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# A Novel *CHMP2B* Splicing Variant in Atypical Presentation of Familial Frontotemporal Lobar Degeneration

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## ABSTRACT

C-truncating variants in the charged multivesicular body protein 2B (*CHMP2B*) gene are a rare cause of frontotemporal lobar degeneration (FTLD), previously identified only in Denmark, Belgium, and China. We report a novel *CHMP2B* splice-site variant (c.35-1G>A) associated with familial FTLD in Spain. The cases were two monozygotic male twins who presented at ages 62 and 66 years with a slowly progressive behavioral variant of frontotemporal dementia and a syndrome mimicking dementia with Lewy bodies, respectively. Functional and in silico analyses supported the pathogenicity of this variant. Our findings contribute new insights into the genetic landscape and clinical heterogeneity of FTLD.

## 1 | Introduction

Frontotemporal lobar degeneration (FTLD) is a pathological umbrella term for a heterogeneous group of neurodegenerative diseases primarily affecting the frontal and temporal lobes of the brain [1]. Clinically, FTLD can present with behavioral changes, speech and language impairment, and pyramidal or extrapyramidal motor dysfunction [1]. Pathologically, FTLD is classified into four main molecular subtypes according to the biochemical composition of intracellular protein inclusions, namely: transactive response DNA-binding protein 43 (FTLD-TDP, which accounts for about 45% of FTLD cases), microtubule-associated protein tau (FTLD-tau, 45%), fused in sarcoma (FTLD-FUS, 9%), and ubiquitin–proteasome system positive inclusions that are negative for TDP-43, tau, and FUS (FTLD-UPS, 1%) [2, 3].

FTLD clinical-pathological correlations are imperfect; however, approximately 20%–25% of cases are caused by autosomal

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dominant variants with strong genetic-pathological associations. The most common FTLD-causing genes are *C9orf72*, *GRN* (both leading to FTLD-TDP), and *MAPT* (linked to FTLD-tau), but other less commonly reported genetic causes have been described [1]. C-truncating variants in the charged multivesicular body protein 2B (*CHMP2B*) gene, associated with FTLD-UPS, have been previously documented only in Denmark [4], Belgium [5], and China [6].

Here, we report a novel splicing variant in the first *CHMP2B*-associated FTLD family identified in Spain. We provide compelling evidence supporting the pathogenicity of this variant and describe its atypical phenotypic expression in two monozygotic (identical) twins.

## 2 | Case Reports

### 2.1 | Family History

Family history was notable for several neuropsychiatric cases of unknown etiology, including the suicide death of 2 second-degree relatives. The patients' father had died at age 86 from late-onset dementia. Their mother had died from a stroke at age 61. The monozygotic twin patients were the third and fourth of five siblings, the rest of whom suffered from no neurological or psychiatric problems. The proband had one healthy daughter. Family history was therefore compatible with an autosomal dominant inheritance pattern (Figure 1).

### 2.2 | Case 1

The index case was a right-handed male with 20 years of formal education. He presented at age 64, at his wife's initiative, with a 2-year history of slowly progressive personality change characterized by compulsive behaviors (e.g., object and animal hoarding), diminished empathy (e.g., social and emotional detachment), and changes in his dietary and eating behavior (e.g., idiosyncratic food preferences, taking food from others' plates). She also reported difficulties in attention and language. The patient exhibited limited awareness of these changes.

At presentation, his Mini-Mental State Examination (MMSE) [7] score was 28/30, and his Clinical Dementia Rating Scale-Sum of Boxes (CDR-SoB) [8] score was 3.5. Neuropsychological assessment revealed executive dysfunction and language impairment characterized by deficits in naming, verbal fluency, and comprehension, with preserved repetition and reading. Episodic memory and visuospatial skills were also relatively preserved. He exhibited no motor neuron signs or other abnormalities on neurological examination. Routine laboratory work-up was unremarkable. Brain magnetic resonance imaging (MRI) and [$^{18}$F]fluodeoxiglucose positron emission tomography-computed tomography ([$^{18}$F]FDG-PET/CT) showed mild global atrophy and normal metabolism (Figure 2). Cerebrospinal fluid (CSF) biomarker analysis [amyloid β 1–42 (Aβ42), phosphorylated tau at threonine-181 (p-tau), total tau (t-tau), and Aβ42/t-tau ratio] ruled out Alzheimer's disease pathophysiology as the underlying etiology. Genetic testing for the *C9orf72* repeat expansion was negative.

