

Single Case – Dementia to Neuropsychology

ABCA7 Mutation in Behavioral Variant of Frontotemporal Dementia: A Case Report

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Keywords

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Abstract

Introduction: Frontotemporal lobar degeneration (FTLD), a major cause of early-onset dementia, includes a heterogeneous group of neurodegenerative disorders with a strong genetic component. Mutations in *MAPT*, *GRN*, and *C9orf72* are found in about 40% of patients with the behavioral variant (bvFTD). More recently, rarer pathogenic variants have been identified in other genes, such as *ABCA7*, initially linked to Alzheimer's disease but increasingly implicated in other neurodegenerative conditions. Here we describe a specific variant which has not previously been reported in the literature. **Case Presentation:** We report the case of a 42-year-old woman who presented with progressive behavioral changes and executive dysfunction, consistent with a bvFTD. A whole-exome sequencing was conducted in a family trio, revealing a heterozygous nonsense variant in the *ABCA7* gene (c.5260C>T, p.Arg1754*). **Conclusion:** This case highlights support the hypothesis of an *ABCA7* loss-of-function associated with early-onset bvFTD. It contributes to expand the genetic spectrum of frontotemporal dementia and underscores the importance of broad genetic testing.

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Introduction

Frontotemporal lobar degeneration (FTLD) is one of the most common causes of presenile dementia after Alzheimer's disease (AD) and encompasses a heterogeneous group of fatal neurodegenerative disorders. These disorders are characterized by a progressive

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deterioration in language, cognition, or behavior, induced by a prominent degeneration of the frontal and anterior temporal lobes. Apathy, diminished empathy, and impairment in social cognition define the behavioral variant of frontotemporal dementia (bvFTD), which accounts for about 50% of frontotemporal dementias (FTD) [1]. The behavioral variant of FTD has a strong genetic component, with a family history in ~30% of patients and mutations identified in genes such as C9orf72, progranulin (GRN), or microtubule-associated protein tau (MAPT), in up to 40% of case. These loss-of-function (LOF) mutations ultimately lead to the accumulation of pathological proteins, including tau and TDP-43 [2].

Beyond these well-established mutations, genome-wide association studies have identified additional, less frequent genetic contributors, such as missense variants in the ABCA7 gene. Initially identified in 2011 as a genetic risk factor for AD [3], ABCA7 has since been implicated in other neurodegenerative conditions (e.g., Parkinson's disease and FTD). These findings suggest a complex and poorly understood association of genetic factors contributing to neurodegeneration [4].

ABCA7, a member of the ABCA transporter superfamily, encodes a protein involved in the clearance of amyloid-beta ($A\beta$), thereby playing a role in AD pathophysiology [5]. However, ABCA7 is also implicated in lipid transport across cellular membranes and in the regulation of endocytosis, functions that may link it to neurodegenerative processes beyond AD [6]. Haploinsufficiency is generally considered the likely pathogenic mechanism, where loss of ABCA7 function disrupts key biomolecular pathways and contributes to neurodegeneration [7]. Several polymorphisms within ABCA7 have been described. Here, we report the identification of a heterozygous c.5260C>T variant, likely pathogenic and predicted to result in premature termination of the protein (p.Arg1754), in a young patient presenting with progressive cognitive and behavioral impairment. The patient fulfilled clinical criteria for bvFTD, and no alternative cause was identified during the diagnostic workup. To our knowledge, this specific variant has not previously been described in the literature [8]. These other known ABCA7 mutations in FTD cases are listed in Table 1.

Case Report

This 42-year-old woman was referred to our Memory Clinic due to progressive cognitive and behavioral changes evolving over 4 years, with no known family history of neurodegenerative or psychiatric disorders. Her relatives reported progressive apathy and a lack of initiative. She acknowledged having increasing difficulty planning her daily activities and described a passive attitude toward time, without experiencing distress or boredom. She described herself as less patient, more irritable, and increasingly indifferent to how others perceived her. Her tendency toward frankness intensified, at times manifesting as emotional insensitivity and a reduced awareness of the impact of her words, suggesting impaired cognitive empathy. Signs of behavioral disinhibition were also observed, including the recent onset of unusual vulgarity, which began 2 years earlier. She reported a new tendency toward impulsivity but was unable to provide concrete examples of recent impulsive behaviors. She also reported a progressive loss of appetite over the past 2 years, with no change in food preferences or the emergence of cravings, particularly for sweets. She denied any compulsive eating behavior or hyperorality.

During the assessment, stereotypical behaviors were observed, such as repetitive and unnecessary hand movements and oral-lingual stereotypies. Her emotional responses were occasionally incongruent with the context, such as episodes of inappropriate laughter. We were also struck by her passivity; she did not initiate conversation, and her responses were terse and vague.

