associated with the p.H157Y variant with exacerbated neurocognitive impairments.

INTRODUCTION

Emergent research points to the importance of the innate immune system and microglia in the pathogenesis of neurodegenerative diseases.^{1–3} The *TREM2* gene (triggering receptor expressed on myeloid cells 2) encodes a transmembrane glycoprotein mainly expressed in cells of myeloid lineage.^{4–6} This receptor consists of an extracellular IgV domain, stalk domain, transmembrane domain

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Genetic variants in *TREM2* (triggering receptor expressed on myeloid cell 2) have been reported as risk factors for different neurodegenerative diseases, including Alzheimer's disease and frontotemporal dementia.

WHAT THIS STUDY ADDS

⇒ We described for the first time new associations between the heterozygous p.H157Y variant in *TREM2* with clinical presentations of the behavioural variant of frontotemporal dementia (bvFTD) and motor neuron disease—frontotemporal dementia (FTD-MND).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings invite new research to further understand genetic-phenotype variability within subjects carrying new *TREM2* variants and its impact on neurodegeneration.

and a short cytoplasmic tail.⁷ Recent studies have identified variants in *TREM2* that are risk factors not only for Alzheimer's disease (AD)^{8–9} but also for other neurodegenerative diseases such as frontotemporal dementia (FTD),¹⁰ Parkinson's disease (PD)^{3–11} and amyotrophic lateral sclerosis (ALS).⁴ However, a complete understanding of the influence of these variants on clinical presentation, including the symptom profile, cognitive correlates and neuropathology, has not yet been established.

With the progress of genetic research in FTD, several *TREM2* variants are associated with familial and sporadic FTD.^{7–10–12–13} The effect of these *TREM2* variants in the central nervous system remains unknown, but most are located in exon 2, which encodes the IgV domain, a highly conserved region of the protein.¹⁴ Homozygous loss-of-function mutations in *TREM2*, such as p.Q33X, p.Y38C and p.T66M, are associated with either Nasu-Hakola disease with bone involvement^{15–17} or an early-onset behavioural variant frontotemporal dementia (bvFTD)-like phenotype lacking bone involvement.¹⁶ Interestingly, Guerreiro *et al* reported the first *TREM2* compound heterozygous



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mutation (p.[(Y38C)]; [(D86V)]) in a Turkish family affected by FTD-like dementia.¹⁶ Most carriers of homozygous *TREM2* variants in the IgV domain exhibit behavioural changes, frontal cognitive deterioration, seizures, akinetic-rigid syndrome and frontotemporal lobar atrophy without clinical or radiological evidence of bone involvement.^{16,18} Functional studies show that mutations such as p.Y38C and p.T66M strongly affect the uptake of certain apolipoproteins and lipoproteins.¹⁹ Apart from the literature identifying rare homozygous (and compound heterozygous) *TREM2* variants in FTD-like syndromes, the heterozygous p.R47H variant of *TREM2* has now been well established to increase the risk for late-onset Alzheimer's disease (LOAD).^{8,9}

New evidence suggests that the p.H157Y variant located in the stalk domain of *TREM2* is involved in neurodegenerative pathogenesis.^{14,20,21} Jiang *et al* found that a heterozygous p.H157Y variant was strongly associated with LOAD risk in Han Chinese populations.^{5,22} Although potential mechanisms remain unclear, they might involve increased shedding and thus reduced cell surface levels of *TREM2*. To the best of our knowledge, no studies have reported associations between the heterozygous p.H157Y variant with clinical presentations related to bvFTD and motor neuron disease-frontotemporal dementia (FTD-MND).

Here, we report two patients from unrelated Colombian families and the third case from the USA of Mexican origin with a heterozygous *TREM2* exon 3 variant (c.469C>T, p.H157Y, rs2234255). The two Colombian cases exhibited a bvFTD clinical profile and the third case presented with a motor neuron disease (MND). We performed exhaustive clinical, neuropsychological, neuroimaging and genetic assessments, including individualised gene atrophy mapping of these patients.

MATERIALS AND METHODS

All patients underwent clinical assessment by a multidisciplinary team composed of neurologists, psychiatrists, neuropsychologists, geneticists and geriatricians from the Memory Clinic at the Center for Memory and Cognition at Hospital San Ignacio in Bogotá, and the University of California, San Francisco Memory and Aging Center (UCSF MAC). Both clinical teams followed the Rascovsky criteria²² to diagnose bvFTD cases, Gorno-Tempini *et al* criteria²³ to diagnose linguistic variants of FTD, and the Strong criteria to diagnose FTD-MND cases.²⁴ After clinical assessment, blood samples were extracted to assess genetic characterisation of *TREM2*, Ng-FTD, Ng-FTD-MND, HC subjects. Finally, participants of all groups were scanned using structural MRI. All participants provided written informed consent in agreement with the Declaration of Helsinki.

Clinical and neuropsychological assessment

Our protocol included different instruments to evaluate the overall cognitive status (Montreal Cognitive Assessment (MoCA)²⁵), executive function (Hayling B test,²⁶ Ineco Frontal Screening battery²⁷), behavioural symptoms (Frontal System Behavioural scale (FrSBe)²⁸ and social cognition (Reading Mind in the Eyes test²⁹; online supplemental information S1-S3). After clinical assessment, blood samples were extracted to assess genetic characterisation of *TREM2*, Ng-FTD, Ng-FTD-MND and HC participants (online supplemental information S1-S2).

Behavioural single-case analysis: Crawford method

This method allows for the comparison of single cases against a control sample score with different sizes. This method treats the control sample as statistics rather than parameters and is robust for non-normal distributions and small control samples (ie,

$n=5$). Additionally, it presents low rates of type I error and has proven useful for single-case studies³⁰⁻³⁴ (online supplemental information S3).

Genetic analysis: study 1

Genomic DNA was extracted from blood samples of the bvFTD participants by the salting-out method.³⁵ Targeted sequencing was done at the Center for Neurodegenerative Disease Research (CNDP) at the University of Pennsylvania using a custom targeted multineurodegenerative disease sequencing panel (MiND-Seq), which covered the coding regions of 45 genes recognised as causative of AD, PD, FTL and ALS, as well as several other genes identified as risk factors for other neurodegenerative diseases; risk factor genes include *MAPT*, *GRN*, *VCP*, *TARDBP*, *CHMP2B*, *CSF1R*, *PSEN1* and *TREM2*.³⁶ This panel employs next-generation sequencing technology using Haloplex Enrichment Custom Kit (Agilent) according to the manufacturer's protocol; sequencing was conducted on Illumina Mi-Seq. All cases were tested for a C9orf72 hexanucleotide repeat expansion as previously described³⁷ (online supplemental information S4).