Based on clinical and complementary test information, a diagnosis of a behavioral variant of frontotemporal dementia (bvFTD) was initially considered [10]. However, the observed slow rate of cognitive and functional decline during the first 4 years of follow-up led the clinical team to withhold a definitive diagnosis of frontotemporal dementia. He was referred for evaluation by an experienced psychiatrist, who determined that a personality disorder was a potential explanation for the patient's symptoms. All of the above led to considering the possibility of a bvFTD phenocopy syndrome [11]. Nonetheless, after 6 years of follow-up, the patient's MMSE score had declined to 25/30, and

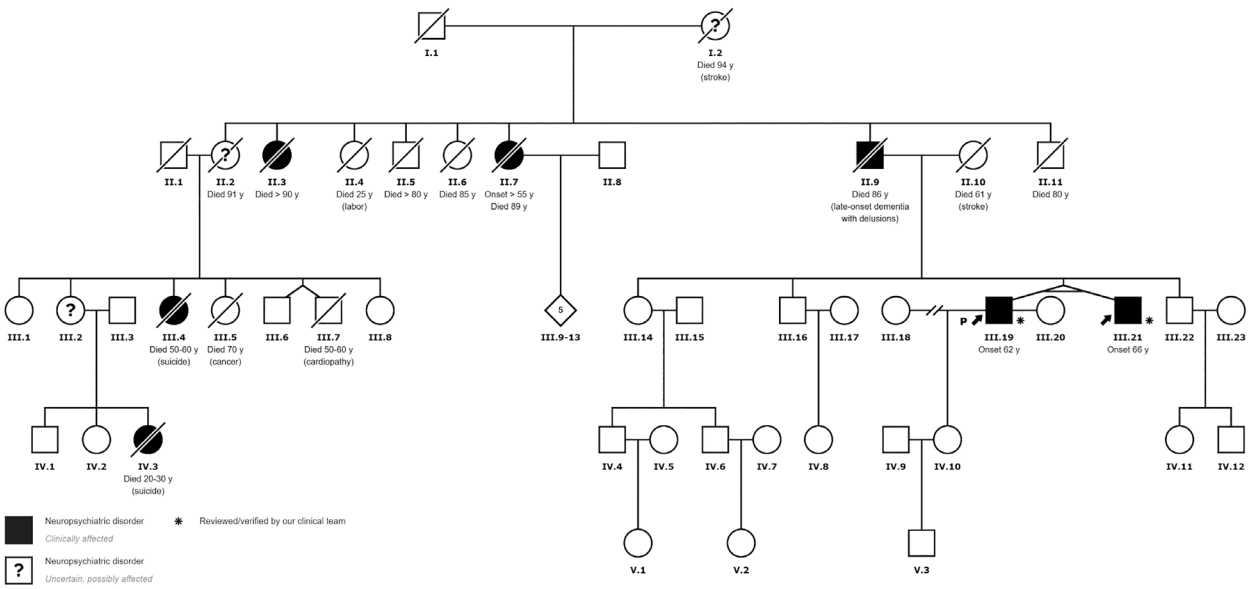


**FIGURE 1** | Pedigree chart. The arrows mark the cases reported in the main text. Letter P indicates the proband (case 1). Years (y) are the ages at onset or death. Death cause is given in parentheses when known. Detailed clinical data could not be obtained for all affected family members due to limited informant recall and their sparse contact with second-degree family members living in another city. The assessment of these relatives by our clinical team was not possible either because they had already deceased at the time of our patients' evaluation.

