Supplementary Information

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

S1. Materials and Methods

Patients recruitment

Study 1

The two cases (patient 1 and patient 2) with a heterozygous p.H157Y variant (TREM2 group) were diagnosed with bvFTD and presented a similar profile of executive dysfunction and abnormal behavior characterized by apathy, disinhibition, and strikingly affective exaltation symptoms.

Five healthy, right-handed males were recruited as a healthy control group (HC). Participants in this group were matched for sex, age, and education (mean age = 61.34 years, SD=3.9; mean years of formal education=11.3; SD=2.9) to patients 1 and 2 of the TREM2 group. HC subjects had no history of neurological or psychiatric conditions. The second group of five male sporadic bvFTD patients with neither genetic *TREM2* variants nor family antecedents were recruited (Ng-FTD group). This group was also matched for sex, age, and education (mean age=62.81 years, SD=6.1; mean years of formal education=10.61; SD=3.7) to patients 1 and 2 of the TREM2 group and HC.

Study 2

The Mexican origin case (patient 3), with a heterozygous p.H157Y variant, presented a similar profile of executive dysfunction and abnormal behavior characterized by apathy and disinhibition and later developed MND.

A group of eleven male FTD-MND patients with neither genetic *TREM2* variants nor family antecedents were recruited (Ng-FTD-MND group). All ADSP sample phenotype and demographic data were obtained from dbGAP.

Neuropsychological assessment. Study 1

General cognitive assessment

The general cognitive states of the TREM2 cases and subjects in both control groups were assessed using the Montreal Cognitive Assessment (MoCA)[1]. This test comprises an assessment of short-term memory, visuo-spatial/executive skills (including alteration, phonetic fluency, and abstraction), attention, working memory, language, and orientation. The maximum score is 30 points; a score of 25 or below indicates impairment.

Executive functioning

Executive functions were assessed through the Ineco Frontal Screening (IFS) battery [2], a sensitive tool for neurodegenerative disease assessment [3,4]. This test includes eight tasks: (i) motor programming (Luria series, 'fist, edge, palm'); (ii) conflicting instructions (hitting the table once when the administrator hits it twice or hitting it twice when the administrator hits it only once); (iii) motor inhibitory control; (iv) numerical working memory (backward digit span); (v) verbal working memory (months backwards); (vi) spatial working memory (modified Corsi tapping test); (vii) abstraction capacity (inferring the meaning of proverbs); and (viii) verbal inhibitory control (modified Hayling test).

Hayling test

As a complementary measure for assessing inhibitory control in all groups, we used the extended version of the Hayling test [5]. This test has been used to measure verbal inhibitory control. It has proven to be sensitive to verbal disinhibition in patients with neurodegenerative disorders [6,7].

Behavioral changes

Behavioral symptoms assessed with the Frontal System Behavioral scale (FrSBe) comprised three subfactors tracking changes in apathy, disinhibition, and executive

function impairments [8]. The FrSBe has been validated for tracking behavioral changes in patients with neuropsychiatric diseases [9].

Social cognition task (Theory of mind)

We employed the Reading the Mind in the Eyes Test (RMET) [10] to assess the emotional inference of the theory of mind. The RMET is a validated, computerized test in which 36 images are presented, each showing the region of the face from midway along the nose to just above the eyebrows. The participant is forced to choose which of four words best describes what the person in the picture is thinking or feeling. The RMET has been previously used to assess social cognitive functioning in patients with bvFTD [6,7].

S2. Materials and Methods

Neuropsychological assessment. Study 2

General cognitive assessment

The general cognitive states were assessed using the Montreal Cognitive Assessment (MoCA) [1]. The maximum score is 30 points; a score of 25 or below indicates impairment.

Executive Functioning

To assess the executive frontal functions the participant was administered with the Stroop task [11]. This task particularly tracks mental speed, selective attention, and inhibitory control.

Behavioral Changes

To assess behavioral changes the participant was assessed with the Neuropsychiatric Inventory [12,13](NPI). The NPI encompasses an assessment of delusions, hallucinations, conduct and sleep problems, depression, anxiety, and changes in eating patterns in dementia [7] .

Social Changes

We assessed the presence of social norms difficulties in the patient by tracking the particular items tracking changes in social behavior in the domain of disinhibition of the NPI [12,13] . Those changes include a loss of social norms in the social context, mocking others in public, speaking with strangers in familial ways and giving them hugs.

