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- Include neurodegenerative disease in the differential diagnosis for any patient presenting with new-onset psychosis and behavioral changes in mid-to-late adulthood

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# New-Onset Delusions Heralding an Underlying Neurodegenerative Condition: A Case Report and Review of the Literature

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### ABSTRACT

**Objective:** To present a striking case of new-onset psychosis in a middle-aged woman subsequently diagnosed with behavioral variant frontotemporal dementia (bvFTD). To review the data regarding key red-flag features that may suggest a diagnosis of a neurodegenerative process, and specifically bvFTD, rather than a primary psychotic disorder. To examine the role of genetics, especially mutations of the microtubule-associated protein tau (*MAPT*) gene, in familial cases of frontotemporal dementia (FTD).

**Data Sources:** The pertinent literature was searched online (PubMed, Google Scholar) using the following search terms: *frontotemporal dementia (FTD)*, *Pick's disease*, *behavioral variant FTD (bvFTD)*, *psychosis*, *delusions*, *MAPT*, and *genetics*. No date or language limit was applied.

**Study Selection:** The case report was generated through detailed assessment of clinical notes, imaging studies, and laboratory results. The brain autopsy was carried out and summarized by our neuropathology team. Previously published literature was selected for inclusion in the review section based on relevance to the topic.

**Results:** A neurodegenerative etiology for psychosis (and specifically bvFTD) should be suspected in patients with progressive deficits in executive function, language, or memory. Other key warning features include the presence of a strong family history of a late-life psychotic disorder (or institutional placement or suicide), loss of empathy, impaired recognition of facial expression, or the development of emotional blunting and apathy, abnormal movements, or seizures.

**Conclusions:** Neurodegenerative disease should be on the differential diagnosis for any patient presenting with new-onset psychosis and behavioral changes in mid to late adulthood. Should red-flag features be present, early referral to a clinic specializing in dementia is recommended for further evaluation. This case highlights that *MAPT* mutations can be associated with psychosis in FTD and should be considered in the genetic workup. Ongoing research into the cellular and neural circuit mechanisms of psychosis in neurodegenerative disease may shed light on pathologic processes underlying psychosis in primary psychiatric disorders.

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**Clinical Points**

- Identifying cases of new-onset psychosis later in life due to neurodegenerative disease such as frontotemporal dementia can be challenging.
- A neurodegenerative etiology should be suspected in patients with a strong family history, progressive decline in executive functioning, loss of empathy, or abnormal movements, which should lead to a dementia specialty clinic referral.
- *MAPT* gene mutations can be associated with psychosis in frontotemporal dementia and should therefore be part of the genetic workup.

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**Table 1. Specific Clinical Features That May Raise Suspicion for a Neurodegenerative Process Rather Than a Primary Psychiatric Process**

History	Examination
Family history of early dementia (< 65 years) or institutionalization for psychiatric/cognitive symptoms	Progressive domain-specific abnormalities on neuropsychological testing (eg executive, visuospatial, language), impaired empathy, without obvious mood or affective correlate.
New-onset psychiatric symptoms or personality change at age 40+ years, without preceding psychiatric history	Display of “primitive” reflexes (eg, grasp reflexes)
Predominance of uncharacteristic behavioral disinhibition, socially inappropriate behavior, or loss of empathy, without other psychiatric symptoms (eg, absence of auditory hallucinations or delusions)	Upper or lower motor neuron signs (eg, hyperreflexia, fasciculations) Parkinsonism Apraxia Abnormal eye movements (eg, limitation of vertical gaze) Alien limb phenomena <sup>a</sup> Cortical sensory loss <sup>b</sup>

<sup>a</sup>Alien limb phenomena are defined as involuntary, often purposeful-appearing movements of a limb, over which the patient experiences a lack of agency.

<sup>b</sup>Cortical sensory loss is defined as a higher order sensory dysfunction in which the elemental components of sensation (pain, temperature, vibration, proprioception) are intact, but the patient has difficulty in identifying objects using touch alone. This can be evaluated by placing a familiar object such as a coin or a key in the patient’s hand while her eyes are closed and asking her to identify the object. Alternatively, the examiner can outline a number on the patient’s palm while her eyes are closed and ask the patient to identify the number.