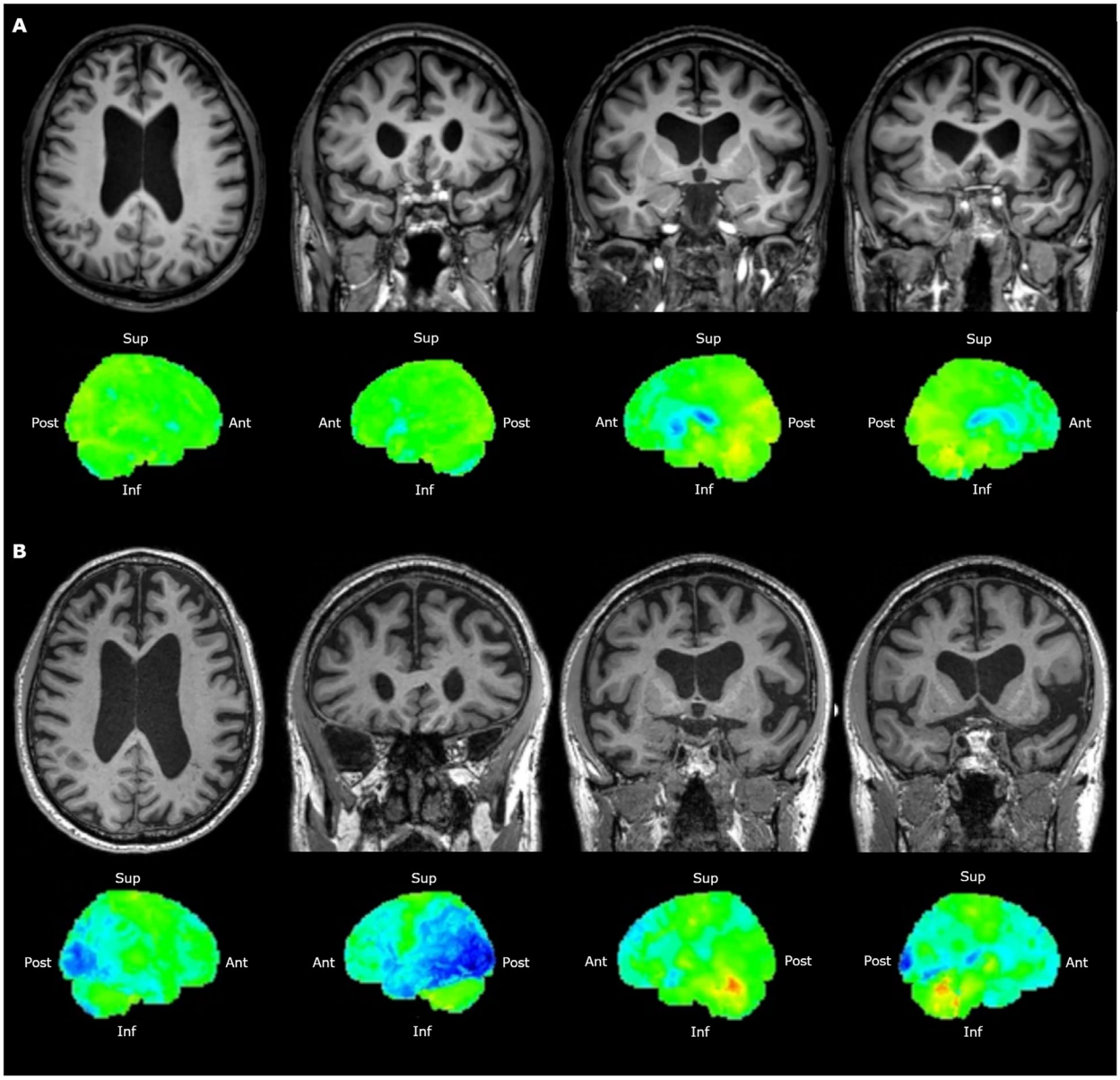


**FIGURE 2** | Neuroimaging findings. Neuroimaging findings in Cases 1 (Panel A) and 2 (Panel B). The upper row in each panel displays T1-weighted magnetic resonance imaging (MRI), left to right: axial, and coronal slices showing anterior cingulate and orbitofrontal, frontal insula, and anterior temporal regions [9]. All MRI images are in radiological orientation. The bottom row in each panel displays 3-dimensional stereotactic surface projection (3D-SSP) analyses of [$^{18}$F]fluodeoxiglucose positron emission tomography-computed tomography ([$^{18}$F]FDG-PET/CT) images, left to right: right lateral, left lateral, right medial, and left medial. Orientation in the body is described as anterior (Ant), posterior (Post), superior (Sup), and inferior (Inf). The intensity normalization is based on the cerebellum as a reference region. Green colors indicate normal glucose metabolism, blue colors indicate hypometabolism, and orange-red colors indicate high metabolic activity. (A) Case 1 showed mild global atrophy and normal metabolism of the brain. (B) Case 2 exhibited prominent, left-lateralized, atrophy and hypometabolism of occipitoparietotemporal and frontal regions, with preservation of the posterior cingulate cortex.

his CDR-SoB score had reached 4. The gradual but persistent cognitive and functional deterioration, in conjunction with progressive atrophy evident on longitudinal MRI assessments quantified through visual atrophy scales [9] ultimately supported a diagnosis of a slowly progressive neurodegenerative disease.

