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Clinico-pathological study of patients with C9ORF72 associated frontotemporal dementia presenting with delusions

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Manuscripts

Clinico-pathological 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 (FTD) associated with *C9ORF72* mutations, but clinico-pathological studies addressing the association between *C9ORF72* mutations and delusions are lacking.

Method: Seventeen pathologically proven frontotemporal lobar degeneration subjects associated with C*9ORF72* mutations were identified from Neurodegenerative Disease Brain Bank. Four of 17 *C9ORF72* mutation cases 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 four had unclassifiable FTLD-TDP, with characteristics of both type A and type B. Three cases had additional tau pathology and another had α-synuclein pathology.

Conclusion: *C9ORF72* carriers with well-defined delusions likely associated with additional pathologies and parietal atrophy in neuroimaging. Patients presenting with middle age 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

Running Head:

Delusions in *C9ORF72* associated FTD

1 **Background**

2   Frontotemporal dementia (FTD) is the second most common cause of early

3 onset dementia and is characterized by changes in personality, behavior or

4 language [1,2]. FTD is associated with neurodegeneration of the frontal and

5 temporal lobes and occurs in both sporadic and genetic forms. A hexanucleotide

6 repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*) was

7 recently reported as the most frequent genetic cause of behavioral variant FTD

8 (bvFTD), FTD with motor neuron disease (FTD-MND) and amyotrophic lateral

9 sclerosis (ALS) [3,4]. Several clinical studies on *C9ORF72* patients highlight a

10 high prevalence of psychotic features (delusions and hallucinations) associated

11 with this mutation [5-8].

12   Delusional symptoms are frequently linked to schizophrenic psychoses but

13 are also observed in neurodegenerative diseases [9]. It has been suggested that

14 the dysfunction of dopaminergic neurons projecting to the striatum contributes

15 to delusion formation in patients with schizophrenia [10], however other

16 hypotheses also have been proposed for the neurobiological basis of delusions

17 with schizophrenia. Delusions also have been linked to frontal cortex

18 dysfunction causing deficits in cognitive control or executive functions. This

19 may result in premature probabilistic reasoning bias and/or lack of top-down

20 control leading to release of other brain areas and manifesting as delusions [11,12].

21   Although patients with FTD show severe frontal, temporal and basal

22 ganglia dysfunction, delusions have been considered a relatively rare feature of

23 FTD [13-15], and the presence of delusions in FTD has ranged from 2.3% to 12.7%

24 in clinical cohorts [15,16]. However, delusions appear to be more common in

25 patients with *C9ORF72* mutations; 50% in 32 cases [5] and 42% in 14 cases [6]. The

1   anatomical underpinnings of delusions in FTD remain unclear, and *C9ORF72*

2   cases may contribute to an understanding of the neurobiological basis of

3   delusions.

4   Here, we report the clinical, neuropsychological, neuroimaging, and

5   neuropathological findings of patients with FTD and delusions who, at autopsy,

6   showed frontotemporal lobar degeneration with TAR DNA-binding protein

7   inclusions (FTLD-TDP) associated with the *C9ORF72* mutation, who had

8   delusions along the clinical course of their disease.

9

Method

11   All 17 patients belonging the University of California, San Francisco

12   (UCSF) Neurodegenerative Disease Brain Bank, with a neuropathological

13   diagnosis of FTLD-TDP due to *C9ORF72* expansion were included. Diagnosis of

14   *C9ORF72* expansion was made by genetic testing and confirmed by the finding

15   of p62 positive /TDP-43 negative intraneuronal inclusions in cerebellum and

16   hippocampus [17]. All subjects and their informants signed an institutional

17   review board-approved research consent form to participate in the study.

18   Patients were seen at the Memory and Aging Center at the UCSF between 2004

19   and 2010 and had undergone at least one neurological evaluation, including

20   extensive neuropsychological assessment and neuroimaging. Medical history

21   including psychiatric history is confirmed independently by neurologist and

22   research nurse through caregiver interviews using structured questionnaires.

23   Out of the 17 patients identified as *C9ORF72* expansion positive, four of them

24   presented with well-defined delusions during the disease evolution. Delusion

25   was defined according to the Diagnostic and Statistical Manual of Mental

1 Disorders, Fourth Edition (DSM-IV) as "a false belief based upon an incorrect

2 inference about external reality that is firmly sustained despite what almost

3 everyone else believes and despite what constitutes incontrovertible and

4 obvious proof or evidence to the contrary, the belief is not one ordinarily

5 accepted by other members of the person's culture or subculture" [18]. Clinical

6 data collected included the time of onset of delusions in relation to other

7 symptoms, previous psychiatric history, the presence of associated

8 hallucinations, and the phenomenological content of the delusions. Subjects'

9 demographic characteristics are summarized in Table 1.