Most primary psychotic disorders are diagnosed in early adulthood; however, a notable minority of individuals are diagnosed after the age of 40 years.<sup>1</sup> These individuals pose a diagnostic challenge, as the overlap with neurodegenerative causes of psychosis becomes increasingly prevalent with advancing age. A neurodegenerative etiology for psychosis should be suspected in any patient with progressive deficits in executive function, language, or memory. Other red-flag features may include new-onset seizures, abnormal movements, or a prominent family history of a dementing or progressive psychotic illness in mid to late adulthood (summary provided in Table 1). In such cases, a number of diagnostic tests are recommended (overview provided in Table 2).<sup>2,3</sup> Should a neurodegenerative etiology be suspected, prompt referral to a clinic specializing in dementia is important to aid early diagnosis, ensure optimal care for the patient, and provide counseling and guidance for family or guardians. In this review, we focus specifically on the clinical features that may suggest a diagnosis of behavioral variant frontotemporal dementia (bvFTD). We emphasize that the *MAPT* mutation can be a cause of late-onset psychosis, as exemplified by the case of Ms A, which follows.

**CASE REPORT**

Ms A, a 39-year-old woman, was brought for an evaluation after 18 months of changes in personality, behavior, and judgment. She had separated from her husband, and the Department of Social Services had taken over custody of her children due to concern for neglect.

She became homeless, although she strongly asserted to be living in an apartment she had bought. She also claimed to have \$49,000 in a local bank, which was not true. She declared that her estranged father had died and that his ashes had been sent to her, although relatives denied this. There was no personal history of psychiatric illness or major medical illness. Her mother and maternal grandfather both experienced progressive psychiatric symptoms with onset in their 40s. Her mother died aged 51 (cause of death not available).

Troubled by the dramatic change in Ms A’s behavior, a close friend reached out to a neurologist at our hospital (K.R.D.) to request an evaluation. At her first neurology visit, Ms A exhibited labile affect. Her language was fluent and prosodic, and she could generate 14 words beginning with the letter S. Digit span was 7 digits forward, 5 backward. Her clock drawing was appropriate and there were no frontal release signs. Other aspects of the neurologic examination findings were normal.

Two months after the first clinic visit, Ms A was arrested and taken to jail after stealing a van from her ex-husband’s house. She was sent to a local emergency department for evaluation, where she claimed that the policeman who arrested her “made love to her and made her breakfast in the morning at the jail.” At a neurology clinic visit several weeks later, she scored 30/30 on the Mini-Mental State Examination, but her thoughts were delusional and she was deemed unsafe to manage her own affairs. She was admitted to a psychiatric hospital, where neuropsychological testing demonstrated deficits in executive function but intact

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## DISCUSSION

**Table 2. Recommended Workup for Suspected Neurodegenerative Cause of a Psychiatric Presentation**

Diagnostic Test	Potential Abnormalities
Structural imaging (MRI brain/CT head)	Cortical atrophy greater than expected for age, may be focal or asymmetric
Functional imaging (FDG-PET brain, SPECT)	Focal hypometabolism (frontal hypometabolic activity is more sensitive for bvFTD than abnormalities on structural imaging)
Neuropsychological and specialized cognitive testing	Impaired executive function Impaired language or memory Impaired recognition of facial expression (Impaired empathy—not part of routine testing)
EEG	Slowing Disorganized background Epileptiform features
CSF testing (for patients with rapidly progressive symptoms, seizures, or other features concerning for encephalitis)	Evidence of infection/inflammation Testing for prion disease CSF biomarkers of Alzheimer's disease
Genetic testing (for patients with prominent family history)	<i>MAPT, C9orf72, GRN</i> Consider testing for Huntington's disease, cerebellar ataxias, adult-onset leukodystrophies, Alzheimer's disease, Lewy body disease, Wilson's disease (depending on clinical presentation)

Abbreviations: bvFTD = behavioral variant frontotemporal dementia, CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalography, FDG-PET = fluorodeoxyglucose-positron emission tomography, MRI = magnetic resonance imaging, SPECT = single-photon emission computed tomography.

memory. The results of structural brain imaging were not available. A fluorodeoxyglucose positron emission tomography (FDG-PET) brain scan revealed decreased metabolism in the frontal and temporal poles and caudate heads bilaterally (Figure 1). Genetic testing (Mayo Clinic Laboratories) detected a DNA sequence change in the microtubule-associated protein tau (*MAPT*) gene at exon 10 (1907C>T) corresponding to an amino acid change of proline 636 to leucine (P301L). This result was consistent with frontotemporal lobar degeneration due to a tauopathy linked to a mutation in the *MAPT* gene.