### 2.3 | Case 2

His monozygotic male twin, a right-handed individual with 12 years of formal education, was unmarried and living alone. He presented at age 66 with language impairment and delusional beliefs about his neighbor poisoning him with chemical substances.

At the first visit, his MMSE score was 16/30, and neuropsychological testing revealed widespread cognitive impairment consistent with mild dementia. He soon developed dyscalculia, speech stereotypies, hyperorality, and motor impairment characterized by right-dominant akinetic-rigid syndrome. He exhibited no motor neuron signs. Blood analyses were normal. Brain MRI and [$^{18}$F]FDG-PET/CT imaging revealed

left-predominant occipitoparietotemporal and frontal hypometabolism, with preservation of the posterior cingulate cortex (Figure 2). CSF biomarkers [Aβ42, amyloid β 1–40 (Aβ40), p-tau, t-tau, and Aβ42/Aβ40 ratio] ruled out Alzheimer's disease pathophysiology.

Based on the clinical presentation and imaging findings, including parkinsonism, psychotic symptoms (interpreted as probable visual hallucinations), and posterior brain changes with a cingulate island sign, he was initially diagnosed with dementia with Lewy bodies [12] and was prescribed donepezil 10 mg per day. After 4 years of follow-up, he was dependent for basic activities of daily living, and his MMSE score had declined to 6/30.

### 2.4 | Genetic Analysis

Diagnostic uncertainty and the emergence of additional neuropsychiatric cases in the family prompted a deeper genomic study of the index case. Whole exome sequencing revealed that the proband harbored a novel heterozygous *CHMP2B* variant in the canonical splice acceptor site of intron 1 (NM_014043.4:c.35-1G>A), which was confirmed by Sanger sequencing. Importantly, disease-causing variants were ruled out in other genes related to FTLD, amyotrophic lateral sclerosis, Alzheimer's disease, and dementia with Lewy bodies (Table 1). The G-to-A change caused a shift in the reading frame that resulted in a premature stop codon, predicting a C-truncated protein composed of only the first 16 amino acids (p.Asp12Glyfs*5). The variant had not been reported in the most comprehensive population database (gnomAD v4.1.0) and was strongly predicted to be deleterious by two deep learning models, spliceAI (score = 0.99) [13] and Pangolin (score = 1) [14]. The variant was subsequently identified by Sanger sequencing in his affected brother. Written informed consent was obtained from both patients.

To confirm the variant's pathogenicity, peripheral blood RNA of both siblings was reverse-transcribed and amplified using polymerase chain reaction. Sanger sequencing of the cDNA identified a wild-type transcript and a variant transcript skipping exon 2 that was not found in RNA samples from non-variant carriers (Figure 3). The detection of the aberrant transcript confirmed that the variant altered the normal splicing of *CHMP2B* and led to classifying the variant as pathogenic according to the ACMG guidelines (PVS1 + PM1 + PS3) [15].