S3. Materials and Methods

Neuropsychological assessment. Study 1 and 2

Behavioral single-case analysis

To compare the neuropsychological performance of patients in study 1 and 2 and respective controls. Thus, in study 1 the two TREM2 cases were compared with a group of Ng-FTD patients and with a group of HC. In study 2, the case 3 were compared with a group of Ng-FTD-MND patients collected in the U.S and with a group of Ng-FTD patients collected in Colombian. To run comparisons between groups, we used the modified one-tailed Crawford's test [14,15]. This methodology allows for the assessment of significance through comparison of multiple individuals' test scores with values derived from small samples. This modified test presents low values of type I error and is more robust for non-normal distributions; it has been reported in recent single case studies [6,16,17]. Because we are reporting case studies, only values with $p<.05$ were considered statistically significant in all comparisons. Effect sizes obtained using the same methods are reported as point estimates (zcc as effect size for the modified t-test with covariate analysis) [18].

S4. Materials and Methods

Genetic analysis. Study 1 and 2

Sequencing Alignment and Variant Calling

Paired-end reads were aligned to the GRCh37 reference human genome using Burrows-Wheeler Alignment Tool (BWA-MEM version 0.7.8) [19]. The SAM files were processed using Genome Analysis Toolkit (GATK) best-practices pipeline that includes marking of duplicate reads using Picard tools (v1.83), local realignment around indels, and base recalibration via GATK (v3.2.2) [20]. Variant calling and small INDELs were performed using GATK HaplotypeCaller.

The functional impact of variants was evaluated using combinate prediction models using Polymorphism Phenotyping v2 (PolyPhen-2) [21], MutationTaster [22], Provean [23], and Genomic Evolutionary Rate Profiling (GERP++) [24]. Finally, variants were compared with the allelic frequency reported in Latin individuals in the 1000 Genomes Project database using a chi-square test with a 95% confidence level [25]. For expected values below 5, Fisher's exact test was used.

S5. Materials and Methods

Structural brain measures. Study 1

Imaging recordings

TREM2 cases, HC, and Ng-FTD groups were scanned in a Philips Achieva 3 T Scanner with a 16-channel SENSE antenna. The anatomical and 3D T1-weighted images were recorded with the following parameters: repetition time = 7.9 ms, echo time = 3.8 ms, ACQ matrix 220 × 220 pixels, voxel size 0.5 × 0.5 × 0.5 mm, 310 sections.

S6. Materials and Methods

Structural brain measures. Study 2

Imaging recordings

TREM2 and Ng-FTD-MND cases image acquisitions were obtained on either a 1.5T, 3T, or 4T scanner, following previous procedures[26,27]. The first available MRI acquisition was used for each patient. Acquisition was performed with the Magnetom VISION system (Siemens, Iselin, NJ). A volumetric magnetization prepared rapid gradient-echo MRI (MPRAGE, TR/TE/TI = 10/4/300 milliseconds) was used to obtain T1-weighted images of the entire brain, 15-degree flip angle, coronal orientation perpendicular to the double spin-echo sequence, 1.0 × 1.0 mm2 in-plane resolution and 1.5mm slab thickness.

S7. Materials and Methods

Structural brain measures. Study 1 and 2

Data analysis of Neuroimaging

Images were preprocessed using the DARTEL Toolbox, in accordance with previously described procedures [28]. Then, modulated 12-mm full-width half-maximum kernel-smoothed [29] images were normalized to the MNI space and analyzed through general linear models for second level analyses on SPM-8 software. To explore regional gray matter (GM) reduction in the cases relative to control groups in two studies, we performed two-sample tests, including total intracranial volume as a confounding covariate ($p < 0.001$, uncorrected, extent threshold = 50 voxels). Given the sample size and the exploratory nature of our study, this threshold avoids detrimental effects of liberal primary thresholds on false positives. Explicit recommendations based on neuroimaging simulations suggest a primary $p < .001$ as a default lower limit and stringent primary thresholds or correction methods only for highly powered studies [30]. Similarly, other simulations [31] suggest even more liberal uncorrected thresholds ($p < .005$ with an extent threshold of 20 voxels) to produce a desirable balance between Types I and II error rates that may be comparable to an FDR correction of $p = .05$ [31]. Moreover, this uncorrected statistical threshold is commonly used in previous Voxel-based morphometry (VBM) [32-

[35] studies. Furthermore, we employed a large voxel extent threshold (50 voxels) to avoid the emergence of false positive or spurious results, as it occurs with more lenient ones – e.g., 10 voxels; for more details see explicit suggestions from the Organization for Human Brain Mapping (OHBM)[36].