10

11 Neuropsychological data

12 The patients underwent a detailed neuropsychological battery during their

13 visits. General intellectual function was assessed using the UCSF screening

14 battery described elsewhere [19].

15

16 Genotyping

17 The presence of expanded GGGGCC hexanucleotide repeats in C9orf72 was

18 detected using the repeat-primed PCR reaction as described elsewhere [3]. PCR

19 products were run on an ABI3730 DNA Analyzer and analyzed using the Peak

20 Scanner Software.

21

22 Neuroimaging

23 Each patient was scanned with a structural Magnetic Resonance Imaging

24 (MRI) on a 1.5T or 3T scanner within one year of the first UCSF visit.

25 Structural T1-weighted images were preprocessed for voxel-based morphometry

1 (VBM) using Diffeomorphic Anatomical Registration Through Exponentiated

2 Lie (DARTEL) running in Statistical Parametric Mapping (SPM) 8 with Matlab.

3 Group comparison of VBM gray matter images were conducted between 4

4 pathologically proven FTLD-TDP subjects with *C9ORF72* mutation who had

5 delusions and remaining 13 subjects who did not.

6

7 <u>Neuropathology</u>

8   All patients were subjected to an extensive dementia-oriented postmortem

9 assessment at UCSF or at the University of Pennsylvania, following a standard

10 protocol described previously [20,21]. The brains were procured within 18 hours

11 post-mortem. The majority of the brains was cut into 8–10 mm-thick coronal

12 slabs and alternately fixed, in 10% neutral buffered formalin for 72h, or rapidly

13 frozen; the remaining were hemi-sectioned sagittally with one hemisphere fixed

14 in 10% neutral buffered formalin and the other rapidly frozen. Tissue blocks

15 covering dementia-related regions of interest were dissected from the fixed

16 slabs and basic and immunohistochemical stains were applied following

17 standard diagnostic procedures developed for patients with dementia [21]. All

18 immunohistochemical runs included positive control sections to exclude

19 technical factors as a cause of absent immunoreactivity. FTLD-TDP subtyping

20 followed the current "harmonized" nomenclature [22]. All cases were also screened

21 for p62 positive /TDP-43 negative intraneuronal inclusions, pathognomonic

22 markers of *C9ORF72* expansion in amygdala [10,23], a brain area involved in

23 different kind of delusions. Finally, the presences of additional overlapping

24 neurodegenerative disorders were compared between the two groups.

25

Results

Case presentation

<u>Case 1</u>

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 years, 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 exam, he had mild cogwheeling in the

1 arms, mild to moderate hypomimia, and mild bradykinesia. Cognitive testing

2 revealed deficits in all domains except for copying tasks and language. His

3 working memory and executive function were most severely impaired (see Table

4 1). Past medical history was unremarkable for psychiatric symptoms. His

5 family history was negative for dementia. His medications included Fluoxetine

6 (30 mg) and Quetiapine (150 mg). MRI revealed bilateral frontal atrophy. He

7 died suddenly by choking at the age of 64, eight years after the onset of his

8 symptoms.

9 Neuropathological exam demonstrated brain atrophy (weight: 1170 grams),

10 with most severe degenerative changes involving the dorsal and opercular

11 frontal cortices, as well as the dorsal striatum. Microscopic examination

12 revealed hippocampal sclerosis. Immunohistochemical analysis showed

13 unequivocal evidence of FTLD-TDP, featuring TDP-43 immunoreactive

14 inclusions in many cortical regions examined, especially the dorsal and

15 opercular frontal regions. TDP-43 pathology were consistent with FTLD-TDP,

16 with features of type A and type B [22]. Argyrophilic grain disease, a 4-repeat

17 tauopathy was noted in limbic areas and orbital frontal cortex.

18

19 <u>Case 2</u>

20 Mr. B, a left-handed man started to believe that his wife was cheating on

21 him around the age of 40. This delusion spontaneously remitted after several

22 years, however, it reemerged at age of 62. The couple underwent marriage

23 counseling, but the delusion did not remit again. Concomitantly, he developed

24 difficulty in completing his usual tasks, such as fixing light sockets or cars.

25 Subsequently, he had difficulty in understanding directions and conversation.

1 Other language problems included poor repetition, and reduction in speech. He

2 became apathetic, but showed increase in appetite. He had no awareness of his

3 cognitive deficits.

4 Mr. B was evaluated at the UCSF at the age of 65 years. On neurological

5 examination, language was abnormal with evidence of paraphasic errors and

6 some difficulty with reading. He exhibited Parkinsonism with masked faces and

7 reduced blink frequency, however, there was no increased tone at rest, no

8 tremor, and he walked without difficulty. Verbal and visual memories were

9 moderately impaired, but visuospatial abilities remained normal.

10 Neuropsychological tests confirmed the language deficits and showed moderate

11 executive dysfunction (for details see Table 1). Past medical history was

12 unremarkable. His medications were Donepezil and Fexofenadine (60mg).