**TABLE 1** | Studied genes.

| | | | | |
|---|---|---|---|---|
| *ABCA1* | *ABCA7* | *ADAM10* | *ADH1C* | *ALS2* |
| *ANG* | *ANXA11* | *APP* | *ARHGEF28* | *ARPP21* |
| *ATP13A2* | *ATP1A3* | *ATP6AP2* | *ATP8B4* | *ATXN2* |
| *C19orf12* | *C21orf2* (=*CFAP410*) | *C9orf72* | *CCNF* | *CHCHD10* |
| *CHCHD2* | *CHMP2B* | *CP* | *CTSF* | *CYLD* |
| *DAO* | *DCTN1* | *DJ1* (=*PARK7*) | *DNAJB2* | *DNAJC12* |
| *DNAJC6* | *EIF4G1* | *ERBB4* | *EWSR1* | *FBXO7* |
| *FIG4* | *FTL* | *FUS* | *GBA* | *GCH1* |
| *GIGYF2* | *GLB1* | *GLE1* | *GLUD2* | *GRN* |
| *HNRNPA1* | *HNRNPA2B1* | *HTRA2* | *ITM2B* | *KIF5A* |
| *LRRK2* | *MAPT* | *MATR3* | *NEFH* | *NEK1* |
| *NPC1* | *NPC2* | *OPTN* | *PDGFB* | *PDGFRB* |
| *PFN1* | *PINK1* | *PLA2G6* | *POLG* | *PRKN* (=*PARK2*) |
| *PRKRA* | *PRNP* | *PRPH* | *PSEN1* | *PSEN2* |
| *PTS* | *RAB39B* | *SETX* | *SIGMAR1* | *SLC18A2* |
| *SLC20A2* | *SLC30A10* | *SLC30A3* | *SLC39A14* | *SLC6A3* |
| *SMPD1* | *SNCA* | *SNCAIP* | *SNCB* | *SOD1* |
| *SORL1* | *SPG11* | *SPR* | *SQSTM1* | *SS18L1* |
| *SYNJ1* | *TAF1* | *TAF15* | *TARDBP* | *TBK1* |
| *TBP* | *TH* | *TIA1* | *TREM2* | *TRPM7* |
| *TUBA4A* | *UBQLN2* | *UCHL1* | *UNC13A* | *VAPB* |
| *VCP* | *VPS13C* | *VPS35* | *WDR45* | *XPR1* |

*Note:* List of the 110 genes screened in the index case. The selection of genes of interest for analysis was based on previously described associations with dementing neurodegenerative diseases, amyotrophic lateral sclerosis, or parkinsonian syndromes.

