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## Clinicopathological Study of Patients With *C9ORF72*-Associated Frontotemporal Dementia Presenting With Delusions

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### Abstract

**Background**—Several clinical studies point to a high prevalence of psychotic symptoms in frontotemporal dementia associated with *C9ORF72* mutations, but clinicopathological studies addressing the association between *C9ORF72* mutations and delusions are lacking.

**Method**—Seventeen patients with pathologically proven frontotemporal lobar degeneration (FTLD) associated with *C9ORF72* mutations were identified from Neurodegenerative Disease Brain Bank. Of the 17 cases with *C9ORF72* mutation, 4 exhibited well-defined delusions. The clinical history, neurological examination, neuropsychological testing, neuroimaging analysis, and postmortem assessment of the patients with delusions were evaluated and compared with the other cases.

**Result**—The content of the delusions was mixed including persecution, infidelity, and grandiosity. All cases showed parkinsonism; voxel-based morphometry analysis showed greater precuneus atrophy in patients with delusions than those without delusions. All 4 had unclassifiable FTLD with TAR DNA-binding protein inclusions, with characteristics of both type A and type B. Three cases had additional  $\tau$  pathology and another had  $\alpha$ -synuclein pathology.

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**Conclusion**—*C9ORF72* carriers with well-defined delusions likely associated with additional pathologies and parietal atrophy in neuroimaging. Patients presenting with middle-aged onset of delusions should be screened for *C9ORF72* mutations, especially if family history and parkinsonism are present.

### Keywords

*C9ORF72*; neurodegeneration; frontotemporal dementia; delusion; neuropathology; neuroimaging

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### Background

Frontotemporal dementia (FTD) is the second most common cause of early onset dementia and is characterized by changes in personality, behavior, or language.<sup>1,2</sup> Frontotemporal dementia is associated with neurodegeneration of the frontal and temporal lobes and occurs in both sporadic and genetic forms. A hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*) was recently reported as the most frequent genetic cause of behavioral variant FTD (bvFTD), FTD with motor neuron disease (FTD-MND), and amyotrophic lateral sclerosis (ALS).<sup>3,4</sup> Several clinical studies on patients with *C9ORF72* mutation highlight a high prevalence of psychotic features (delusions and hallucinations) associated with this mutation.<sup>5–8</sup>

Delusional symptoms are frequently linked to schizophrenic psychoses but are also observed in neurodegenerative diseases.<sup>9</sup> It has been suggested that the dysfunction of dopaminergic neurons projecting to the striatum contributes to delusion formation in patients with schizophrenia<sup>10</sup>; however, other hypotheses also have been proposed for the neurobiological basis of delusions with schizophrenia. Delusions also have been linked to frontal cortex dysfunction causing deficits in cognitive control or executive functions. This may result in premature probabilistic reasoning bias and/or lack of top-down control leading to release of other brain areas and manifesting as delusions.<sup>11,12</sup>

Although patients with FTD show severe frontal, temporal, and basal ganglia dysfunction, delusions have been considered a relatively rare feature of FTD,<sup>13–15</sup> and the presence of delusions in FTD has ranged from 2.3% to 12.7% in clinical cohorts.<sup>15,16</sup> However, delusions appear to be more common in patients with *C9ORF72* mutations: 50% in 32 cases<sup>5</sup> and 42% in 14 cases.<sup>6</sup> The anatomical underpinnings of delusions in FTD remain unclear, and cases with *C9ORF72* mutation may contribute to an understanding of the neurobiological basis of delusions.

Here, we report the clinical, neuropsychological, neuroimaging, and neuropathological findings of patients with FTD and delusions who, at autopsy, showed FTD with TAR DNA-binding protein inclusions (FTLD-TDP) associated with the *C9ORF72* mutation, who had delusions along the clinical course of their disease.