During subsequent years, Ms A's symptoms progressed, and she required full-time supervision in a locked unit in a nursing home. At 5 years from presentation, she exhibited increasing agitation, repetitive behaviors, and inappropriate actions such as eating her own vomit and getting into other patients' beds. She produced no spontaneous verbal output but was able to sing songs from memory. At 10 years, she could not sit or lie down for more than a few minutes. She put any object she encountered into her mouth. She showed no recognition of friends or family. She died at age 49, 10.5 years after her initial presentation, from presumed aspiration.

An autopsy examination of the brain revealed significant frontotemporal atrophy. The microscopic pathology was consistent with frontotemporal lobar degeneration (described in detail in Figure 2).

### Behavioral Variant Frontotemporal Dementia as a Cause of New-Onset Psychosis

In 1892, Czech psychiatrist Arnold Pick described a 71-year-old man with “progressive loss of language and a failing mind,” with asymmetric cortical atrophy at autopsy. In the early 1920s, Alzheimer identified the characteristic intracellular inclusions associated with this atrophy, labeling them Pick bodies, and shortly thereafter the condition was named “Pick's disease.”<sup>4</sup> It has since become apparent that the original Pick's disease is one subtype of frontotemporal lobar degeneration (FTLD), characterized by the aggregation of insoluble protein in neurons and glial cells. FTLD neuropathology is associated with a spectrum of clinical phenotypes that are collectively known as *frontotemporal dementia* (FTD). The expressed clinical syndrome depends primarily on the neuroanatomic location of pathology. The current classification subdivides FTD into 3 subtypes: bvFTD, nonfluent/agrammatic variant primary progressive aphasia, and semantic variant primary progressive aphasia. bvFTD is the most common variant in the United States and Europe, accounting for 50%–60% of FTD cases in these regions.<sup>5,6</sup>

Patients with bvFTD typically present with a preponderance of psychiatric and behavioral symptoms.<sup>7–10</sup> Usually, there is relative sparing of sensory-motor functioning and certain aspects of cognition (such as memory and visuospatial skills). As a result, patients often present to psychiatric services before their neurologic diagnosis is made. One retrospective study revealed that 52% of patients diagnosed with bvFTD had previously received a diagnosis of a primary psychiatric disorder.<sup>11</sup> This is not surprising since the estimated prevalence of FTD is approximately 2 orders of magnitude lower than that of primary psychotic disorders; 15–22 per 100,000 for FTD<sup>6</sup> vs ~4 per 1,000 for primary psychosis.<sup>12</sup> However, such misdiagnoses can have the negative effect of isolating patients from family and friends<sup>13</sup> and may increase the risk of institutionalization for criminal behavior either in jail or in psychiatric institutions<sup>14</sup> (more common in FTD than in Alzheimer's disease<sup>15</sup>).

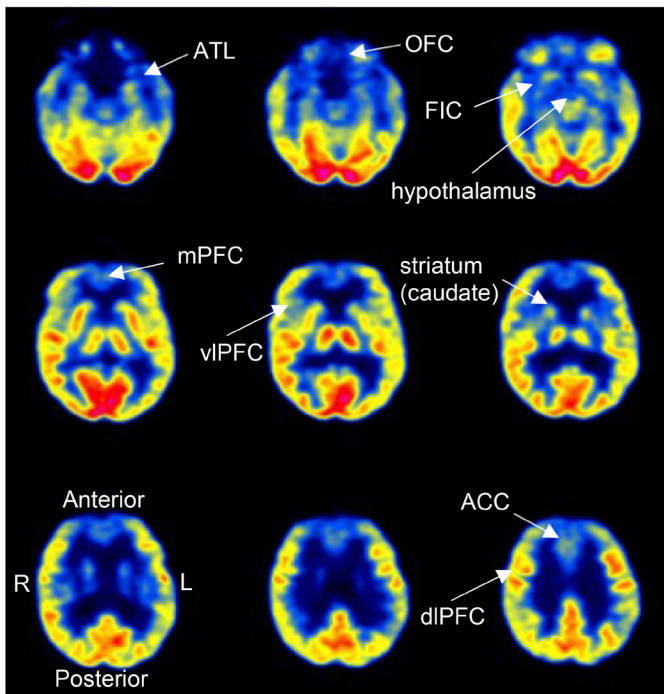
In bvFTD, neuropsychiatric symptoms are present in the majority of patients and often reflect the specific cortical and subcortical neural circuits affected by the pathology (Figure 1B). Negative symptoms, such as apathy, inertia, and emotional blunting, tend to be encountered frequently and early in the disease course<sup>16</sup> and have been linked to dysfunction in the anterior cingulate cortex and anterior temporal lobe (ATL).<sup>5</sup> Social behavior problems, difficulty with emotional processing, and loss of empathy are also highly characteristic of bvFTD and are associated with right-sided brain abnormalities,<sup>17</sup> particularly in the ATL, frontoinsular regions, anterior rostral medial frontal regions, and striatum.<sup>5,18</sup> These brain regions, as well as others, including the temporoparietal junction, superior temporal sulcus, and amygdala, have been associated with theory of mind (awareness of another person's mental state)