Genetic analysis: study 2

The genomic DNA of patient with FTL underwrote Whole-genome sequencing (WGS) at the New York Genome Center (New York City, New York, USA) or HudsonAlpha Institute for Biotechnology (Huntsville, Alabama, USA) on an Illumina HiSeq-X, with 150 bp paired-end reads to obtain 30X sequencing coverage. Candidate variants were validated by Sanger sequencing at the UCLA Neuroscience Genomics Core (Los Angeles, California). The case was also tested for C9orf72³⁷ (online supplemental information S4).

Structural brain imaging

All participants were scanned using structural MRI parameters with settings harmonised at post-recording (online supplemental information S7-S9). We analysed the grey matter (GM) volume of all participants and compared the atrophy pattern across groups (online supplemental information S7-S9).

Gene atrophy overlap

The overlap between atrophy and the *TREM2* gene expression was implemented following previous procedures using the Allen Human Brain database³⁸ (online supplemental information S8, online supplemental tables 4 and 5).

RESULTS

Study 1: case 1

A male patient around 50s from Colombia with 9 years of formal education. He has exhibited behavioural symptoms, including apathy-related disinhibition, irritability, planning problems and violation of social norms, impacting his work and domestic spheres. Further, he presented episodes of affective exaltation, including sleep disturbances, increased loquacity and mistrust of caregivers with durations of up to 4 days. The motor assessment revealed unilateral myoclonus in upper limbs and trunks, echopraxia and marked apraxia of gait. Moreover, the patient exhibited neurological dysphagia (fluids and solids) and orolingual automatism without dysphonia. Family history showed that his grandmother developed dementia at the age of 70s (I:1). His mother started exhibiting behavioural changes related to 'hiding things' at the age of 60s (II:2). One brother (III:11) died at the age of 70s due to neurodegenerative disease. In contrast, 3 siblings out of 10 (III:3, III:5, III:10) exhibited cognitive

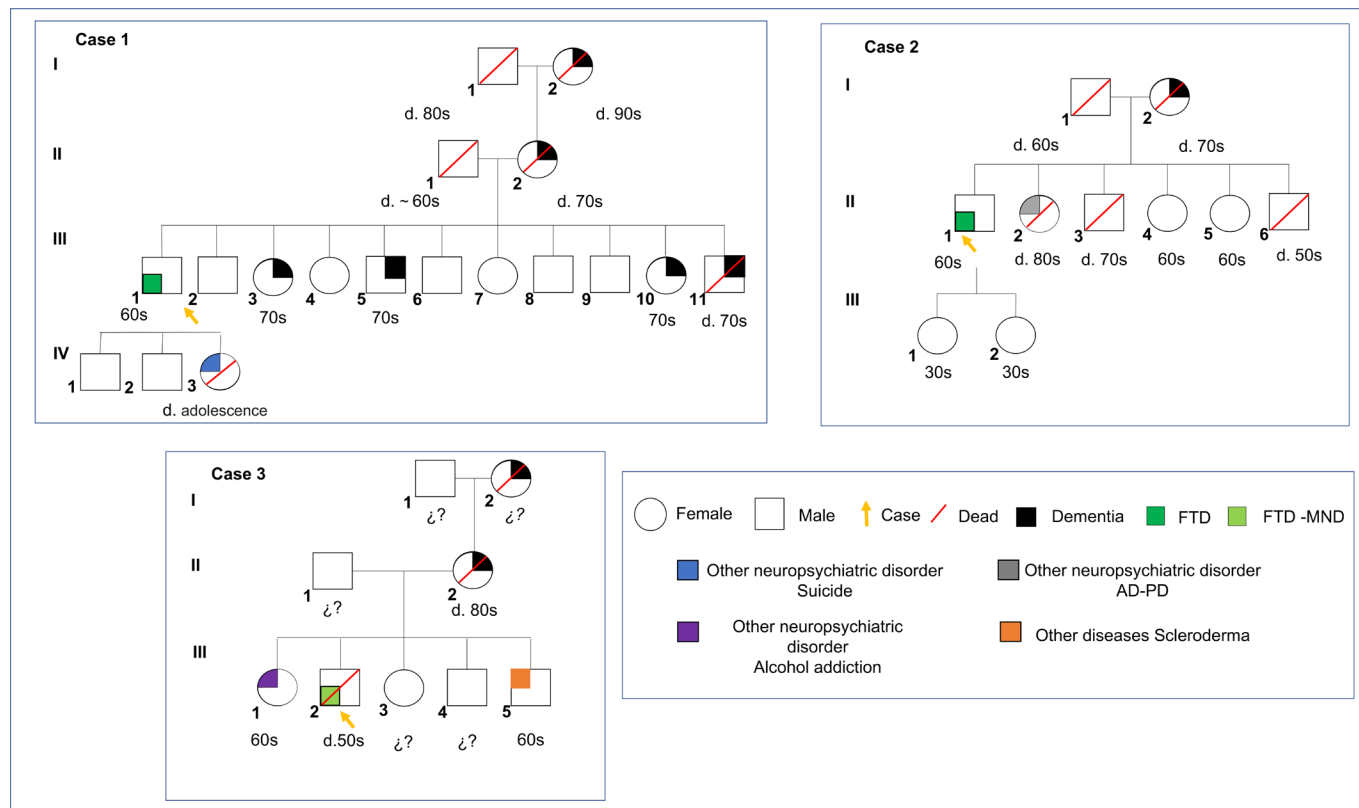


Figure 1 Pedigree of the two unrelated Colombian families (A, B) and one Mexican case in which the heterozygous mutation p.H157Y in TREM2 was found. Numbers following the letter 'd' represent the death age of the subject. The arrowhead indicates the proband with heterozygous p.H157Y variant. Black painting symbols represent affected subjects with dementia. White symbols represent unaffected family members. Green labels represent cases reported in study 1 (case 1 and case 2: FTD) and study 2 (case 3: FTD-MND). The red slash symbol was used to identify dead individuals. Blue, purple and grey colours indicate individual cases with neuropsychiatric disorders, including suicide, alcohol addiction and Parkinson's disease (PD), respectively. Orange colour depicts a case with a somatic disease (scleroderma). FTD, frontotemporal dementia; FTD-MND, motor neuron disease-frontotemporal dementia.

symptoms and behavioural disorders consisting of apathy and mutism. His daughter committed suicide at adolescence (IV:3) (figure 1).