S8. Materials and Methods

Gene expression and atrophy pattern Study 1 and 2

To establish the potential link between the atrophy pattern of each case and the *TREM2* gene expression, we calculated their overlap using data from the Allen Human Brain database [37]. We established the localization of the gene (in MNI coordinates) from a healthy donor with demographic characteristics like those of our cases [specimen name: H0351.1009 (57 years-old, male, white); probe name: A_23_P167941]. As in previous reports [38,39], five-mm radius spherical ROIs were constructed with each coordinate to create the gene expression map. We reported regions in which the overlap covered at least 50 voxels.

S9. Supplementary Results

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 = .0003, zcc = -6.26, Case 2 t = -2.983, p = .042, zcc = -4.12) and the Ng-FTD group (t = -3.32, p = .001, zcc = -4.41). Additionally, Ng-FTD presented significantly lower scores than HC in MoCA scores (t = -4.572, p = .001, zcc = -4.84) (Table 2).

Executive functions

Both TREM2 cases showed lower scores on total IFS than HC (Case 1 t = -8.16, p = .0009, zcc = -5.12; Case 2 t = -6.24, p = .0001, zcc = -5.75) and Ng-FTD group (Case 1 t = -3.86, p = .009, zcc = -3.11; Case 2 t = -2.45, p< .05, zcc = -2.92). In addition, TREM2 cases exhibited lower Hayling scores than HC (Case 1 t = -2,65; p< .05, zcc = -4.11; Case 2 t = -2,89; p< .05, zcc = -4.22). No differences were observed between TREM2 cases and the Ng-FTD group in Hayling scores (Table 2).

Behavioral changes

TREM2 cases showed significantly higher scores in total FrSBe than HC (Case 1 t = 48.78, p = .00009, zcc = 6.34; Case 2 t = 53.18, p = .00009, zcc = -7.46). Case 2 exhibited lower total FrSBe scores than Ng-FTD group (t = 2.29, p < .05, zcc = 2.11); no differences were observed between Case 1 and the Ng-FTD group. Individualized analyses on each FrSBe subfactor revealed higher scores for TREM2 cases compared to HC (Apathy: Case 1 t = 17.11, p = .009, zcc = 4.11; Case 2 t = 13.18, p = .009, zcc = 4.44; Disinhibition: Case 1 t = 58.18, p = .0009, zcc = 6.14; Case 2 t = 69.19, p = .0009, zcc = 6.21; Executive Functions: Case 1 t = 65.16, p = .0009, zcc = 6.22; Case 2 t = 69.99, p = .0009, zcc = 6.56). Analyses also revealed higher scores in disinhibition for both TREM2 cases compared to Ng-FTD group (Case 1 t = 58.18, p = .0009, zcc = 6.14; Case 2 t = 69.19, p = .0009, zcc = 6.21). No other contrast produced significant results (Table 2).

Social cognition

Both TREM2 cases attained significantly lower scores for social cognition (RMET) compared to HC (Case 1 t = -2.78, p < .05, zcc = -3.34; Case 2 t = -3.18, p < .05, zcc = -4.13). No differences were observed when TREM2 cases were compared to the Ng-FTD group (Table 2).

Study 2

General cognitive state

In the MoCA, Case 3 did not exhibit significant differences when compared with Ng-FTD-MND (Case 3 t= 0.21, p = .80, zcc = 0.01) nor with the Ng-FTD group (Case 3 t = 0.87, p = .22, zcc = 0.02) (Table 2).

Executive functions

Case 3 showed lower scores on the total of correct trials in Stroop task compared to Ng-FTD-MND cases (Case 3 t = 3.99, p< .05, zcc = -4.11). No other contrasts reached significant results (Table 2).