### Method

All 17 patients belonging to the University of California, San Francisco (UCSF) Neurodegenerative Disease Brain Bank, with a neuropathological diagnosis of FTLD-TDP

due to *C9ORF72* expansion were included. Diagnosis of *C9ORF72* expansion was made by genetic testing and confirmed by the finding of p62-positive/TDP-43-negative intraneuronal inclusions in cerebellum and hippocampus.<sup>17</sup> All patients and their informants signed an institutional review board-approved research consent form to participate in the study. Patients were seen at the Memory and Aging Center at the UCSF between 2004 and 2010 and had undergone at least 1 neurological evaluation, including extensive neuropsychological assessment and neuroimaging. Medical history including psychiatric history is confirmed independently by neurologist and research nurse through caregiver interviews using structured questionnaires. Of the 17 patients identified as *C9ORF72* expansion positive, 4 of them presented with well-defined delusions during the disease evolution. Delusion was defined according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) as “a false belief based upon an incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary, the belief is not one ordinarily accepted by other members of the person’s culture or subculture.”<sup>18</sup> Clinical data collected included the time of onset of delusions in relation to other symptoms, previous psychiatric history, the presence of associated hallucinations, and the phenomenological content of the delusions. Patients’ demographic characteristics are summarized in Table 1.

### Neuropsychological Data

The patients underwent a detailed neuropsychological battery during their visits. General intellectual function was assessed using the UCSF screening battery as described elsewhere.<sup>19</sup>

### Genotyping

The presence of expanded GGGGCC hexanucleotide repeats in *C9ORF72* was detected using the repeat-primed polymerase chain reaction (PCR) reaction as described elsewhere.<sup>3</sup> The PCR products were run on an ABI3730 DNA analyzer and analyzed using the Peak Scanner Software.

### Neuroimaging

Each patient was scanned with a structural magnetic resonance imaging (MRI) on a 1.5- or 3-T scanner within 1 year of the first UCSF visit. Structural T1-weighted images were preprocessed for voxel-based morphometry (VBM) using Diffeomorphic Anatomical Registration Through Exponentiated Lie running in Statistical Parametric Mapping 8 with MatLab. Group comparison of VBM gray matter images was conducted between 4 patients having pathologically proven FTLTDP with *C9ORF72* mutation who had delusions and remaining 13 patients who did not.

### Neuropathology

All patients were subjected to an extensive dementia-oriented postmortem assessment at UCSF or at the University of Pennsylvania, following a standard protocol described previously.<sup>20,21</sup> The brains were procured within 18 hours postmortem. The majority of the

brains was cut into 8- to 10-mm thick coronal slabs and alternately fixed, in 10% neutral buffered formalin for 72 hours, or rapidly frozen; the remaining were hemi-sectioned sagittally with 1 hemisphere fixed in 10% neutral-buffered formalin and the other rapidly frozen. Tissue blocks covering dementia-related regions of interest were dissected from the fixed slabs, and basic and immunohistochemical stains were applied following standard diagnostic procedures developed for patients with dementia.<sup>21</sup> All immunohistochemical runs included positive control sections to exclude technical factors as a cause of absent immunoreactivity. The FTLD-TDP subtyping followed the current “harmonized” nomenclature.<sup>22</sup> All cases were also screened for p62-positive/TDP-43-negative intraneuronal inclusions, pathognomonic markers of *C9ORF72* expansion in amygdala,<sup>10,23</sup> a brain area involved in different kind of delusions. Finally, the presence of additional overlapping neurodegenerative disorders was compared between the 2 groups.

## Results

### Case Presentation

**Case 1**—Mr A, a right-handed man, presented first symptoms at the age of 56. Previously psychiatrically healthy, he became fixated on specific topics, developed paranoia about his neighbors and became frightened by them when they performed yard work. As the disease progressed he also became suspicious of close friends. At the age of 58, he vocalized that he felt his life was threatened and that his wife had been replaced by a demon. He did not have any self-awareness that these thoughts were irrational and false. He was seen by a psychiatrist and a neurologist at the age of 60, after he made obscene gestures to a woman and propositioned his neighbor’s wife. He was started with quetiapine first at 25 mg, increasing to a maximum of 150 mg. It reduced his fears, especially about his wife; however, he progressively became more fearful of others around him.

At the age of 61, he became quieter, mellower, and progressively slower. Fluoxetine started at that time reduced his inappropriate behaviors in public. He habitually strolled around the house and exhibited motor restlessness. He developed increased interest in chocolate. His personal grooming declined. At the age of 62, he went out alone and returned after 8 hours sunburned and dehydrated; he reported that he had been looking for his friend who was actually living in another state.