Study 1: case 2

A male patient around 50s from Colombia with 8 years of formal education. He exhibited behavioural and affective symptoms. He showed disinhibition-behavioural symptoms, affective exaltation, impulsivity, risky financial behaviour, sexual disinhibition, logorrhoia, sleep disturbances and difficulties following social norms. He also exhibited executive dysfunction and an inability to perform self-care activities. The motor assessment presented frequent motor automatisms, neutral right flexor plantar response, left extensor and bilateral palmomental responses as positive neurological signs. His mother died at the age of 70s with behavioural and cognitive changes associated with dementia (I:2). Also, a sister was diagnosed with both PD and AD (II:2) (figure 1).

Study 2: case 3

A male around 50s with 14 years of education was diagnosed with bvFTD and MND after a clinical consensus review. He has exhibited inappropriate behaviours, disinhibition, irritability and impaired ability to follow social norms. Moreover, he developed verbal stereotypes, including expressions such as 'yep', 'right', 'you got it' and 'that's right'. MRI revealed essentially symmetric, moderate frontotemporal atrophy, as well as extensive, confluent bilateral white matter hyperintensities in the

frontal regions, extending posteriorly and several frontal subcortical cysts. Autopsy revealed FTLD, TDP-43 inclusions type B, MND and other markers (see results in figure 2). His mother had an adult-onset behavioural syndrome and died of dementia around 80s (II:2). He had two brothers and two sisters in their early 60s. His oldest brother was diagnosed with an autoimmune disease (scleroderma) (III:5) around 60s. His younger sister had alcohol addiction (III:1) around 60s. The maternal grandmother died late of dementia (I:2). A cousin on the maternal side developed dementia in his 60s (figure 1).

Neuropsychological assessment

Study 1

General cognitive state

In the MoCA, case 1 and case 2 exhibited significantly lower scores than both HCs (case 1 $t=-5.903$, $p=0.0003$, $zcc=-6.26$; case 2 $t=-2.983$, $p=0.042$, $zcc=-4.12$) and the Ng-FTD group ($t=-3.32$, $p=0.001$, $zcc=-4.41$). Additionally, Ng-FTD presented significantly lower scores than HC in MoCA scores ($t=-4.572$, $p=0.001$, $zcc=-4.84$) (table 1).

Executive functions

Both TREM2 cases showed lower scores on total IFS (Ineco Frontal Screening) than HC (case 1 $t=-8.16$, $p=0.0009$, $zcc=-5.12$; case 2 $t=-6.24$, $p=0.0001$, $zcc=-5.75$) and Ng-FTD group (case 1 $t=-3.86$, $p=0.009$, $zcc=-3.11$; case 2 $t=-2.45$, $p<0.05$, $zcc=-2.92$). In addition, TREM2 cases