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**Figure 1. Functional Neuroanatomy of bvFTD**

**A. FDG-PET brain scan of Ms A<sup>a</sup>**



**B. Key anatomic components of cortical and subcortical neural circuits associated with psychiatric symptoms in bvFTD<sup>b</sup>**

Behavior	Anatomic components of relevant neural circuits
Apathy	ACC, ATL, dIPFC, OFC
Disinhibition	OFC, vIPFC
Perseverative behaviors	dIPFC, ACC
Loss of empathy	mPFC, right ATL, FIC, striatum
Hyperorality/dietary changes	FIC, OFC, striatum, hypothalamus
Executive deficits	dIPFC, vIPFC

<sup>a</sup>Demonstrates decreased metabolism in in the medial prefrontal regions, temporal cortex, and caudate head bilaterally. Blue areas indicate hypometabolic regions, including the anterior temporal lobe, the orbitofrontal cortex, the ventrolateral prefrontal cortex, and the anterior cingulate cortex. The dorsolateral prefrontal cortex was relatively spared at the time of the FDG-PET scan. Other neural circuit components associated with psychotic features in FTD (Figure 1B) are also labeled.

<sup>b</sup>Please see article for further details and references.

Abbreviations: ACC = anterior cingulate cortex, ATL = anterior temporal lobe, bvFTD = behavioral variant frontotemporal dementia, dIPFC = dorsolateral prefrontal cortex, FDG-PET = fluorodeoxyglucose-positron emission tomography, FIC = frontoinsula cortex, L = left, mPFC = medial prefrontal cortex, OFC = orbitofrontal cortex, R = right, vIPFC = ventrolateral prefrontal cortex.

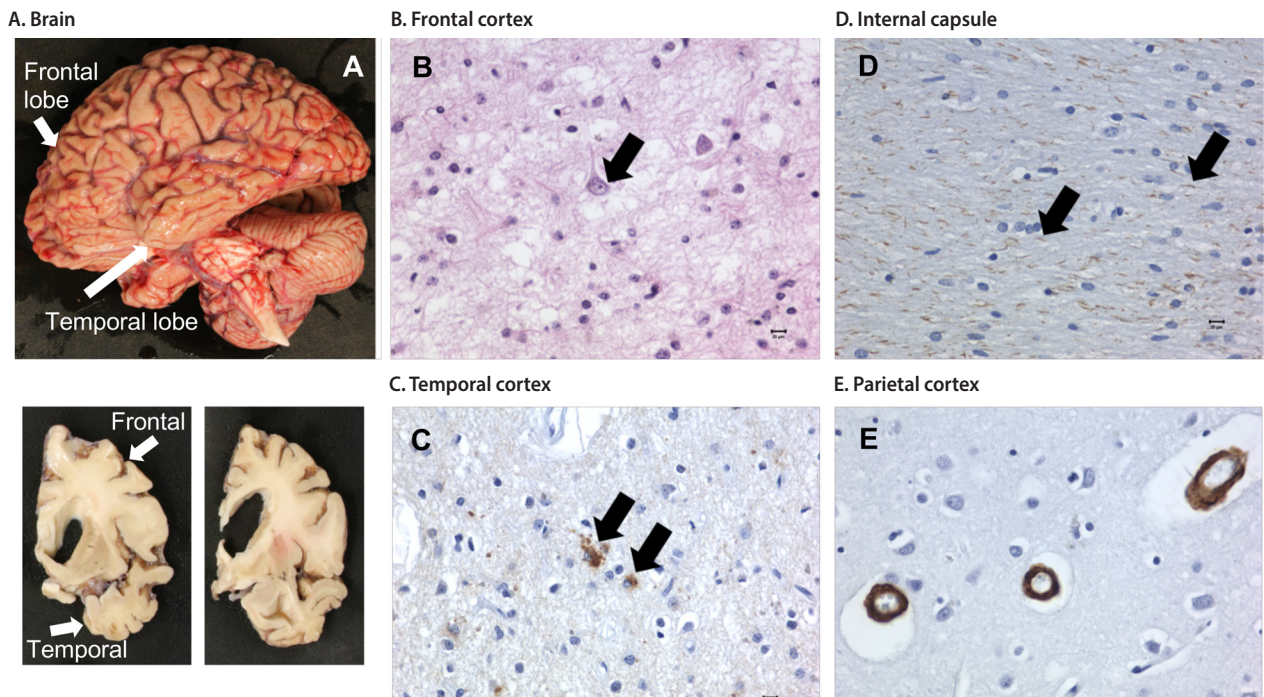
and affective perspective-taking (ability to infer another person's emotions), which are critical for empathy.<sup>19</sup> Other prominent deficits, such as disinhibition and compulsions, typically occur later in the bvFTD disease course and are thought to reflect the anatomic progression of pathology into the orbitofrontal and frontoinsula cortex.<sup>5,17</sup> Changes in eating behavior in FTD, another late feature, appear to involve changes in the right ventral anterior insula, striatum, and orbitofrontal cortex,<sup>20</sup> as well as the hypothalamus.<sup>21</sup> The brain regions associated with psychosis may vary for different FTD genetic mutations. For example, a quantitative imaging study found that psychotic symptoms in