Mr A was evaluated at the UCSF Memory and Aging Center at the age of 62. He demonstrated utilization behavior and perseverations and was impulsive and easily distracted. On neurological examination, he had mild cogwheeling in the arms, mild to moderate hypomimia, and mild bradykinesia. Cognitive testing revealed deficits in all domains except for copying tasks and language. His working memory and executive function were most severely impaired (see Table 1). Past medical history was unremarkable for psychiatric symptoms. His family history was negative for dementia. His medications included fluoxetine (30 mg) and quetiapine (150 mg). Magnetic resonance imaging revealed bilateral frontal atrophy. He died suddenly by choking at the age of 64, 8 years after the onset of his symptoms.

Neuropathological examination demonstrated brain atrophy (weight: 1170 g), with most severe degenerative changes involving the dorsal and opercular frontal cortices, as well as the dorsal striatum. Microscopic examination revealed hippocampal sclerosis. Immunohistochemical analysis showed unequivocal evidence of FTLD-TDP, featuring TDP-43 immunoreactive inclusions in many cortical regions examined, especially the dorsal and opercular frontal regions. TDP-43 pathology was consistent with FTLD-TDP, with features of type A and type B.<sup>22</sup> Argyrophilic grain disease (AGD), a 4-repeat tauopathy, was noted in limbic areas and orbital frontal cortex.

**Case 2**—Mr B, a left-handed man started to believe that his wife was cheating on him around the age of 40. This delusion spontaneously remitted after several years, however, it reemerged at age of 62. The couple underwent marriage counseling, but the delusion did not remit again. Concomitantly, he developed difficulty in completing his usual tasks, such as fixing light sockets or cars. Subsequently, he had difficulty in understanding directions and conversation. Other language problems included poor repetition and reduction in speech. He became apathetic but showed increase in appetite. He had no awareness of his cognitive deficits.

Mr B was evaluated at the UCSF at the age of 65 years. On neurological examination, language was abnormal with evidence of paraphasic errors and some difficulty with reading. He exhibited parkinsonism with masked faces and reduced blink frequency; however, there was no increased tone at rest, no tremor, and he walked without difficulty. Verbal and visual memories were moderately impaired, but visuospatial abilities remained normal. Neuropsychological tests confirmed the language deficits and showed moderate executive dysfunction (for details see Table 1). Past medical history was unremarkable. His medications were donepezil and fexofenadine (60 mg). Family history was unknown because he was adopted. Structural imaging showed generalized atrophy, with frontal predominance.

The parkinsonism, executive loss, and memory dysfunction all progressed, followed by the appearance of progressive apathy. At the age of 68, he had difficulty in swallowing, increased tone in all extremities, upper limb fasciculations, and a prominent jaw jerk. He died from pneumonia at the age of 70, 7 years after the onset of symptoms.

Fresh brain weight was 1066 g. Neuropathology showed atrophy with most severe degenerative changes in the frontal lobes, in particular, the anterior orbital and inferior frontal gyri and the anterior cingulate cortex. Immunohistochemical analysis showed FTLD-TDP with features of type A and type B, consistent with unclassifiable FTLD-TDP. Co-occurring 4-repeat  $\tau$  pathology was seen and characterized by deposition of neurofibrillary tangles and astrocytic inclusions mostly in limbic areas, inferior temporal gyrus, and in precentral gyrus. This tauopathy did not fit into existing criteria for a specific entity and was classified as an atypical tauopathy.

**Case 3**—Mr C, a right-handed man, presented with problems in his management skills and an increased number of business-related judgment errors at the age of 46. Three years later, he had uncharacteristic loss of empathy for his wife who was hospitalized at that time. At

the age of 51, he closed his business and found a job for a local manager of a discount store, but he soon started to have trouble at work. He had the grandiose delusion that “they were saving a large store for him.” He became socially withdrawn and spent more time watching television. He was fired at the age of 53 years due to his inability to keep the store in good condition, but his delusion continued.

Also around that time, he became emotionally and physically more distant from his wife, refused to do jobs around the house, and showed increasing apathy. He exhibited other strange behaviors such as sneaking into the home and peeking around the corner at his wife. He maintained the grandiose delusion that someone was saving highly paid jobs for him. He became more rigid and inflexible about his schedule at home, showing anxiety if meals were not served on time. He became irritable and developed environmental dependence playing with items placed in front of him and mimicking other people’s actions. Also, he developed compulsive symptoms such as repetitive checking of the temperature. Later on, he inappropriately greeted strangers and developed a preference for sweets.