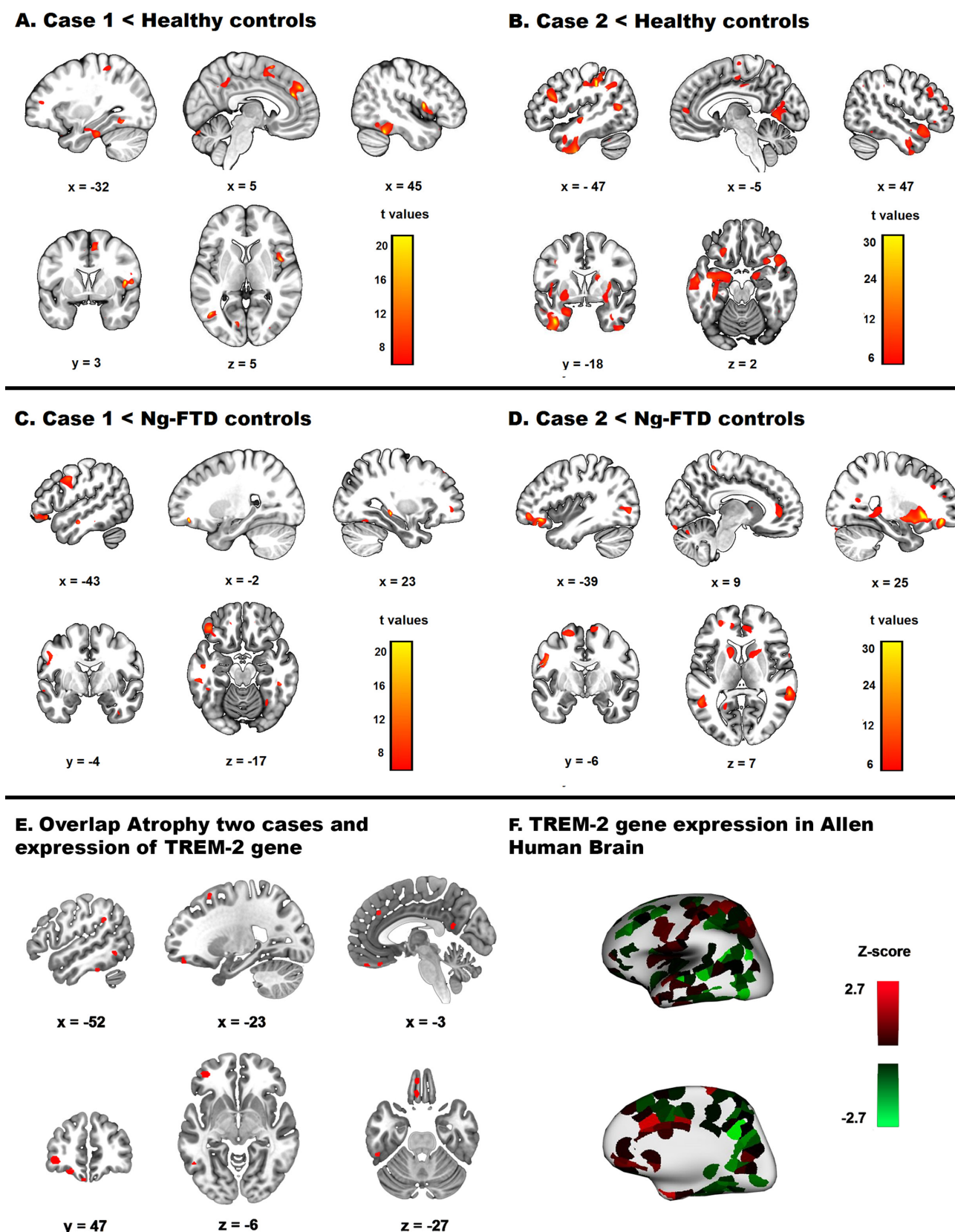


Figure 2 Neuropathological findings in the Mexican case. (A) TDP-43 mislocalisation is seen in neurons from the upper cortical layers of the middle frontal gyrus. Pathological TDP-43 is seen either as granular diffuse cytoplasmic inclusions in neurons not displaying the normal nuclear TDP-43 staining or as skein-like cytoplasmic inclusions. (B) Granular diffuse pathological cytoplasmic TDP-43 immunoreactivity in the lower motor neurons of the cervical cord. (C) Abundant perivascular neuronal and glial tau cytoplasmic aggregate in the cerebral cortex, the pathognomonic lesion of chronic traumatic encephalopathy. (D) Abundant argyrophilic thorny astrocytes in clusters (ATAC) at the juxtacortical white matter of the subgenual cingulate gyrus. FTD, frontotemporal dementia; TREM2, triggering receptor expressed on myeloid cell 2.

Table 1 Demographic and neuropsychological data comparison between TREM2 cases, Ng-FTD controls and HC

	TREM2	TREM2	TREM2	Ng-FTD	HC	Ng-FTD-MND
	Case 1	Case 2	Case 3	Controls (n=5)	(n=5)	Controls (n=11)
Demographic data						
Age (years), SD	63	61	56	62.8, SD (6.1)	61.3, SD (3.9)	61.16, SD (11.6)
Education (years), SD	9	8	14	10.6, SD (3.7)	11.3, SD (2.9)	15.5, SD (2.0)
Neuropsychological data						
General cognitive assessment						
MoCA	12	9	20	15.9, SD (1.9)	26.5, SD(2.1)	21.5, SD(12.5)
Executive function						
Total IFS score	9	5		16.3, SD (2.6)	22.1, SD (1.9)	22.1, SD (1.9)
Hayling test	16	18		23.5, SD (9.6)	10.6, SD (2.6)	10.6, SD (2.6)
Stroop test			55			38.7, SD (34.9)
Social cognition						
RMET	8	6		13.3, SD (2.1)	14.3, SD (1.1)	14.3, SD (1.1)
Social changes in NPI			5			2.7, SD (3.7)
Behavioural changes						
FrSBe Total	134	188		115, SD (33.5)	9.5, SD (1.1)	9.5, SD (1.1)
FrSBe Apathy	22	18		38.5, SD (10.8)	3.1, SD (.6)	3.1, SD (.6)
FrSBe Disinhibition	55	58		28.6, SD (11.7)	3.1, SD (.6)	3.1, SD (.6)
FrSBe Executive functions	49	77		47.6, SD(12.4)	3.3, SD(.4)	3.3, SD(.4)
NPI Total scores			73			21.9, SD (21.7)

Data shown as mean with SD reported.

FrSBe, Frontal Systems Behavioural Scale; HC, healthy control; IFS, Ineco Frontal Screening; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; RMET, Reading Mind in the Eyes Test.

exhibited lower Hayling scores than HC (case 1 $t = -2.65$; $p < 0.05$, $zcc = -4.11$; case 2 $t = -2.89$; $p < 0.05$, $zcc = -4.22$, [table 1](#)).

Behavioural changes

TREM2 cases showed significantly higher scores in total FrSBe (Frontal Systems Behavioural Scale) than HC (case 1 $t = 48.78$, $p = 0.00009$, $zcc = 6.34$; case 2 $t = 53.18$, $p = 0.00009$, $zcc = -7.46$). Case 2 exhibited lower total FrSBe scores than Ng-FTD group ($t = 2.29$, $p < 0.05$, $zcc = 2.11$). Individualised analyses on each FrSBe subfactor revealed higher scores for TREM2 cases compared with HC ([table 1](#)).

Social cognition

Both TREM2 cases attained significantly lower scores for social cognition (RMET) compared with HC (case 1 $t = -2.78$, $p < 0.05$, $zcc = -3.34$; case 2 $t = -3.18$, $p < 0.05$, $zcc = -4.13$). Complementary results are provided in online supplemental information S9 and [table 1](#).

Study 2

General cognitive state

In the MoCA, no differences when compared with Ng-FTD-MND nor with the Ng-FTD group were observed (online supplemental information S9 and [table 1](#)).

Executive functions

Case 3 showed lower scores on the total of correct trials in Stroop task compared with Ng-FTD-MND cases (case 3 $t = 3.99$, $p < 0.05$, $zcc = -4.11$, [table 1](#)).

Behavioural changes

Case 3 showed significantly higher scores on the total scores of the NPI than Ng-FTD-MND cases (case 3 $t = 3.83$, $p < 0.05$, $zcc = -3.71$). The patient exhibited worst scores of agitation, apathy, disinhibition, motor problems, sleep disturbances and eating habits ([table 1](#)).

Social changes

Case 3 showed significantly higher scores on the items tracking social norms (NPI disinhibition score) than Ng-FTD-MND cases (case 3 $t = 3.07$, $p < 0.05$, $zcc = -3.22$) ([table 1](#)). Complementary results are provided in online supplemental information S9 and [table 1](#).