Behavioral 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< .05, zcc = -3.71). Moreover, analyzing the NPI sub-scores, the patient exhibited worst scores of agitation (Case 3 t = 2.79, p< .05, zcc = -2.91), apathy (Case 3 t = 3.29, p< .05, zcc = -3.32), disinhibition (Case 3 t = 2.30 p< .05, zcc = -2.29), motor problems (Case 3 t = 2.55 p< .05, zcc = -2.79), sleep disturbances (Case 3 t = 3.22, p< .05, zcc = -3.22), and eating habits (Case 3 t = 3.70, p< .05, zcc = -3.41). No other contrasts reached significant results (Table 2).

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< .05, zcc = -3.22) (Table 2).

Supplementary Table 1. Brain regions (local maxima) showing significant atrophy in Case 1

Contrast	**Region**	**Cluster *k***	**x**	**y**	**z**	**Peak *t***	**Peak *z***
Case 1 < HC	R supplementary motor area	1834	6	12	61	70.87	5.72
	L cingulate gyrus	569	-4	-30	43	52.07	5.45
	R rolandic operculum	342	46	3	9	48.79	5.40
	L middle temporal gyrus	186	-44	-64	9	35.72	5.11

	R cerebellum	856	45	-46	-27	32.70	5.03
	R insula	224	26	24	-8	24.02	4.72
	L supramarginal gyrus	80	-52	-48	33	21.40	4.60
	L insula	442	-38	-33	-17	18.09	4.43
	L fusiform gyrus	103	-33	-55	-12	17.88	4.42
	L postcentral gyrus	52	-24	-34	72	16.63	4.34
	R vermis	53	3	-82	-24	16.56	4.33
	R parietal superior lobule	57	18	-69	61	14.41	4.18
	L cuneus	57	-12	-78	6	13.63	4.12
	L paracentral lobule	94	-6	-19	55	11.80	3.95
	R inferior temporal gyrus	131	64	-54	-9	10.66	3.83
	L middle frontal gyrus	61	-32	45	12	8.29	3.53
	L postcentral gyrus	196	-39	-34	52	8.05	3.49
	L postcentral gyrus	1834	-27	-37	55	7.83	3.46
Case 1 < bvFTD controls	R middle frontal gyrus/superior orbital	59	24	45	-12	34.99	5.09
	L middle frontal gyrus/BA9	82	-36	12	37	23.56	4.70
	R precentral gyrus	95	40	-1	48	20.78	4.57
	L middle frontal gyrus	94	-34	32	27	17.01	4.36
	L middle frontal gyrus/BA8	64	-30	36	48	10.30	3.79
	L fusiform gyrus	56	-27	-48	-8	9.16	3.65
	L fusiform gyrus		24	45	-12	34.99	5.09
	R middle frontal gyrus/superior orbital	59	-36	12	37	23.56	4.70
	L middle frontal gyrus/BA9	82	40	-1	48	20.78	4.57
	R precentral gyrus	95	-34	32	27	17.01	4.36
	L middle frontal gyrus	94	-30	36	48	10.30	3.79
	L supramarginal gyrus	64	-27	-48	-8	9.16	3.65
	R cerebellum	56	24	45	-12	34.99	5.09
	R fusiform gyrus		-36	12	37	23.56	4.70
	R transverse temporal gyrus/BA 42	59	40	-1	48	20.78	4.57
	L calcarine	82	-34	32	27	17.01	4.36

	R precentral gyrus	95	-30	36	48	10.30	3.79

L: Left; R: Right

Supplementary Table 2 Brain regions (local maxima) showing significant atrophy in Case 2