Table 1. Reported cases of ABCA7 mutations associated with FTD phenotypes

First author, year	Clinical phenotype of FTD	Variant type	Genetic variant (HGVS)	Zygosity	Neuropathological confirmation
Antonell et al. [9] (2020)	svPPA	Partial deletion	Not reported	Not reported	Not available
Campbell et al. [10] (2022)	svPPA	Frameshift	p.E709fs	LP	Not available
	bvFTD	Nonsense	p.E1679X	LP	AD pathology with vascular lesions
Ciani et al. [5] (2019)	bvFTD	Missense	c.5585C>A p.Pro1862His	Heterozygous	Not available
	bvFTD	Missense	c.5389A>C p.Asn1797His	Heterozygous	Not available
Csaban et al. [11] (2022)	AD/FTD: behavioral changes, aphasia, visuospatial impairment	Missense (VUS)	c.3682C>T p.Arg1228Cys	Heterozygous	Not available
	AD/FTD: memory and visuospatial impairment, dyscalculia, apraxia	Missense (VUS)	c.5869G>T p.Asp1957Tyr	Heterozygous	Not available
	Vertical gaze palsy, ataxia, memory impairment	Nonsense	c.2250C>A, p.Tyr750*	Heterozygous	Not available
Snyder et al. [12] (2023)	bvFTD	Missense	p.I1878M	Not reported	Not available
	bvFTD	Nonsense	p.W1214*	Not reported	Not available
Sun et al. [13] (2021)	AD/FTD	Missense (VUS)	c.2933T>C, p.I978T	Not reported	Not available
Wagner et al. [14] (2021)	svPPA	Frameshift	c.2126_2132del, p.(Glu709AlafsTer86)	Homozygous	Not available

FTD, frontotemporal dementia; svPPA, semantic variant of primary progressive aphasia; bvFTD, behavioral variant of frontotemporal dementia; AD, Alzheimer's disease; VUS, variant of uncertain significance; LP, likely pathogenic.

The neurological examination did not show any sensory or motor impairment or pyramidal or extrapyramidal signs. Neuropsychological assessment revealed executive dysfunction, with a secondary impact on episodic memory, characterized by difficulties in planning, organization, and cognitive flexibility. Attention lapses were frequent. Language assessment showed a mild anomie syndrome, with lexical access improving with cues or sustained effort. Her speech was generally sparse but did not reveal phonemic or semantic paraphasias, syntactic deficits, or signs of apraxia of speech. Psychomotor slowing was striking throughout the assessment. No signs of praxis, gnosis, or visuospatial impairment

were observed. The MoCA score increased from 20/30 in 2023 to 18/30 in 2025; the BREF score was 10/18 in 2025.

Brain MRI showed mild cortical atrophy, more pronounced than expected for her age, particularly in the insular and posterior parietal regions. Hippocampal volumes were preserved. No signal abnormalities were observed in the basal ganglia, brainstem, or white matter. A brain 18F-FDG PET-CT revealed hypometabolism in the orbitofrontal, frontomedial, anterior temporal cortices, and bilateral thalami. An extensive biological workup was performed. Anti-neuronal and surface antibodies were absent. Protein electrophoresis showed no abnormalities. No vitamin deficiencies were detected. Urinary organic acid analysis was unremarkable, as was the venous ammonia level. Amino acid quantification in blood, urine, and CSF yielded reassuring results. Numerous serologies were conducted, all returning unremarkable findings, including a QuantiFERON® test. Hematopoietic typing was normal. Screening for Wilson's disease through copper and ceruloplasmin measurements was also unremarkable. CSF analysis was overall reassuring, notably showing no pleocytosis. Protein and glucose levels were within normal ranges. Testing for anti-encephalitis antibodies was negative, as were AD biomarkers (levels of β -amyloid 40 and 42, p-tau, t-tau, A β 40/42, and tau/A β 42 ratios were within normal range). The 14-3-3 protein was not detected.

A genetic panel for young-onset dementia (including *C9orf72*, *GRN*, and *MAPT*) came back negative. Whole-exome sequencing (WES) was conducted on the patient and her parents. It identified a heterozygous nonsense variant in the *ABCA7* gene (c.5260C>T, p.Arg1754*), inherited from her father (shown in Fig. 1). This variant is classified as likely pathogenic (class IV), based on the cognitive and behavioral impairment showed by the patient.