FTD are correlated with gray matter atrophy in select subcortical and cortical circuits including anterior insular, left thalamus, and cerebellum in *GRN* mutation carriers; left frontal lobe in *C9orf72* mutation carriers; and temporal lobe in *MAPT* mutation carriers.<sup>22</sup>

Although no single clinical feature is pathognomonic for FTD psychosis rather than a primary psychotic disorder, certain abnormalities of thought processing, such as difficulty with abstract reasoning, stereotypical thinking, and repetitive or ritualized behaviors, are more commonly associated with FTD than primary psychotic disorders,<sup>16</sup> although the precise neural substrate for these symptoms remains unknown. A smaller proportion of FTD patients (~20%–30%) exhibit positive psychotic symptoms such as paranoid delusions and hallucinations,<sup>16,23</sup> and these are seen at higher frequency (40%–60%) in patients with specific genetic FTD variants, such as the *C9orf72* mutation.<sup>24–26</sup> The content of psychotic thoughts can be variable in FTD. For example, a striking feature of Ms A's delusions was their positive or even fantastical quality, which has been noted in other case reports of FTD.<sup>27</sup> However, given a lack of systematic study comparing clinical data on the phenomenological differences between FTD psychosis and idiopathic primary psychosis, the content and quality of delusions may not represent a reliable distinguishing feature. In several case series, the reported delusions varied across patients, from paranoid or persecutory to grandiose (involving famous people) or somatic (eg, body part distortion or parasitosis).<sup>28,29</sup> It is also not always clear whether such disordered thoughts are true delusions (fixed beliefs) versus confabulations (more fleeting in nature, as may have been the case for Ms A). It is our clinical impression that the emotional impact of delusions may sometimes help to distinguish bvFTD from a primary psychiatric process. We have found that in FTD, the psychosis tends to be less emotionally salient or distressing to the patient and less associated with feelings of anxiety, guilt, and tension, perhaps in the setting of the global loss of emotional awareness that is characteristic of the condition.<sup>16</sup>

The presence of a strong family history of a late-life psychotic disorder, early-onset dementia, or placement in an institution should raise suspicion for an underlying neurodegenerative condition. An estimated 20%–40% of patients with FTD have a positive family history, and this follows an autosomal dominant pattern in the majority of cases.<sup>30</sup> It is important to specifically ask whether any family member was institutionalized or died young with psychiatric or neurologic symptoms or from suicide, and it may be necessary to probe deeply as these family members may be forgotten or rarely talked about, due to associated stigma. Family history is also an important risk factor in primary psychotic disorders (~10%–30% of schizophrenia<sup>31</sup>); however, progression to death over several years is less common.

You are prohibited from making this PDF publicly available.

**It is illegal to post this copyrighted PDF on any website.****Figure 2. Neuropathologic Features of Ms A**

**Panel A:** Macroscopic inspection of the brain was notable for symmetric atrophy, predominantly involving the frontal and temporal lobes, with relative sparing of the parietal lobes. The fresh brain weighed 940 g (normal ~1200–1400 g). Anatomic regions most affected are labeled with arrows.