Contrast	**Region**	**Cluster *k***	**x**	**y**	**z**	**Peak *t***	**Peak *z***
Case 2 < HC	L parietal inferior lobule	1408	-46	-36	42	241.10	6.68
	R anterior cingulum	2250	3	51	9	95.70	5.97
	L middle temporal gyrus	417	-44	-64	9	85.24	5.88
	L middle frontal gyrus	1206	-33	30	30	66.92	5.67
	R insula	6188	26	23	-8	61.62	5.60
	L middle temporal gyrus	11016	-38	3	-39	57.45	5.54
	L cerebellum	135	-51	-51	-33	51.15	5.44
	R calcarine	358	15	-57	16	48.96	5.40
	R middle frontal gyrus	563	39	15	39	29.83	4.94
	R mid cingulum	496	8	-12	36	20.94	4.58
	L precentral gyrus	237	-38	8	37	20.00	4.53
	R fusiform gyrus	213	30	-49	-6	16.53	4.33
	L inferior temporal gyrus	89	-51	-45	-15	16.40	4.32
	R superior temporal gyrus	986	58	-37	9	14.90	4.22
	R angular gyrus	144	42	-60	40	11.01	3.87
	Inferior frontal gyrus/BA46	124	43	44	10	10.47	3.81
	L precuneus	56	-9	-61	67	10.41	3.81
	R postcentral gyrus	80	66	-13	30	10.13	3.77
	L superior frontal gyrus	219	-18	50	42	9.28	3.67
	R parietal superior lobule	145	15	-52	66	8.74	3.60
	R anterior cingulum	57	4	23	-5	8.35	3.54
	R postcentral gyrus	72	30	-36	46	7.77	3.45
	R superior frontal gyrus	102	-22	11	48	7.67	3.43
	R postcentral gyrus	117	60	-19	48	7.01	3.32
	R postcentral gyrus	1408	54	-19	37	6.37	3.19
Case 2	R middle frontal gyrus/superior orbital	4441	24	45	-12	98.64	6.00
	L inferior frontal gyrus/pars triangularis	1507	-40	26	22	50.56	5.43

< bvFTD controls	L middle frontal gyrus/BA 9	287	-36	12	37	48.27	5.39
	R precentral gyrus	299	40	-1	48	33.05	5.04
	R hippocampus	535	30	-27	-8	32.96	5.03
	L parahippocampal gyrus	1333	-30	-27	-17	31.37	4.99
	R middle temporal gyrus	980	60	-7	-9	29.26	4.92
	R superior temporal gyrus	1041	62	-39	7	28.84	4.90
	L middle temporal gyrus	321	-52	-49	6	27.69	4.86
	L middle frontal gyrus	66	-34	59	16	25.26	4.77
	L inferior temporal gyrus	344	-68	-28	-17	20.50	4.56
	R inferior temporal gyrus/BA 20	365	38	-4	-41	19.43	4.50
	L middle frontal gyrus	82	-27	48	6	16.85	4.35
	R angular gyrus	181	42	-63	42	14.91	4.22
	R middle frontal gyrus	172	46	27	43	13.65	4.12
	R superior frontal gyrus/ BA 8	183	-10	23	43	12.63	4.03
	R middle frontal gyrus	51	31	18	40	12.38	4.01
	R anterior cingulum	501	15	44	-2	11.96	3.97
	R middle frontal gyrus	81	34	12	31	11.69	3.94
	L caudate	375	-14	12	6	11.62	3.94
	R precuneus	106	8	-42	58	11.10	3.88
	R medial frontal gyrus/ BA 10	110	-14	45	6	10.32	3.80
	L supramarginal gyrus	93	-45	-49	36	9.25	3.66
	R cerebellum	81	36	-40	-44	8.63	3.58
	R fusiform gyrus	104	60	-4	-27	8.34	3.54
	R transverse temporal gyrus/BA 42	66	36	-28	12	8.06	3.49
	L calcarine	75	-21	-55	9	7.87	3.46
	R precentral gyrus	187	55	3	36	7.87	3.46

L: Left; R: Right

Supplementary Table 3. Brain regions (local maxima) showing significant atrophy in Case 3 compared to Ng-FTD-MND

	MNI coordinates		
Region	**x**	**y**	z
Bilateral caudate	-2/2	-6	18

Bilateral putamen	-6/6	-5	21
Bilateral Thalamus	-12	-18	18

Supplementary Table 4. Overlapping brain regions between the *TREM2* gene expression in case 1 and case 2 vs. Donor H0351.1009

	MNI coordinates		
Region	**x**	**y**	z
Superior Temporal gyrus	−59	−24	1
Inferior temporal gyrus	-50	-6	38
Orbitofrontal cortex	-48	8	42
Left superior frontal gyrus	−15	59	20
Middle frontal gyrus	45	53	−7
Precentral gyrus	-59	2	37
Fusiform gyrus	-38	-58	-14
Inferior parietal lobule	−45	−46	53
Left Precuneus	−25	−76	41
Supramarginal gyrus	−59	−47	30

Supp Table 5. Overlapping brain regions between the *TREM2* gene expression in case 3 vs. Donor H0351.1009

	MNI coordinates		
Region	**x**	**y**	z
Bilateral caudate	-2/2	-6	18
Bilateral putamen	-6/6	-5	21

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