Although we do not provide autopsy-confirmed evidence of FTD neuropathology, we ruled out other potential causes of cognitive and behavioral impairment in young adults, including infectious, dysimmune, metabolic, and paraneoplastic disorders or a prionose (e.g., Creutzfeldt-Jakob disease). Moreover, the progressive course was suggestive of a neurodegenerative disease, and the criteria for bvFTD were met [1], which makes FTD the probable diagnosis.

Although the father reported no cognitive symptoms and his spouse had not noticed any behavioral changes, comprehensive neuropsychological and neurological evaluations were strongly recommended. This case report was prepared in accordance with the Case Report (CARE) guidelines.

Discussion

We report the case of a 42-year-old woman presenting with a probable bvFTD according to the Rascovsky criteria of 2011 [1], carrying a heterozygous nonsense mutation in the *ABCA7* gene (c.5260C>T, p.Arg1754), considered a likely pathogenic variant. To our knowledge, this is the first published case involving this specific mutation in a patient with FTD [8].

A genetic etiology is suspected in 30–40% of FTD cases, either based on a positive family history or the identification of autosomal dominant mutations in the *C9orf72*, *GRN*, or *MAPT* genes [2]. Rarer mutations have been reported in other genes, such as *VCP* and *TBK1*, and also lead to TDP-43 protein aggregation. In addition, some genetic risk factors are shared across multiple neurodegenerative disorders. For instance, mutations in the *ABCA7* gene, originally identified as a risk factor for AD, have also been implicated in other neurodegenerative conditions, including two sporadic cases of FTD [5]. These findings suggest that distinct neurodegenerative disorders can result from common pathogenic pathways.

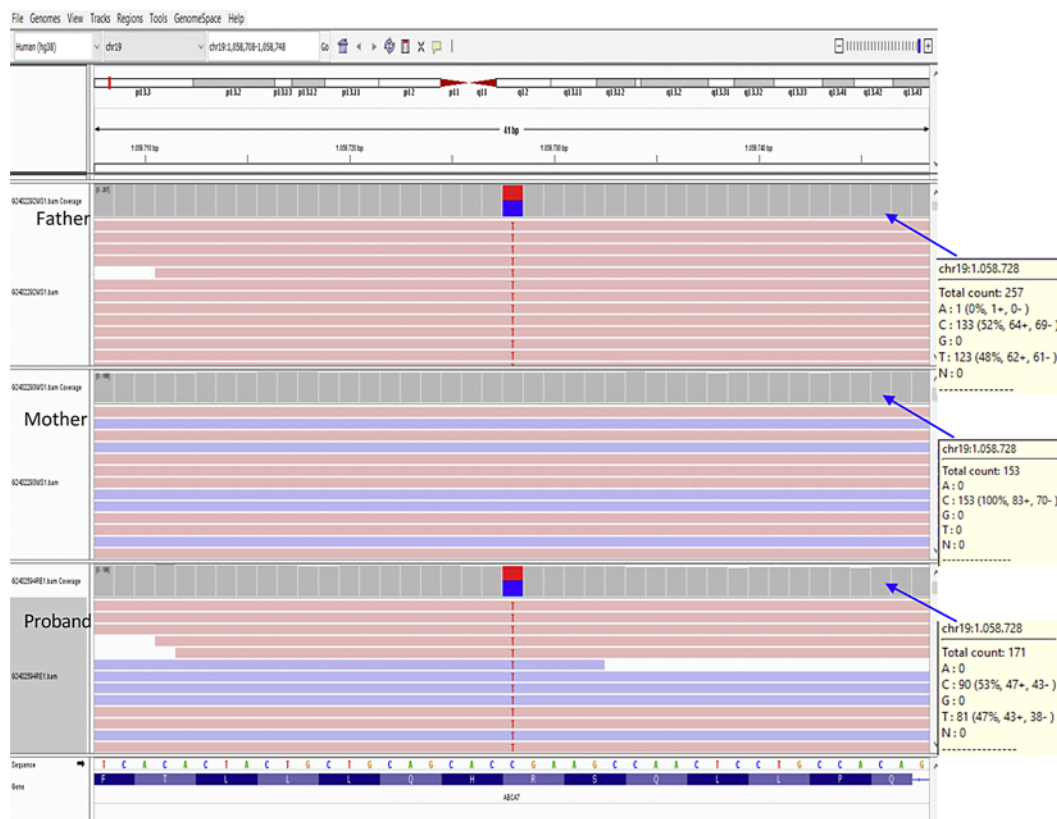


Fig. 1. Trio WES: the sequence alignment at the ABCA7 variant position in the proband and her parents. This figure displays WES reads of chromosome 19 in a trio comprising the proband, her mother, and her father. The ABCA7 variant is present in the proband and her father, but absent in the mother, as highlighted by the red and blue squares at the center of the figure.