Mr C was evaluated at the UCSF at the age of 54 years. On neurological examination, he had a fine resting and action tremor on the left hand. Tone was increased in the arm with evidence of paratonia on the left greater than right. Gait changes were notable for a decreased arm swing on the left. He had no awareness of his deficits or delusion. He performed poorly on neuropsychological assessment of frontal and executive function with relatively intact language and visuospatial function (for details see Table 1). Past medical history was significant for hypercholesterolemia, borderline hypertension, and a loss of hearing after a motor accident. Family history was significant for a strong history of autosomal-dominant dementia with parkinsonism in many relatives. His mother died at age 60 with similar symptoms of dementia and parkinsonism, but she did not have an autopsy. The patient’s MRI showed mild frontal lobe and striatal atrophy.

He died of pneumonia at the age of 59, 13 years after the onset of his symptoms. Neuropathological examination showed general atrophy and marked ventricular dilatation. The fresh brain weighed 1050 g. TDP-43 immunopositive neuropil threads were found in multiple regions of the central nervous system and features were consistent with unclassifiable FTLT-DTP. In addition, he showed AGD restricted to limbic area.

**Case 4**—Mr D, a right-handed man, started to exhibit social withdrawal and executive dysfunction in his late 30s. He became reluctant to join in conversations, completed tasks more slowly, and had difficulty concentrating and multi-tasking. In his 40s, he became careless and failed to finish his tasks at work. By his late 40s, he became even slower and less talkative. At the age of 54, he developed auditory hallucinations and delusions, believing that various “friends” were talking to him and to each other through TV. Also, he thought that people were watching him through the bathroom mirrors. He believed he was a “sex God” and that various neighbors dated him. He also believed that an imposter replaced his physician. He occasionally accused his wife of infidelity. He exhibited less emotion but inappropriately laughed at serious TV shows. At the age of 56, his speech output declined and his response time became delayed, he walked more slowly. He accompanied his family to work but did little work by himself. Table manners deteriorated and he ate enormous

quantities of food voraciously in a messy fashion, including eating food off the floor. He also became apathetic.

Mr D was evaluated at the UCSF Memory and Aging Center at the age of 57. His affect was flat, his speech was effortful, and he was perseverative, stimulus-bound, and demonstrated poor insight. His neurological examination showed jerky ocular pursuit, increased arm tone with cogwheeling in the left greater than right, slowed finger taps, fasciculations throughout the arms and legs, a fine postural tremor of the outstretched hands, and a slow stooped gait. His examination was also notable for delayed response times, marked utilization behavior, and inability to perform tasks. Neuropsychological testing showed moderate impairments in episodic memory encoding and consolidation; impaired language comprehension, verbal agility, and repetition; marked executive impairment; and impaired abstract reasoning, with relatively spared visuospatial skills (see Table 1).

His past medical history includes hypertension, ankylosing spondylitis, and prostate resection. Regarding family history, his mother was diagnosed with Parkinson disease dementia and had a brain autopsy showing neuronal loss in the substantia nigra without Lewy bodies. His medications included donepezil (10 mg), quetiapine (800 mg), divalproex sodium (500 mg), and trazodone (300 mg). His MRI showed moderate bilateral lateral parietal atrophy as well as bifrontal atrophy, vermian atrophy, and bilateral caudate atrophy.

He died at 58 years of age. The fresh brain weighed 1340 g. Neuropathological examination showed atrophy with most severe degenerative changes involving the prefrontal and perirolandic cortices, substantia nigra, and lower motor neurons of the brainstem and spinal cord. Immunohistochemical analysis showed an unclassifiable FTLD-TDP with frequent granular or compact neuronal cytoplasmic inclusions, in superficial and deep layers of affected cortices, subcortical, and brainstem and spinal cord structures. Although primary motor cortex showed TDP-43 pathology, no corticospinal tract demyelination was observed, making motor neuron disease a more appropriate pathological characterization than ALS. In addition, Lewy body pathology was observed in the dorsal motor nucleus of the vagus, corresponding a very early Parkinson disease Braak stage I.<sup>24</sup>

All the 17 cases fulfilled the most recent bvFTD clinical consensus criteria.<sup>2</sup> Among the remaining 13 cases lacking well-defined delusions, 1 case showed confabulation that disappeared within 2 years from its appearance. The other cases did not show any other psychotic symptoms. Seven cases had motor neuron symptoms to variable extent, and 1 case had family history of ALS. Two cases have parkinsonism. Mean age at disease onset is 60.4 years old and mean age at death is 68.2 years old. Neuropathologically, in addition to TDP-43 pathology, 3 nondelusional cases had additional non-Alzheimer disease (AD)  $\tau$  pathology.