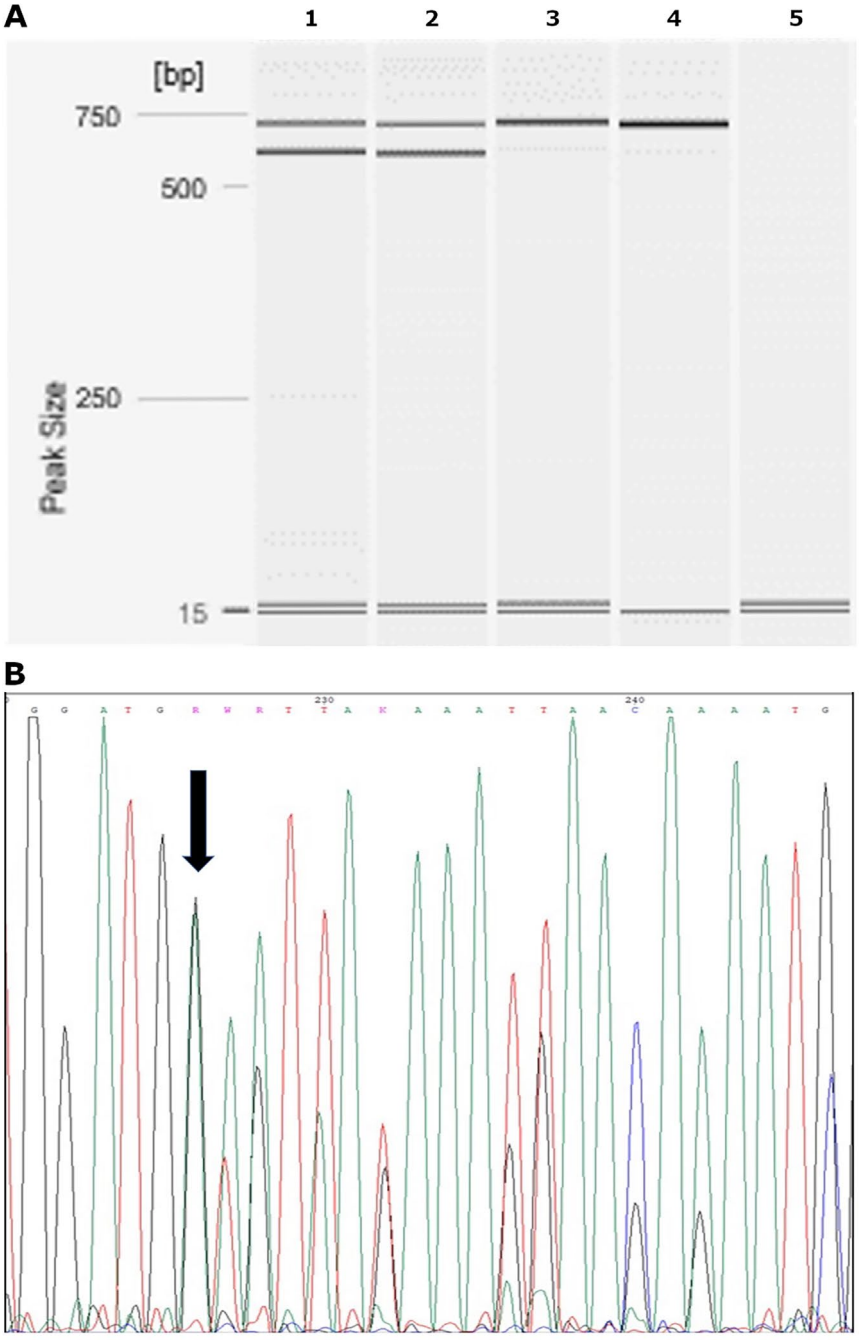


**FIGURE 3** | Genetic analysis. Functional RNA study of the genetic variant identified in the *CHMP2B* gene (NM_014043.4:c.35-1G>A). (A) In the reverse-transcription polymerase chain reaction (RT-PCR) image, two bands can be observed in Lanes 1 and 2 (cDNA samples from the two patients carrying the mutation): One band of 750 bp and another, smaller band, of approximately 660 bp. In contrast, a single band appears in Lanes 3 and 4 (samples from non-mutation carriers). Lane 5: Negative control (no template cDNA). (B) Sanger sequencing of cDNA sample from a patient carrying the heterozygous *CHMP2B* variant.

## 3 | Discussion

This report presents a novel splice-site variant in Spain's first pedigree with *CHMP2B*-associated FTLD. *CHMP2B* (chromosome 3) is a 6-exon gene encoding a 213-amino acid protein of the endosomal sorting complex required for transport-III (ESCRT-III). ESCRT-III is involved in the endosomal-lysosomal and autophagy pathways, essential for the lysosomal degradation of endocytosed and cytoplasmic cellular components [16]. Genetic variants in *CHMP2B* are the primary known cause of FTLD-UPS, a neuropathological subtype characterized by hippocampal and frontal neuronal cytoplasmic inclusions that stain for markers of the ubiquitin-proteasome system, such as ubiquitin and p62, but are negative for TDP-43, tau, and FUS [2]. Neuronal accumulation of aberrant endosomes and autophagic organelles has been

observed in *CHMP2B* variant carriers and other neurodegenerative diseases, presumably reflecting the impairment in endosomal-lysosomal trafficking [2, 16–18].

While multiple *CHMP2B* variants have been identified, only those loss-of-function variants resulting in C-terminal truncations of the CHMP2B protein are considered pathogenic. In contrast, the pathogenicity of missense variants remains unclear [6, 16]. C-truncating variants in *CHMP2B* have been previously identified only in Denmark [4], Belgium [5], and China [6]. The variants found in both a Danish FTLD pedigree (c.532-1G>C) and a Chinese patient (c.532-2A>T) occurred in the splice acceptor site of intron 5. They were predicted to translate into proteins lacking the final wild-type 36 amino acids. In a Belgian familial FTLD patient, a nonsense variant was identified in exon 5 (c.493C>T), predicting the deletion of the final 49 amino acids of the protein. Here, we report two affected monozygotic twins harboring a heterozygous variant in the splice acceptor site of intron 1 (c.35-1G>A). We demonstrate that the splicing variant reported impacts RNA processing, resulting in a truncated mRNA. However, functional studies are needed to confirm its effects at the protein level. The variant reported herein, as previously shown for similar variants in *CHMP2B*, may result in a truncated protein, impairing endosomal function through a gain-of-function mechanism [5]. On the other hand, it may result in the loss of the entire protein through nonsense-mediated decay. In this sense, the depletion of CHMP2B has been demonstrated to alter dendritic branching and induce synaptic defects [19], thus supporting the notion that this variant is pathogenic through a loss-of-function mechanism. Functional studies will be needed to determine whether the splicing variant is pathogenic through a loss-of-function or gain-of-function mechanism.