**Panels B–E:** Microscopic sections of the frontal and temporal cortices showed severe neuronal loss with gliosis, vacuolization, and aggregates of tau in glia and neurons (including middle frontal gyrus, superior temporal gyrus, anterior cingulate cortex). Parietal and occipital cortex were relatively unaffected. The basal ganglia, in particular the caudate nucleus, also showed evidence of neuronal loss and glial tau inclusions. Subcortical and deep white matter showed evidence of modest vascular disease.

**Panel B:** Severe neuronal loss. Arrow denotes rare remaining neuron in glial fibrillary background.

**Panel C:** Tau immunostain: most common inclusion was sparsely granular to globular glial inclusions (denoted by arrows), but neuronal cytoplasmic tau-positive inclusions were occasionally present, particularly in the dentate gyrus.

**Panel D:** Tau immunostain: arrows denote white matter threads.

**Panel E:** A- $\beta$  immunostain: amyloid plaques and Lewy bodies were not present, although amyloid deposition was seen surrounding small and medium sized parenchymal vessels in the gray matter, consistent with cerebral amyloid angiopathy.

The temporal progression of disease will help to differentiate neurodegenerative from primary psychiatric disorders, although predicting the course of illness is often most difficult during the early stages of the illness when diagnostic uncertainty remains high. Over a timeframe of months to years, close attention should be paid to the development of neurologic signs suggestive of frontal network disease or motor neuron or basal ganglia dysfunction, as well as domain-specific impairments on neuropsychologic testing. Approximately 12.5% of bvFTD patients develop neurologic signs consistent with motor neuron pathology (eg, amyotrophic lateral sclerosis), including upper and lower motor neuron signs, dysarthria, and pseudobulbar affect. In 20% of patients, a parkinsonian syndrome may develop, which sometimes includes features of corticobasal syndrome (CBS; can be associated with asymmetric motor signs and alien limb phenomena—involuntary, often purposeful-appearing movements of a limb, over which the patient experiences a lack of agency) or progressive supranuclear palsy (PSP, associated with loss of balance and impaired voluntary eye movements).<sup>14</sup> In some cases, the temporal order of these symptoms is reversed, with motor symptoms

being most salient initially or concurrent with behavioral changes.

Full neuropsychological testing may reveal progressive domain-specific impairments, particularly in executive function (for example, on the Wisconsin Card Sorting task, the Stroop test, the Controlled Oral Word Association Test, and the Trail Making Test—Parts A and B). Unfortunately, many patients with primary psychiatric disease also show deficits in executive function. Therefore, this pattern of performance is not entirely specific for FTD. In addition, the degree of behavior and personality changes in bvFTD is often out of proportion to the executive dysfunction captured by neuropsychological testing. More specific deficits may include vulnerabilities in semantic knowledge, less likely to be affected in psychiatric disease, as well as deficits in emotional and social cognition. Recognition of facial expression is often profoundly impaired in FTD and most prominent for negative emotions such as fear and disgust.<sup>5</sup> Patients with FTD also have significantly reduced empathy scores compared to normal controls, as reported by caregivers.<sup>18</sup> These reflect a diminished capacity to imagine the perspective of another (cognitive empathy) and a reduced

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**Table 3. Summary of the Major Familial bvFTD Genetic Variants**

Mutation (Chromosomal Location)	Protein Directly Affected	Protein Function	Inheritance and Penetrance	Clinical Phenotype
<i>MAPT</i> (17q21.2)	Tau	Microtubule stability	Autosomal dominant with 95% penetrance	Motor symptoms including parkinsonism are prominent. Less apathy. Age at onset mid-50s (20 to 80 years)
<i>C9ORF72</i> (9p21.2)	Expansion of a non-coding GGGGCC hexanucleotide repeat in the <i>C9orf72</i> gene interferes with normal <i>C9ORF72</i> protein expression	Unknown	Autosomal dominant with incomplete penetrance (50% symptomatic by age 60)	Psychosis and other neuropsychiatric symptoms are prominent. Can present as bvFTD, ALS, or FTD with features of ALS. Age at onset mid-50s (20 to 80 years)
<i>GRN</i> (17q21.31)	Progranulin	Inflammation, repair, development	Autosomal dominant with reduced penetrance (90% symptomatic by age 70)	Apathy, executive dysfunction, and social withdrawal are prominent. Less disinhibition/compulsive behavior. Age at onset mid-60s (30 to 80 years)

Abbreviations: ALS = amyotrophic lateral sclerosis, bvFTD = behavioral variant frontotemporal dementia, *C9ORF72* = chromosome 9 open reading frame 72 gene, FTD = frontotemporal dementia, *GRN* = progranulin gene, *MAPT* = microtubule-associated protein tau gene.