### Neuroimaging Results

The VBM analysis showed greater atrophy in left parietal precuneus area at the level of uncorrected  $P < .005$  in the 4 cases with delusions compared with other 13 cases without delusions (Figure 1). In the small volume correction analysis for left parietal precuneus area, the atrophy was also significant at a Family Wise Error-corrected  $P$  level of  $<.05$ .

## Neuropathological Analyses

p62-Positive/TDP-43-negative characteristic inclusions in the amygdala were seen in most of the 17 cases and no notable difference was found between the 2 groups. Among the 13 patients without delusions, 3 showed overlapping AGD restricted to limbic areas and 1 showed an atypical tauopathy.

## Discussion

We report the clinical, neuropsychological, neuroimaging, and neuropathological findings in 4 cases having FTLT-DTP with delusions associated with *C9ORF72* mutations. *C9ORF72* mutation cases account for 12% of familial and 3% of sporadic FTD cases.<sup>3,6</sup> Pathologically, *C9ORF72* mutations are associated with FTLT-DTP, type B,<sup>25</sup> as well as type A,<sup>5</sup> or a unclassifiable type that features both type A and type B characteristics. Additionally, depositions of ubiquitin or p62-positive/TDP-negative characteristic inclusions are found in cerebellum, hippocampus, and thalamus. These inclusions contain dipeptide-repeat proteins translated in an ATG-independent fashion from the hexanucleotide repeats and are pathognomonic of *C9ORF72* expansion. On structural imaging, in addition to atrophy in frontal, insular, and anterior temporal areas commonly affected in bvFTD, patients with *C9ORF72* mutations show atrophy in parietal, occipital, cerebellar, and thalamus.<sup>6-8,26</sup>

Psychotic features (particularly delusions) are seen in up to 50% of *C9ORF72* mutation carriers,<sup>5,6</sup> a much larger frequency than in other FTLT types.<sup>15</sup> Therefore, the distinctive anatomical and neurochemical features of *C9ORF72* may reveal insights into the neurobiological basis of psychosis.<sup>5-8,27</sup>

Before the discovery of *C9ORF72* mutation, delusions were thought to be a relatively rare symptom in patients with FTD. Some of these reports show patients with younger onset FTD who were diagnosed with psychotic disorders before the dementia onset.<sup>28,29</sup> Paranoid delusions were the most frequent symptoms in these series. Other case reports showed complex delusions,<sup>30</sup> grandiose delusions,<sup>31</sup> and Cotard delusions.<sup>32</sup> Snowden et al reported that most of the delusions with their *C9ORF72* mutation cases were somatic delusions such as alterations in temperature perception, preoccupation with bowel movements, and leg pain,<sup>5</sup> which was different from our series showing various delusions.

Delusions are a relatively common symptom in AD and dementia with Lewy bodies (DLBs) than FTD. A review article reported a median prevalence of 36% (9.3%–63%) for delusions in AD, most involving delusion of theft, which can be included in the persecutory delusion category.<sup>10,33</sup> Studies focusing on the underlying biological background of delusions in AD have suggested that persecutory delusions occur early in the disease course and are associated with neurochemical and neuropathological changes in frontostriatal and temporal-limbic circuits.<sup>34</sup> On the other hand, delusional misidentification in AD is associated with greater global cognitive deficits and advanced limbic pathology.<sup>34</sup> In patients with DLB, hallucinations are the most frequent psychotic symptoms, with a prevalence from 63% to 78%, followed by misidentifications (56%) and paranoid delusions (25%–28%).<sup>35,36</sup>



Paranoid or persecutory delusions in patients with DLB were hypothesized to be associated with dysfunction in the frontal cortex in addition to occipital cortex dysfunction.<sup>35</sup>