The presentation of the index case with a slowly progressive personality change aligns with previous literature identifying bvFTD as the most frequent phenotype among *CHMP2B* variant carriers. Psychosis, dyscalculia, and progressive aphasia have also been documented early in the disease course, as was observed in the second case. Disease progression frequently leads to mutism and extrapyramidal signs. Neuroimaging in *CHMP2B*-related FTLD typically shows mild global atrophy at diagnosis, with some cases exhibiting prominent parietal involvement. The usual age of onset is between 46 and 70 years, and disease duration ranges from 3 to more than 20 years [6, 16, 20].

The history of suicide in this family warrants attention, given prior studies suggesting a higher prevalence of suicidality among bvFTD patients and FTLD mutation carriers [21–23]. Indeed, a parental history of suicide has been recently reported in one *CHMP2B* variant case [6]. However, the notion of the *CHMP2B* variant being the cause of the two suicide cases in this family remains speculative, as segregation analysis data are not yet available. Equally speculative is whether the phenotypic differences within these two monozygotic twins are explained only by nongenetic (i.e., environmental) factors, or if they could result from different tissue-specific variant effects in the brain. Nevertheless, individuals with a family history of personality change, suicide, or dementia with Lewy bodies may benefit from screening for *CHMP2B* variants. Future studies should better elucidate the prevalence and natural history of *CHMP2B*-associated FTLD.

Taken together, the findings of this report provide valuable insights into the genetic landscape, disease mechanisms, and clinical heterogeneity of FTLD. Our data underscore the importance of comprehensive genetic testing with a low threshold for suspicion, which has important implications for achieving a definitive FTLD diagnosis.

### Author Contributions

S.R.-G., O.D.-I., and I.I.-G. conceived and designed the study. S.R.-G., S.B., D.A., J.P.-B., V.C., I.S., M.B.S.-S., J.G.C., J.S.-G., M.Á.S.-S., Á.C., J.T.-S., R.R.-G., D.A., J.F., A.L., O.D.-I., and I.I.-G. carried out the acquisition and analysis of data. S.R.-G., S.B., O.D.-I., and I.I.-G. drafted the manuscript.


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The family tree was built using TreeStudio v2.0.8242 © (Health in Code S.L.).


### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## References


1. M. Grossman, W. W. Seeley, A. L. Boxer, et al., "Frontotemporal Lobar Degeneration," *Nature Reviews. Disease Primers* 9, no. 1 (2023): 40.

2. I. R. A. Mackenzie and M. Neumann, "Molecular Neuropathology of Frontotemporal Dementia: Insights Into Disease Mechanisms From Postmortem Studies," *Journal of Neurochemistry* 138, no. S1 (2016): 54–70.

3. S.-C. Ling, M. Polymenidou, and D. W. Cleveland, "Converging Mechanisms in ALS and FTD: Disrupted RNA and Protein Homeostasis," *Neuron* 79, no. 3 (2013): 416–438.

4. G. Skibinski, N. J. Parkinson, J. M. Brown, et al., "Mutations in the Endosomal ESCRTIII-Complex Subunit CHMP2B in Frontotemporal Dementia," *Nature Genetics* 37, no. 8 (2005): 806–808.

5. J. Van Der Zee, H. Urwin, S. Engelborghs, et al., "CHMP2B C-Truncating Mutations in Frontotemporal Lobar Degeneration Are Associated With an Aberrant Endosomal Phenotype In Vitro," *Human Molecular Genetics* 17, no. 2 (2008): 313–322.

6. C. Li, Y. Wen, M. Zhao, et al., "A Novel Splice-Site Mutation in CHMP2B Associated With Frontotemporal Dementia: The First Report From China and Literature Review," *Molecular Genetics & Genomic Medicine* 11, no. 8 (2023): e2222.

7. M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-Mental State": A Practical Method for Grading the Cognitive State of Patients for the Clinician," *Journal of Psychiatric Research* 12, no. 3 (1975): 189–198.