Genetic findings

The most plausible candidate to explain the phenotype exhibited by the three cases was a heterozygous missense in exon 3 of the *TREM2* gene (p.H157Y). Targeted sequencing confirmed this variant in the three cases. Diverse prediction programmes were used as a filter to predict how the amino acid exchange found would affect protein function, considering the physical properties of amino acids, sequence homology, domain involvement and allelic frequency. From the analysis of these predictors, Polyphen and Proven scores indicated a potentially deleterious effect of the p.H157Y variant. The conservation score calculated was 3.6–4.7. Other variants were found among these cases. Patient 1 (III:9), another non-synonymous missense variant in *TREM2* (p.R62H), was identified. It was not possible to differentiate between the possibilities of co-inheritance or compound heterozygosity of these variants based on the available data. Patient 2 (II:1), two additional gene variants were found: (1)

Table 2 The rates are the percentage of mutation carriers in the Colombian and global population, using the 1000 Genomes Project

Cases	Gene	Position at cDNA	Protein change	rs	Variant type	GMAF	Colombian rate
Case 1	<i>TREM2</i>	c.469C>T	p.H157Y	rs2234255	Missense	0.0028	0.020
	<i>TREM2</i>	c.185G>A	p.R62H	rs143332484	Missense	0.0049	0.016
	<i>VAPB</i>	c.510G>A	p.M170I	rs143144050	Missense	0.0010	0.000
	<i>DCTN1</i>	c.1998G>A	p.T666=	rs149900553	Synonymous	0.0008	1000
	<i>SETX</i>	c.6507G>A	p.G2169=	rs34073320	Synonymous	0.0098	0.037
	<i>LRRK2</i>	c.4624C>T	p.P1542S	rs33958906	Missense	0.0132	0.069
Case 2	<i>TREM2</i>	c.469C>T	p.H157Y	rs2234255	Missense	0.0028	0.020
	<i>OPTN</i>	c.1339>G	p.M447V		Missense	ND	ND
	<i>SNCA</i>	c.216G>A	p.Thr72=	rs144758871	Synonymous	ND	ND
Case 3	<i>TREM2</i>	c.469C>T	p.H157Y	rs2234255	Missense	0.0028	0.020
	<i>MFSD8</i>	c.1153G>C	p.G385R	rs11098943	Missense	ND	ND

DCTN1, dynactin subunit 1; GMAF, global minor allele frequency; *LRRK2*, leucine-rich repeat kinase 2; *MFSD8*, major facilitator superfamily domain-containing protein 8; ND, no data; *OPTN*, optineurin; *SETX*, senataxin; *SNCA*, synuclein alpha; *TREM2*, triggering receptor expressed on myeloid cells 2; *VAPB*, VAMP-associated protein B and C.

a synonymous variant in the *SNCA* gene (p.Thr72=) and (2) a variant in *OPTN* gene (p.M447V) that maps to the region of interaction with huntingtin. Patient 3 (III:2), a non-synonymous variant in *MFSD8* (p.Gly385Arg), was also detected. While this variant is not rare in Latino/Admixed American controls in gnomAD (allele frequency 0.063), rare coding variants in *MFSD8* have been implicated in FTLT 27. Thus, we cannot exclude the possibility that the *MFSD8* variant also contributes to disease in this individual (table 2).

Neuroimaging assessment

Study 1

Global atrophy of cases compared with healthy controls

Compared with HC, both cases exhibited significant atrophy in the frontal, temporal, parietal and cerebellar regions. In addition, case 1 showed significant GM reduction in the right

supplementary motor area, right rolandic operculum, left supra-marginal gyrus, left precuneus and left paracentral lobule (online supplemental table 1, figure 3A). Case 2 showed significant atrophy in the left parietal inferior lobule, left precentral gyrus, right superior temporal gyrus, right angular gyrus, right inferior frontal gyrus, left precuneus and bilateral superior frontal gyrus (online supplemental table 1, figure 3B).

Global atrophy of cases compared with the Ng-FTD group

Compared with the Ng-FTD group, both patients showed significant atrophy in the middle frontal gyrus, precentral gyrus and fusiform gyrus (online supplemental tables 1 and 2; figure 3C D). In addition, case 2 exhibited significant GM reduction in other frontal, temporal, parietal, basal ganglia, hippocampal and parahippocampal, and cerebellar regions (online supplemental information and tables 1 and 2, figure 3D).

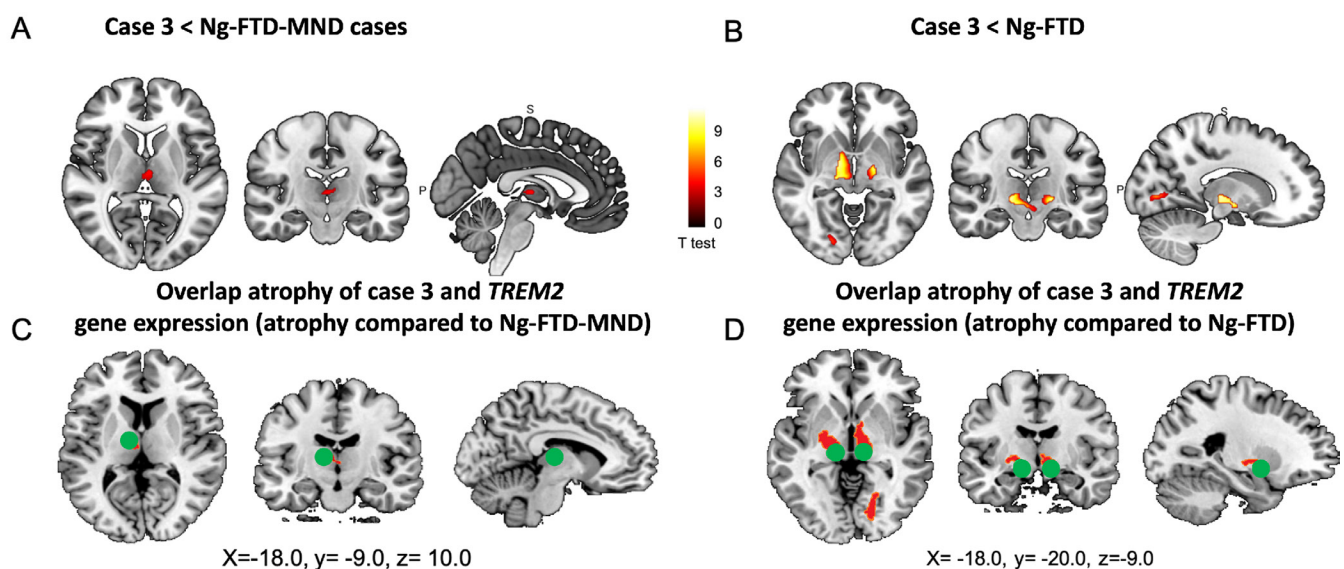


Figure 3 Brain atrophy pattern and gene expression overlap in study 1. (A) Atrophy pattern of case 1 compared with healthy controls. (B) Atrophy pattern of case 2 compared with HC. (C) Atrophy pattern of case 1 compared with Ng-FTD controls. (D) Atrophy pattern of case 2 compared with Ng-FTD controls. All brain areas reported reached $p < 0.001$, uncorrected, and had an extent threshold of 50 voxels. (E) Overlap between atrophied regions in cases 1 or 2 and sites of expression of the *TREM2* gene. (F) Three-dimensional surface rendering and medial view of *TREM2* gene expression in donor H0351.1009 (Allen Human Brain). FTD, frontotemporal dementia.