Several studies on schizophrenia suggest that development of delusion is associated with a dysfunction of dopamine regulation in the ventral striatum, which leads to aberrant assignment of salience to stimuli.<sup>11,37</sup> Also, dysfunction in brain areas associated with executive behavioral control such as the prefrontal cortex (PFC) may lead to alterations in affective state, disinhibition, and ways of thinking that might increase the risk of delusion formation.<sup>38</sup> Prefrontal cortex was found to be implicated in prediction-error processing,<sup>39,40</sup> and reality monitoring tasks,<sup>41</sup> structural volume loss in the PFC correlates with symptoms of delusion.<sup>42</sup> Thalamic dysfunction may also result in reduced ability to adjust sensory responsiveness to ongoing behaviors in patients with schizophrenia.<sup>43</sup> Psychosis in schizophrenia is associated with source-monitoring deficits whereby self-initiated behaviors become attributed to outside sources, and one of the functions of the thalamus is to adjust sensory responsiveness in accordance with the behavioral contextual cues. Lower numbers of cerebellar Purkinje neurons also seen in association with psychosis in patients with schizophrenia and bipolar disorder.<sup>44</sup> The decreased synthesis and release of reelin from cerebellar granule cells could be associated with the pathophysiology that regulate GABAergic neuron dysfunction in the cerebellum of these patients.

There are a variety of neurological disorders strongly associated with psychosis. Often, psychosis occurs in association with temporal lobe dysfunction and is seen in patients with temporal lobe epilepsy, herpes simplex encephalitis, and autoimmune encephalitis that target the temporal lobes.<sup>45-47</sup> Disorders of the basal ganglia and brain stem have a higher prevalence of delusions than expected and psychosis as is seen with Huntington disease, Fahr syndrome, and Wilson disease.<sup>48-50</sup> These results suggest that various neurobiological substrates may predispose to delusions.

Why, then did the 4 cases having FTD with *C9ORF72* mutations presented here exhibit delusions? Mahoney et al hypothesize that dysfunction of thalamic and cerebellar projections could be related to the neuropsychiatric features associated with these cases with *C9ORF72* mutation, including hallucinations and delusions.<sup>7</sup> This thalamic and cerebellar pathology is relatively unique to cases having FTD with *C9ORF72* mutation. Although this hypothesis remains appealing, it is important to note that the other 13 cases in our series without delusions also showed changes in thalamus and cerebellar structures.

Thus, based on the above-mentioned knowledge of delusions in other neurodegenerative disorders and schizophrenia, we hypothesized that in addition to PFC dysfunction that is common in patients with FTD, other regions might have contributed to development of delusions in our series of patients.<sup>23</sup> The VBM analysis showed more atrophy in left parietal precuneus area in patients with delusion compared to the nondelusional patients. Although the result is significant even after correction, our sample is small and the time gap latency between delusion onset and MRI acquisition should be taken into consideration. This parietal involvement has also been reported in other *C9ORF72* mutation series.<sup>3,6</sup> Precuneus is involved in discriminating self-relevant information from self-irrelevant information and in retrieving source memories.<sup>51</sup> Therefore, in addition to executive dysfunction, failing to

discriminate between self-relevant and self-irrelevant information and to retrieve the information source must make the patients hypersensitive to all information. Although the precuneus is very vulnerable to AD and to associate with delusions in patients with AD,<sup>52–54</sup> such delusions are typically delusions of theft, rather than bizarre delusions as observed in our *C9ORF72* mutation series. Thus, we speculate that degree of frontal involvement may contribute to the variety of delusions in our cases.

Downey et al suggested a distributed anatomical correlate in thalamo-cerebello-cortical circuitry including parietal cortex as a key terminus to explain altered body schema processing in patients with *C9ORF72*-related FTD.<sup>55</sup> Our findings corroborate their observations. In fact, their results provide a useful framework for interpreting our findings, in particular the candidate mechanism of self/non-self-regulation. However, as they point out, the spectrum of neuropsychiatric phenomena attributable to altered body schema processing is potentially much wider than delusions and hallucinations. Thus, our results have to be interpreted causally. Although precuneus changes may be neuroanatomical basis underlying delusions in patients with *C9ORF72*-related FTD, it is not possible to rule out a broader change in network vulnerable to this disease.