The ATP-binding cassette family A (ABCA) includes 12 members, primarily involved in cell homeostasis and mediating cellular transport processes through the lipid membrane. Given the high lipid content of the brain, mutations in *ABCA* genes are most likely to disrupt lipid homeostasis, potentially contributing to neurodegenerative diseases, although their exact functions remain incompletely understood [15].

Located on chromosome 19p13.3, the *ABCA7* gene spans 47 exons and encodes a protein that transports cholesterol and sphingolipids across cellular membranes [7]. It was described in 2011 as an AD-associated gene [3] and has been implicated with A β clearance and endocytosis [5, 16]. It was later associated with Parkinson's disease and FTD, emphasizing the complex genetic landscape of neurodegeneration and suggesting shared genetic underpinnings across neurodegenerative disorders [4]. The common mechanisms remain incompletely understood and may vary depending on the specific genetic variant involved [6]. Among others, the neuroprotective role of *ABCA7* is thought to arise from its modulation of microglial activity in neurodegenerative processes [16, 17].

The landscape of *ABCA7* mutations associated with increased risk for neurodegenerative conditions is highly polymorphic [7] and includes numerous nonsense and missense variants [5, 6]. Many *ABCA7* variants are predicted to be LOF mutations, leading to premature termination of protein synthesis or the production of a nonfunctional protein. However, quantitative analyses of brain protein and mRNA levels do not consistently support this hypothesis, suggesting that LOF may not be the predominant mechanism for all

variants [6]. However, abnormal RNA expression has been reported in patients carrying pathogenic *ABCA7* variants, particularly in the dorsolateral prefrontal cortex [18], where transcriptomic analyses revealed significant alterations in lipid metabolism, oxidative stress responses, and synaptic signaling pathways [19].

Haploinsufficiency is the most widely proposed pathogenic mechanism, whereby a single functional allele fails to produce sufficient protein to maintain normal function. This case provides additional support for the hypothesis of haploinsufficiency as a potential pathogenic mechanism. The patient carries a heterozygous pathogenic variant, suggesting that a single functional *ABCA7* allele may be insufficient to maintain normal protein function, thereby contributing to disease expression. This aligns with emerging evidence that *ABCA7* haploinsufficiency can impair lipid metabolism, microglial phagocytic activity, and amyloid clearance, ultimately promoting neurodegeneration [20].

Although further studies are needed to better understand the penetrance of the mutation, it appears to be variable, meaning that not all carriers develop the disease. This is supported by the identification of the mutation in asymptomatic individuals [21]. Family-based studies of *ABCA7* mutations have shown different levels of co-segregation, indicating that the variant does not always appear in all affected relatives and that some carriers remain unaffected, consistent with incomplete penetrance [21]. These observations may explain why the patient's father shows no obvious cognitive or behavioral impairment, although he has not been formally evaluated. Moreover, the FTD spectrum is highly heterogeneous, and individuals carrying the same mutation can present with markedly different clinical phenotypes [2], underscoring the importance of thorough cognitive and behavioral assessment.

The genetic basis of neurodegenerative diseases remains complex and not fully understood. In early-onset dementia cases where common causes and frequent pathogenic mutations have been excluded, WES may offer valuable insights. WES can also support presymptomatic screening of at-risk relatives and guide timely clinical management.

Conclusion

This case expands the genetic spectrum of FTD by reporting, for the first time, a diagnosis of probable bvFTD associated with the heterozygous nonsense *ABCA7* variant c.5260C>T (p.Arg1754). While *ABCA7* has been widely recognized as a genetic risk factor for AD, its role in FTD remains poorly defined, with only a handful of sporadic cases reported. Our findings support the hypothesis that *ABCA7* haploinsufficiency may disrupt non-amyloidogenic pathways, such as cellular metabolism and homeostasis, thereby contributing to neurodegeneration beyond the AD spectrum. In patients with early-onset dementia and negative testing for common FTD-causing mutations, rarer variants such as *ABCA7* should be considered, particularly when clinical and imaging features are highly suggestive of bvFTD. Identifying such variants can help guide family screening and prompt closer follow-up of relatives, even before symptoms emerge. This case also underscores the importance of expanding genetic panels to include emerging candidate genes implicated in neurodegeneration.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This study was approved by the Hospital-Faculty Ethics Committee of the University Hospital of Liège (CHU de Liège), and consent for

publication was obtained (Approval No. 2025-478). The CARE checklist is provided as supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000552305>).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Each author contributed to the formal diagnosis of the disease and the clinical follow-up. Chloé Geron, MD: conceptualization, methodology, and writing – original draft. Pierre Maquet, MD, PhD: supervision and writing – review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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