8. J. C. Morris, "The Clinical Dementia Rating (CDR): Current Version and Scoring Rules," *Neurology* 43, no. 11 (1993): 2412.1–2412.2412.

9. L. Harper, G. G. Fumagalli, F. Barkhof, et al., "MRI Visual Rating Scales in the Diagnosis of Dementia: Evaluation in 184 Post-Mortem Confirmed Cases," *Brain* 139, no. 4 (2016): 1211–1225.

10. K. Rascovsky, J. R. Hodges, D. Knopman, et al., "Sensitivity of Revised Diagnostic Criteria for the Behavioural Variant of Frontotemporal Dementia," *Brain* 134, no. 9 (2011): 2456–2477, https://doi.org/10.1093/brain/awr179.

11. F. T. Gossink, A. Dols, C. J. Kerssens, et al., "Psychiatric Diagnoses Underlying the Phenocopy Syndrome of Behavioural Variant Frontotemporal Dementia," *Journal of Neurology, Neurosurgery, and Psychiatry* 87 (2015): jnnp-2014-308284–jnnp-2014-308268.

12. I. G. McKeith, B. F. Boeve, D. W. Dickson, et al., "Diagnosis and Management of Dementia With Lewy Bodies: Fourth Consensus Report of the DLB Consortium," *Neurology* 89, no. 1 (2017): 88–100, https://doi.org/10.1212/WNL.0000000000004058.

13. K. Jaganathan, S. Kyriazopoulou Panagiotopoulou, J. F. McRae, et al., "Predicting Splicing From Primary Sequence With Deep Learning," *Cell* 176, no. 3 (2019): 535–548.e24.

14. T. Zeng and Y. I. Li, "Predicting RNA Splicing From DNA Sequence Using Pangolin," *Genome Biology* 23, no. 1 (2022): 103.

15. S. Richards, N. Aziz, S. Bale, et al., "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology," *Genetics in Medicine* 17, no. 5 (2015): 405–424, https://doi.org/10.1038/gim.2015.30.

16. M. Isaacs, P. Johannsen, I. Holm, et al., "Frontotemporal Dementia Caused by CHMP2B Mutations," *Current Alzheimer Research* 8, no. 3 (2011): 246–251.

17. H. Urwin, A. Authier, J. E. Nielsen, et al., "Disruption of Endocytic Trafficking in Frontotemporal Dementia With CHMP2B Mutations," *Human Molecular Genetics* 19, no. 11 (2010): 2228–2238.

18. C. Ugbode and R. J. H. West, "Lessons Learned From CHMP2B, Implications for Frontotemporal Dementia and Amyotrophic Lateral Sclerosis," *Neurobiology of Disease* 147 (2021): 105144.

19. R. Chassefeyre, J. Martínez-Hernández, F. Bertaso, et al., "Regulation of Postsynaptic Function by the Dementia-Related ESCRT-III Subunit CHMP2B," *Journal of Neuroscience* 35, no. 7 (2015): 3155–3173, https://doi.org/10.1523/JNEUROSCI.0586-14.2015.

20. P. Roos, I. E. Holm, J. E. Nielsen, et al., "CHMP2B Frontotemporal Dementia," in *GeneReviews®*, ed. M. P. Adam, J. Feldman, G. M. Mirzaa, et al. (University of Washington, Seattle, 2020), http://www.ncbi.nlm.nih.gov/books/NBK1199/.

21. L. Fonseca, J. Duarte, Á. Machado, I. Sotiropoulos, C. Lima, and N. Sousa, "Suicidal Behaviour in Frontotemporal Dementia Patients—A Retrospective Study," *International Journal of Geriatric Psychiatry* 29, no. 2 (2014): 217–218, https://doi.org/10.1002/gps.4000.

22. M. Zucca, E. Rubino, A. Vacca, et al., "High Risk of Suicide in Behavioral Variant Frontotemporal Dementia," *American Journal of Alzheimer's Disease and Other Dementias* 34, no. 4 (2019): 265–271, https://doi.org/10.1177/1533317518817609.

23. E. M. Devenney, R. M. Ahmed, G. Halliday, et al., "Psychiatric Disorders in *C9orf72* Kindreds: Study of 1,414 Family Members," *Neurology* 91, no. 16 (2018): 1022, https://doi.org/10.1212/WNL.0000000000006344.