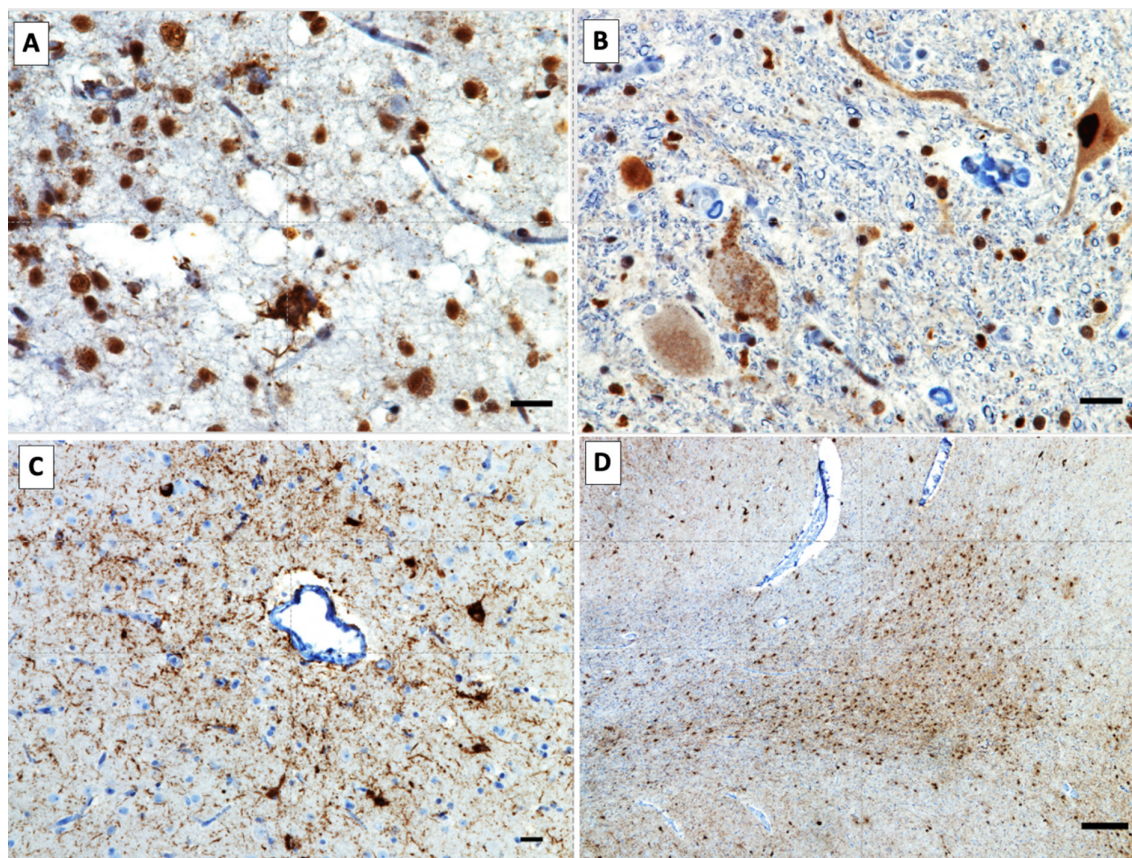


Figure 4 Neuropathological findings in the Mexican case. A) TDP-43 mislocalization is seen in neurons from the upper cortical layers of the middle frontal gyrus. Pathological TDP-43 is seen either as granular diffuse cytoplasmic inclusions in neurons not displaying the normal nuclear TDP-43 staining or as skein-like cytoplasmic inclusions. B) Granular diffuse pathological cytoplasmic TDP-43 immunoreactivity in the lower motor neurons of the cervical cord. C) Abundant perivascular neuronal and glial tau cytoplasmic aggregate in the cerebral cortex, the pathognomonic lesion of chronic traumatic encephalopathy. D) abundant argyrophilic thorny astrocytes in clusters (ATAC) at the juxtacortical white matter of the subgenual cingulate gyrus.

Gene atrophy overlapping

We found a group of atrophy peaks in *TREM2* variant cases that overlapped with an expression of the *TREM2* gene in the Allen database. These coordinates correspond to the left superior frontal, orbital, middle frontal, precentral, inferior temporal, fusiform and supramarginal gyri, left precuneus and inferior parietal lobule (online supplemental table 4, [figure 3E F](#)).

Study 2

Global atrophy of cases compared with the Ng-FTD-MND and Ng-FTD groups

We compared case 3 with an Ng-FTD-MND group and with an Ng-FTD group. Compared with the Ng-FTD-MND group, case 3 exhibited significant atrophy in bilateral basal ganglia (mainly in the pallidum) and bilateral thalamus. Compared with the Ng-FTD group, case 3 showed GM reduction in the bilateral basal ganglia (pallidum), bilateral thalamus and left inferior temporal gyrus (online supplemental table 3, [figure 4](#)).

Gene atrophy overlapping

We found two atrophy peaks in case 3 that overlapped with an expression of the *TREM2* gene in the Allen database. These coordinates correspond to the bilateral basal ganglia and bilateral thalamus (online supplemental table 5, [figure 4](#)).

Postmortem pathological findings

The autopsy revealed FTLD with TDP-43 inclusions type B and MND, which was felt like the primary neuropathological diagnosis. In addition, comorbid chronic traumatic encephalopathy (CTE) stage 4 and additional tauopathies such as ageing-related tau astrogliopathy, argyrophilic thorny astrocytes in clusters and limbic argyrophilic grain disease. Beta-amyloid immunohistochemistry was negative, while the neurofibrillary tangles Braak stage of AD could not be ascertained because of the confounding effect caused by the high severity of CTE ([figure 2](#)).