emotional response to the perception of another individual's emotional state (emotional empathy). Patients with schizophrenia may also have reduced empathy compared to patients with bipolar disorder or major depression and healthy controls<sup>32</sup>; however, this deficit is generally felt to be less salient compared to patients with FTD.<sup>33</sup> However, it is important to note that tests of facial recognition and empathy are not part of routine neuropsychological testing, and although new tools for emotional and social assessment are being developed (eg, EMOTICOM test battery),<sup>34</sup> these have not yet been robustly validated across different patient populations and cultures.

Overall, it is important to note that although psychotic symptoms can be observed in FTD, they rarely occur in isolation and are usually accompanied by marked and progressive changes in behavior and personality, including loss of insight, executive function, empathy, and disordered eating. A useful bedside clinical tool (18 question checklist) has recently been developed by Ducharme et al,<sup>35</sup> for which a score of 11 or greater is strongly suggestive of bvFTD (specificity 93.9%, sensitivity 71.1%), whereas a score of 8 or less is strongly suggestive of a primary psychiatric disorder (specificity 91.3%, sensitivity 77.3%). The checklist incorporates key distinguishing features including prior history of psychiatric symptoms, family history, degree of emotional distress or awareness of current situation, duration of symptoms, presence of stereotypical behaviors, changes in food preferences, and presence or absence of abnormalities on elemental neurologic examination. Ms A would have scored a total of 14 points at initial presentation to the neurology clinic (13 "no" answers in Part A + 1 "yes" answer in Part B, for the possible history of Pick's disease in the patient's mother). Five years into the disease course, Ms A's score would have increased to 16, to take into account her development of stereotypical behaviors and changes in food preference.

#### **MAPT Mutation in bvFTD**

A key feature in Ms A's history was her family history of an early-onset, progressive neuropsychiatric disorder in

conjunction with a genetic mutation in the *MAPT* gene. Through investigations of such familial cases, several gene mutations have now been linked to FTD, and increased understanding of these mutations and their downstream effects on protein and neural circuit function is helping to reveal mechanisms underlying the neurodegenerative pathology. The most common mutations are found on 3 genes: *MAPT*, *C9orf72*, and *GRN* (progranulin). In this review, we focus on the *MAPT* mutations. Other mutations are discussed in detail elsewhere<sup>5,14,36</sup> and are summarized in Table 3.

The *MAPT* gene mutation was first identified in a family with autosomal dominant inheritance, in which the mutation was linked to chromosome 17q21.2,<sup>37</sup> later identified as the *MAPT* gene.<sup>38-40</sup> Patients with this mutation tend to present earlier than those with *C9orf72* or *GRN* mutations (50% with age at onset < 50 years), but the range of onset age is broad.<sup>25,41</sup> The average disease duration is 8 years, with a younger average age at death (62 years) than patients with *C9orf72* or *GRN* mutations; however, this can also range widely.<sup>25</sup> In terms of clinical presentation, patients with the *MAPT* mutation may have less apathy but more prominent motor symptoms (most commonly levodopa-unresponsive parkinsonism) than other genetic variants. Another distinguishing feature is impaired language, particularly errors in word comprehension and object naming.<sup>25</sup> However, the phenotype even within a single family carrying a single *MAPT* mutation can vary, with some members carrying a clinical diagnosis of bvFTD and other members corticobasal syndrome.

An important point arising from the case of Ms A is that patients with a *MAPT* mutation can present with psychosis, a symptom that has been more commonly associated with the *C9orf72* and, to a lesser extent, *GRN* mutations.<sup>25</sup> Thus, *MAPT* should be included, along with *C9orf72* and *GRN*, as part of any genetic testing panel for patients with suspected FTD psychosis. Structural brain imaging characteristics may help point toward a *MAPT* mutation, which may show more prominent temporal lobe than frontal lobe atrophy on MRI than do other genetic mutations.<sup>25</sup>

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Under physiological conditions, the tau protein plays an important role in microtubule stabilization. Different *MAPT* mutations influence the tendency of tau to become hyperphosphorylated and form insoluble neurofibrillary tangles, thus leading to cytoskeletal instability and neurotoxicity to differing extents.<sup>36,42</sup> The most common mutation (P301 L), found in Ms A, is a missense point mutation in exon 10, which reduces the ability of the tau protein to interact with microtubules.<sup>43,44</sup> However, despite the knowledge afforded by these familial mutations, the amount and type of tau pathology do not yet appear to predict a single clinical syndrome with high accuracy (eg, bvFTD vs CBS vs PSP), suggesting that additional factors may influence the clinical expression of disease.