Neuropathological information revealed that 3 of the 4 patients with delusion presented an overlapping tauopathy (2 AGD and 1 atypical tauopathy). This 75% frequency is significantly higher than frequency (23%) of tauopathies in nondelusional cases (3 of 13) and may indicate an association. Patients with AGD are prone to present persecutory delusions.<sup>56,57</sup> Thus, the mixture of  $\tau$  pathology and FTLT-DTP pathology, especially in frontal cortex and ventral striatum, may have contributed to the clinical picture of delusions. In case 4, there was an additional Lewy body pathology. Lewy body pathology is associated with visual hallucinations, which were present in this patient, but the link is weakened because Lewy body pathology was restricted to the dorsal motor nucleus of the vagus nerve. None of the previous 3 patients showed hallucinations in any modality. This may indicate a difference in pathological background between delusions and hallucinations. However, Snowden et al reported that among 4 pathological confirmed cases with psychosis, 1 had  $\tau$  pathology without TDP-43 pathology and the others had TDP-43 pathology without accompanying  $\tau$  pathology.<sup>5</sup> Synergistic effects of FTLT-DTP and certain tauopathies in causing delusions deserve investigation in a larger cohort, once it becomes available.

Although postmortem examination can potentially identify the underlying basis of neuropsychiatric symptoms, its power is limited by the long lag between the onset of delusions and expiration. It is possible that the advance stage of the disease by the time of passing precludes identification of more subtle differences between patients with specific symptoms. It might explain why we could not find any distinctive pathological findings in parietal and precuneus in the delusional group. This also supports the hypothesis that precuneus can be a component of a network that may show differential vulnerability.

Interestingly, all of our 4 cases with delusion had parkinsonism, compared to 2 of the 13 nondelusional cases. However, iatrogenic parkinsonism cannot be discarded as 2 cases with delusion (case 1 and case 4) and 1 nondelusional case were treated with atypical antipsychotics. This may indicate higher sensibility of patients with delusion to dopamine

dysfunction, both associated to delusions and to parkinsonism. Association between delusions and parkinsonism in cases with *C9ORF72* mutation suggests an overlapping vulnerability of certain brain areas to both Lewy body disease and *C9ORF72* mutation-related pathology, even though both have different abnormal protein deposition signatures. One clinicopathological study with 68 patients shows a greater loss of dopaminergic neurons in the substantia nigra of patients with *C9ORF72* mutations than those without.<sup>58</sup> Parkinson disease itself is not associated with *C9ORF72* mutations.<sup>59</sup>

Finally, delusions in our series often preceded the behavioral and cognitive disabilities. This observation may increase the likelihood of misdiagnosis and delayed appropriate treatment. Cases with FTD are often diagnosed as having atypical psychosis such as late-onset schizophrenia or late-life depression with psychotic features.<sup>60</sup> Indeed, patients with FTD receive a prior psychiatric diagnosis significantly more often than patients with AD (FTD, 50.7% vs AD, 23.1%).<sup>61</sup> Clinicians need to consider the possibility of this mutation and assess the family history when a patient presents with middle-aged onset delusions.

## Conclusion

All of our FTD series with the *C9ORF72* mutation presenting delusions had some additional pathology and parkinsonism, which suggests a common anatomy or neurochemistry underlying these delusions. The VBM analysis suggests relationship between precuneus and appearance of delusions, although the number of cases is small enough to draw conclusions. Further work with larger cohorts will be required to investigate the biological correlates of delusions in this genetic FTD group. Their presentations of this mutation carrier are heterogeneous and may be at higher risk of being misdiagnosed with primary psychosis. Clinicians need to consider the possibility of this mutation and assess the family history when a patient presents with middle-aged onset delusions.

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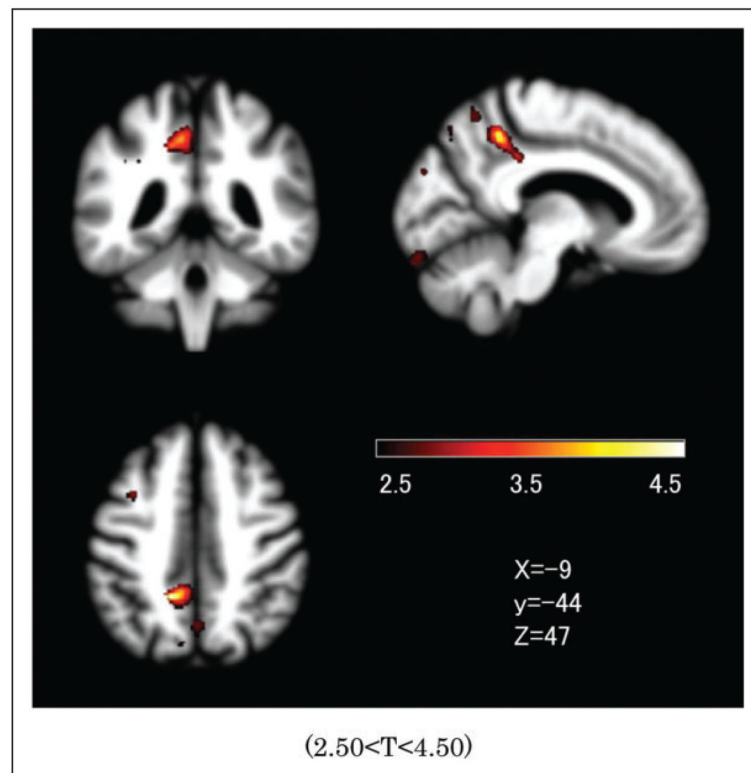
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**Figure 1.** T-score map showing regions greater atrophy in 4 *C9ORF72* mutation carriers with delusions compared to 13 patients without delusions (2.50 < T < 4.50).