DISCUSSION

Here we analysed a possible association of the p.H157Y variant in the *TREM2* gene in two unrelated familial cases from Colombia and in one case from Mexican with a bvFTD and FTD-MND-compatible profile, respectively. Neuropsychological results revealed that the patients of the first study exhibited significantly impaired scores compared with Ng-FTD and HC groups in general cognitive and executive function assessments, social cognition and behavioural symptoms. In addition, the patient of study 2 did not exhibit significant differences in cognitive functioning but showed clinical motor neuron impairments associated with brain atrophy in classical motor-related areas including bilateral basal ganglia in comparison to the Ng-FTD-MND group. On the other hand, atrophy and gene expression-level association study revealed diverse atrophy peaks that overlapped

with *TREM2* gene expression in regions corresponding to the left superior frontal, orbital, middle frontal, precentral, inferior temporal, fusiform and supramarginal gyri, left precuneus, inferior parietal lobule, bilateral basal ganglia and bilateral thalamus. Our findings question a plausible association of the p.H157Y variant in bvFTD and FTD-MND disease progression.

Previous studies reported associations between *TREM2* variants and neurodegeneration, including the Nasu-Hakola syndrome,^{39–41} early-onset⁴² and late-onset AD,^{8, 9} and PD.⁴³ Moreover, different *TREM2* variants have been associated with increased risk of FTD-like syndrome,^{10, 44–47} FTL¹⁸ and bvFTD^{34, 48} without bone cysts disease. Different reports have shown that *TREM2* can increase the genetic risk of neurodegenerative disorders via dysregulation of the immune system.^{8, 9, 49}

The association between *TREM2* mutations and FTD-like syndromes without bone cysts is population specific. *TREM2* mutations have been associated with FTD in Asian,^{44, 45, 50} European,^{16, 46} North American samples,⁷ and in non-stereotypical samples from Latin America-Bolivian³⁹ and Colombian.^{18, 34, 51} The specific *TREM2* variant observed in our study (*TREM2* c.469C>T (p.His157Tyr)) has been previously associated with neurodegeneration in European,⁷ Asian,^{5, 8} Colombian^{34, 51} and Mexican⁵² populations. The p.H157Y missense variant resides in a conserved coding region where the histidine-to-tyrosine exchange at amino acid 157 leads to enhanced shedding of *TREM2* from the cell surface, as well as altered cleavage of the *TREM2* ectodomain during its transport from the ER to the plasma membrane. As a result, reduced levels of *TREM2* on the plasma membrane have been observed for this variant.⁵³ Different reports have shown that *TREM2* is an AD genetic risk factor involved in dysregulation of the immune system.^{8, 9, 49}

Although the *TREM2* p.H157Y variant presents high allele frequency in Latino populations, two out of three algorithms classified this variant as definitely pathogenic.⁵¹ Moreover, a meta-analysis revealed that this variant is associated with neurodegeneration in different populations with an OR=3.65.⁵ The potential pathogenicity of this variant in Latin American populations can vary due to mixed ancestries. Recent reports have shown that in non-stereotypical samples, different genotype-phenotype interactions are often observed.⁵⁴

The potential pathogenicity of the *TREM2* p.H157Y variant has been recently supported in Latin American studies. Hundred Colombian individuals with neurodegenerative diseases have the p.H157Y variant, with almost 50 heterozygous and seven homozygous.⁵¹ The p.H157Y variant was found in a Native American haplotype, and it has been estimated that this allele emerged around 1265 generations ago (95% CI of 1108.5 to 1430.9). Past evidence has shown that the disease burden in Latin American populations is affected not only by the recent admixture processes but also by ancestral migrations.^{51, 55}

Thus, the variant reported in our study has been previously found to be pathogenic in under-represented populations and is associated with neurodegeneration in Asian, European and Latin American samples. Current results add new evidence by showing that this variant can also be associated with FTD syndromes in non-stereotypical populations. Moreover, our pathological findings suggest additional insights. *TREM2* deficiency impairs clearance of pathological TDP-43 and enhances neuronal damage⁵⁶; and TDP-43 and *TREM2* interact in neurodegenerative tissues from patients with FTD-MND.⁵⁶ Case 3 pathological results support these links between *TREM2*, TDP-43 and FTD motor phenotype. Allostatic overload may be an important factor combining genetic and fundamental factors contributing to TDP-43 aggregation associated with FTD.⁵⁷

Functions of *TREM2* such as binding to ApoE and amyloid-beta 42, microglial activation, expression of proinflammatory cytokines and phagocytosis are decreased.^{5, 14} Interestingly, each case has shown additional variants besides heterozygous variant p.H157Y, presenting a specific FTD clinical profile to consider. The first case has shown a second heterozygous *TREM2* variant (p.R62H), which alters the flanking consensus sequence of ligand binding but does not alter protein conformation.⁵⁸ Yeh *et al* showed that p.R62H modestly but significantly reduces uptake of A β -LDL complexes in human monocyte-derived macrophages.¹⁹ In this case 1, we could not possibly differentiate between the possibilities of co-inheritance or compound heterozygosity of these variants. In case 2, two additional variants were revealed: a variant in the *OPTN* gene (p.M447V) and a second synonymous silent polymorphic SNVs in the *SNCA* gene (p.Thr72=). Despite silent SNVs could have biologically important effects, the low allelic frequency (0.00005645) in Latino/Admixed American population does not allow any conclusion on whether they might modulate bvFTD phenotype. Finally, in case 3, a non-synonymous variant in *MSFD8* (p.G385R) was also detected. This variant is presented with an allele frequency of 0.063 in Latino/Admixed Americans; however, some studies suggest that rare coding variants in *MSFD8* could contribute to FTL¹⁸ pathology.¹ Thus, we cannot exclude the possibility that the *MSFD8* variant also could contribute to disease in this individual.