## Recommendations for the Psychiatrist

For patients with any red-flag features, including new-onset psychosis over the age of 40, a symptom course that is refractory to treatment or progressive over time, and/or a strong family history of neurodegenerative disease, we recommend that an elemental neurologic examination be performed. In agreement with recent recommendations regarding the importance of the physical examination in psychiatry,<sup>45,46</sup> we suggest that even a brief neurologic examination, including evaluation for abnormal eye movements, frontal release signs, parkinsonism, and cerebellar and upper or lower motor neuron signs, could provide important early diagnostic information. A 3-minute neurologic examination for the psychiatrist is described by Garden.<sup>47</sup> In addition, structural brain imaging with MRI or CT should be obtained to look for focal atrophy and exclude other structural abnormalities that may account for the patient's presentation. If diagnostic uncertainty remains, we recommend prompt referral to a clinic specializing in dementia, where a detailed cognitive examination, further neuropsychiatric

testing, and functional brain imaging can be pursued, as indicated. Functional brain imaging, for example with FDG-PET, provides additional diagnostic sensitivity for bvFTD (90%); however, results from this neuroimaging technique are associated with lower specificity (68%) because patients with primary psychiatric diagnoses can also exhibit regional hypometabolism, predominantly in the bilateral frontal and temporal lobes.<sup>48</sup> However, in our experience, it would be exceedingly rare for a patient with a primary psychiatric diagnosis to exhibit the profound hypometabolic activity observed on Ms A's scan.

## CONCLUSIONS

Frontotemporal dementia should be on the differential diagnosis for any patient presenting with new-onset psychosis and behavioral changes in mid to late adulthood. A detailed neurologic and psychiatric family history should be obtained, and specific features of aberrant behaviors elicited, such as progressive personality change, uncharacteristic socially inappropriate behavior, or loss of empathy. A brief neurologic examination (including gait, eye movements, cerebellar examination, muscle tone, and reflexes) should be performed and structural brain imaging obtained. Should concerning features in the history, examination, or imaging be present, early referral to a clinic specializing in neurodegenerative disease/dementia is recommended. This report has several limitations. It includes only a single case that was retrospectively constructed, which may restrict its generalizability across the entire FTD spectrum. However, this case serves to highlight that the *MAPT* mutation can be associated with psychosis in FTD, and investigation of this mutation may contribute to the understanding of the neuroanatomical circuits and cellular mechanisms underlying psychiatric symptoms in neurodegenerative disease.

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## POSTTEST

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1. Mr Hollingswood, a 64-year-old man, is brought to your psychiatric office by his wife for a change in behavior that has slowly progressed over the last year. Mrs Hollingswood is concerned that her husband is depressed, as he no longer participates in his usual golf outings and does not appear to enjoy spending time with friends. Occasionally he says inappropriate things in public, which is very uncharacteristic. She tells you that the patient always used to follow a very healthy diet but over the last 6 months has insisted on eating 3 to 5 chocolate-covered donuts after every meal and has gained 24 pounds. Which feature of this history raises the most specific concern for a possible neurodegenerative etiology for this patient's symptoms?
  - a. Inappropriate comments in public
  - b. Patient's age
  - c. Loss of enjoyment in activities
  - d. Change in eating habits
  
2. Rosalita is a 45-year-old woman brought to your psychiatric office by her mother for uncharacteristic behavior. The patient has bipolar disorder, which was diagnosed 5 years ago, but over the last year, her medication has seemed to become less effective. Rosalita was fired from her job in accounting for making errors and for argumentative behavior. She now spends much of the day drawing small doodles in a notepad and does not appear to care about the emotional or financial burden that this places on her family. What is the most appropriate *next* step in clinical assessment?
  - a. Order genetic testing for mutations associated with bvFTD
  - b. Gather a detailed neurologic and psychiatric family history
  - c. Order an FDG-PET scan
  - d. Refer to a specialist dementia clinic
  
3. What are the 3 most common causative gene mutations in FTD?
  - a. *huntingtin*, *C9orf72*, *MAPT*
  - b. *FXN*, *progranulin*, *C9orf72*
  - c. *MAPT*, *C9orf72*, *progranulin*
  - d. *MAPT*, *PRKN*, *PSEN1*

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