**Table 1**

Clinical, Neuropsychological, and Brain Imaging Features of 4 Cases.

Clinical diagnosis	Right-Handed Male	Right-Handed Male	Right-Handed Male	Right-Handed Male
	bvFTD	bvFTD	bvFTD	bvFTD
Disease onset	56	62	46	Late 30s
Initial symptom	Perseveration	Executive dysfunction	Executive dysfunction	Apathy
Delusion onset	58	40s	54	54
Delusion content	Paranoia about neighbors/Capgras	Infidelity	Grandiose	Paranoia/grandiose/Capgras
Prognosis of delusion	Progressive	Continued	Continued	Slight improve with medication
Medication for delusion	Quetiapine	None	None	Quetiapine
Behavioral symptoms	Sexually inappropriate	Reduction in motivation	Apathy/lack of interest	Hyperorality
	Roaming	Increase in appetite	Rigid inflexible in schedule	Apathy
	Stereotypy		Irritable	Utilization behavior
	Loss of personal hygiene		Environmental dependent	Loss of personal hygiene
	Preference for sweets		Preference for sweets	
Family history	Negative	Unknown (adaption)	Mother/maternal family	Mother
Neuropsychological examination				
Mini-Mental State Examination	17/30	20/30	28/30	19/30
CVLT-Short Form <sup>a</sup>	2-3-3-2-0-0	5-4-5-6-4-3	6-6-6-6-6-7	2-3-4-4-3-2
Benson Figure Copy and Recall	14/17 and 6/17	16/17 and 8/17	16/17 and 9/17	16/17 and 8/17
Digit span Forward/Backward	5/2	7/2	7/2	6/3
Stroop inhibition	Unable	9 with 19 uncorrected errors	21 with 5 uncorrected errors	6 with 11 uncorrected errors
Modified Trails, s	Unable	62 s	Unable	Unable
Boston Naming Test	11/15	11/15	13/15	15/15
Phonemic and Category fluency	3 and 5	2 and 6	6 and 13	2 and 2
Geriatric Depression Scale	12	4	0	15
Neuropsychiatric Inventory	45	8	20	52
Delusion Scale	8	2	2	12
Unified Parkinson Disease Rating Scale	9	10	–	6
MRI imaging <sup>b</sup>				
Dorsolateral frontal atrophy	++	+	+	+
Medial frontal atrophy	++	+	–	++
Orbitofrontal atrophy	++	–	+	+
Striatum atrophy	+	+	+	+
Parietal atrophy	++	+	+	++
Cerebellum atrophy	+	–	–	–
Age at death	64	69	60	58



	Right-Handed Male	Right-Handed Male	Right-Handed Male	Right-Handed Male
Clinical diagnosis	bvFTD	bvFTD	bvFTD	bvFTD
Main pathological changes	FTLD-TDP, unclassifiable argyrophilic grain disease	FTLD-TDP, unclassifiable atypical tauopathy	FTLD-TDP, unclassifiable argyrophilic grain disease	FTLD-TDP, unclassifiable Lewy body pathology

Abbreviation: bvFTD, behavioral variant frontotemporal dementia; CVLT, California Verbal Learning Test; FTLD-TDP, Frontotemporal Lobar Degeneration with TAR DNA-binding protein inclusions; MRI, magnetic resonance imaging.

<sup>a</sup> California Verbal Learning Test, 4 times registration, 30-second recall, and 10 minutes recall of 9 words.

<sup>b</sup> + means mild atrophy and ++ means severe atrophy, based on expert neurologist who is blind to patients' clinical information.

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