Having detected these additional variants in all cases, we have found interesting neurocognitive outcomes in our series. The neuropsychological presentation consisted of insidious onset with personality changes, disinhibited behaviour, executive dysfunction and emotional disorders, resembling bvFTD. Similar findings were obtained by Samanci *et al*, who revealed bvFTD-like clinical features in 14 patients carrying several pathogenic *TREM2* variants.⁵⁹ Furthermore, Guerreiro *et al* reported compound heterozygous missense mutations (p.Y38C and p.D86V) associated with personality and behavioural changes at an early age in a Turkish family. This case showed cortical atrophy with periventricular white matter disease, culminating in severe dementia.¹⁶ Giraldo *et al* reported a novel homozygous nonsense mutation (p.W198X) in a Colombian family with an autosomal recessive pattern of inheritance of FTD without bone cysts and with behavioural and personality changes around the ages of 45–50.¹⁸ Although no studies have reported cases of heterozygous p.H157Y variants in patients with FTD, Jiang *et al* showed a similarly increased frequency of this variant is strongly associated with LOAD.⁵

Cases 1 and 2 have shown impairments in general cognition assessment, executive dysfunctions disinhibition compared with HC and the Ng-FTD group. These results suggest a pattern of multidomain, intertwined deficit triggered by FTD.⁶⁰ Furthermore, compared with HC, *TREM2* cases exhibited major apathy and impaired social cognitive skills. Although disinhibition is one of the most typical manifestations of bvFTD,⁶¹ our results revealed increased disinhibition in *TREM2* cases (relative to the Ng-FTD group). This cognitive pattern of alterations was associated with typical atrophy in frontal, temporal, parietal and cerebellar regions.^{22, 62–64} Crucially, case 1 and case 2 showed increased atrophy in the orbitofrontal cortices, anterior cingulate, right superior frontal gyrus, right medial frontal gyrus, precentral gyrus and fusiform gyrus when compared with Ng-FTD cases. Additionally, case 2 exhibited frontal and temporal atrophy but also reduced GM in the basal ganglia, cerebellum, parahippocampus, hippocampus, precuneus and supramarginal gyrus. These findings suggest more severe atrophy progression in cases

1 and 2 that compromise classical areas but also extend to other areas. On the other hand, in study 2, case 3 had a worse GM disease in basal ganglia and thalamus than the Ng-FTD-MND group. Although in this case, preserved general cognitive skills were observed in comparison to the Ng-FTD-MND group, worse executive functioning, significant behavioural changes (apathy, disinhibition, motor problems, sleep and eating disturbances) and loss of social norms were identified. Previous studies have shown a clinical association in 5% of FTD cases and a deficit in executive function that overlaps with MND.⁶⁵

Although the observed effects of the p.H157Y mutation are similar to those generated by most of the mutations in the IgV domain, the biochemical and cellular mechanisms underlying its effects have been little described.^{13 66} In assessing *TREM2* gene expression profiles of brain regions in p.H157Y mutation carriers, we observed a high spatial correspondence between their expression throughout the brain and the atrophy pattern in each case, including frontal (orbitofrontal and cingulate cortex), inferior medial temporal, basal ganglia, precuneus and inferior parietal regions. These brain areas were associated with the cognitive and social cognition deficits characteristic of bvFTD.^{67–74} Similarly, this pattern of brain atrophy associated with *TREM2* variants coincides with other reports.³ Moreover, similar relationships have been found in MRI studies of progressive non-fluent aphasia cases which suggest that the motor impairments are due to atrophy in regions within a left front-insular-basal ganglia network.^{75 76} In this work, we have observed an interesting association between two regions involved in executive function (basal ganglia and thalamic regions) and *TREM2* gene expression levels. Several authors highlight that activated microglia in the vicinity of degenerating motoneurons and the presence of immunologically active macrophages are pathological features of ALS.^{77 78} However, the mechanism underlying which such activation impacts the disease process remains unclear.

The postmortem neuropathological findings of case 3 revealed MND with TDP-43 type B inclusions and severe cystic degeneration of white matter and split septum pellucidum, consistent with comorbid CTE pathology. Moreover, perivascular neuronal and glial tau cytoplasmic aggregate were observed in the cerebral cortex, which is considered a pathognomonic sign of chronic traumatic encephalopathy. The pattern of TDP-43 pathological findings supports the notion of neurodegeneration due to *TREM2* variants. However, the presence of glial tau lesions is suggestive of traumatic encephalopathy and mixed pathology. Although some studies have shown associations between TDP-43 inclusions and brain injury,⁷⁹ most cases have been associated with risk variants in causative genes.⁸⁰ Other reports also found associations between TDP-43 type B inclusions and *TREM2* risk variants.⁵⁶ Future studies should assess the specific changes associated with brain injury in individuals with FTD genotypes.

Moreover, *TREM2* deficiency impairs clearance of pathological TDP-43 and enhances neuronal damage⁵⁶; and TDP-43 and *TREM2* interacts in neurodegenerative tissues from patients with FTD-MND.⁵⁶ Case 3 pathological results support these links between *TREM2*, TDP-43 and the FTD motor phenotype.

Limitations and future directions

Our results have important limitations. First, our study is limited by a small sample size, with three cases reported harbouring the p.H157Y variant in two Colombian families with bvFTD and one from Mexico. One future source of replication comes from genome sequencing studies including FTD cases.⁸¹ Case 3 had Latin American ancestry, and ancestry-related genetic

analysis may require further investigation. Second, the precise molecular mechanisms potentially connecting the effects of the p.H157Y variant to the pathogenesis of FTD are still unknown. Third, although the *TREM2* gene has been reported to be an intermediate risk gene for AD and FTD, the p.H157Y variant was present with a high allelic frequency in several Latin American cohorts. Here, we have shown an interesting association between *TREM* gene expression and the clinical phenotype of FTD; however, further functional studies should be included to confirm this association. On the other hand, our study lacks homogeneity in measurements of cognitive functioning across cases from Colombia and Mexico. Although the assessment of executive functioning and other behavioural symptoms were different between Colombian and Mexican cases, all patients were assessed with conventional measures for tracking those cognitive functions. Future studies should homologate the cognitive and behavioural assessments of samples of patients with genetic antecedents. Finally, sample patients were identified based on genetic diagnosis by targeted sequencing techniques using a gene panel established previously and outside of this study. In future investigations, circulating cell-free mRNA analysis in plasma levels may be considered to predict the functional effects of this variant on phenotype clinical.

CONCLUSIONS

This study offers a suggestive association that the p.H157Y variant could contribute to bvFTD and FTD-MND clinical phenotype. *TREM2* variants exhibit pleiotropic effects producing a wide spectrum of disorders with different clinical phenotypes. In three cases of this report, we found a bvFTD presentation with classical atrophy extending to other brain areas, accompanied by major disinhibition with impairments in general cognition, executive functions and social cognition. In addition, there is strong evidence to alter motor neurons in one case. We found an interesting association between atrophy peaks and *TREM2* gene expression to the susceptibility of FTD. These findings highlight the marked phenotypic variability possible within subjects carrying the same *TREM2* variant.

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