13 Family history was unknown because he was adopted. Structural imaging

14 showed generalized atrophy, with frontal predominance.

15 The Parkinsonism, executive loss and memory dysfunction all progressed,

16 followed by the appearance of progressive apathy. At age 68, he had difficulty

17 swallowing, increased tone in all extremities, upper limb fasciculations, and a

18 prominent jaw jerk. He died from pneumonia at the age of 70, seven years after

19 the onset of symptoms.

20 Fresh brain weight was 1066 grams. Neuropathology showed atrophy with

21 most severe degenerative changes in the frontal lobes, in particular, the

22 anterior orbital and inferior frontal gyri and the anterior cingulate cortex.

23 Immunohistochemical analysis showed FTLD-TDP with features of type A and

24 type B, consistent with unclassifiable FTLD-TDP. Co-occurring 4-repeat tau

25 pathology was seen and characterized by deposition of neurofibrillary tangles

1 and astrocytic inclusions mostly in limbic areas, inferior temporal gyrus and in

2 precentral gyrus. This tauopathy did not fit into existing criteria for a specific

3 entity and was classified as an atypical tauopathy.

4

5 <u>Case 3</u>

6   Mr. C, a right-handed man, presented with problems in his management

7 skills and an increased number of business-related judgment errors at age 46.

8 Three years later, he had uncharacteristic loss of empathy for his wife who was

9 hospitalized at that time. At the age of 51, he closed his business and found a

10 job for a local manager of a discount store, but he soon started to have trouble at

11 work. He had the grandiose delusion that "they were saving a large store for

12 him." He became socially withdrawn and spent more time watching television.

13 He was fired at the age of 53 years due to his inability to keep the store in good

14 condition, but his delusion continued.

15   Also around that time, he became emotionally and physically more distant

16 from his wife, refused to do jobs around the house, showed increasing apathy.

17 He exhibited other strange behaviors such as sneaking into the home and

18 peeking around the corner at his wife. He maintained the grandiose delusion

19 that someone was saving highly paid jobs for him. He became more rigid and

20 inflexible about his schedule at home, showing anxiety if meals were not served

21 on time. He became irritable and developed environmental dependence playing

22 with items placed in front of him and mimicking other people's actions. Also, he

23 developed compulsive symptoms such as repetitive checking of the temperature.

24 Later on, he inappropriately greeted strangers and developed a preference for

25 sweets.

1   Mr. C was evaluated at UCSF at the age of 54 years. On neurological

2   examination, he had a fine resting and action tremor in the left hand. Tone was

3   increased in the arm with evidence of paratonia on the left greater than right.

4   Gait changes were notable for a decreased arm swing on the left. He had no

5   awareness of his deficits or delusion. He performed poorly on

6   neuropsychological assessment of frontal and executive function with relatively

7   intact language and visuospatial function (for details see Table 1). Past medical

8   history was significant for hypercholesterolemia, borderline hypertension and a

9   loss of hearing after a motor accident. Family history was significant for a

10   strong history of autosomal dominant dementia with Parkinsonism in many

11   relatives. His mother died at age 60 with similar symptoms of dementia and

12   Parkinsonism, but she did not have an autopsy. The patient's MRI showed mild

13   frontal lobe and striatal atrophy.

14   He died by pneumonia at the age of 59, thirteen years after the onset of his

15   symptoms. Neuropathological examination showed general atrophy and marked

16   ventricular dilatation. The fresh brain weighed 1050 grams. TDP-43

17   immunopositive neuropil threads were found in multiple regions of the central

18   nervous system and features were consistent with unclassifiable FTLD-TDP. In

19   addition, he showed argyrophilic grain disease restricted to limbic area.

20

21   <u>Case 4</u>

22   Mr. D, a right-handed man, started to exhibit social withdrawal and

23   executive dysfunction in his late 30s. He became reluctant to join in

24   conversations, completed tasks more slowly and had difficulty concentrating

25   and multi-tasking. In his 40s, he became careless and failed to finish tasks at

1 work. By his late 40s, he became even slower, and less talkative. At the age of

2 54, he developed auditory hallucinations and delusions, believing that various

3 "friends" were talking to him and to each other through TV. Also, he thought

4 that people were watching him through the bathroom mirrors. He believed he

5 was a "sex god" and that various neighbors dated him. He also believed that an

6 imposter replaced his physician. He occasionally accused his wife of infidelity.

7 He exhibited less emotion but inappropriately laughed at serious TV shows. At

8 the age of 56, his speech output declined and his response time became delayed,

9 he walked more slowly. He accompanied his family to work but did little work

10 by himself. Table manners deteriorated and he ate enormous quantities of food

11 voraciously in a messy fashion, including eating food off the floor. He also

12 became apathetic.

13   Mr. D was evaluated at the UCSF Memory and Aging Center at the age of

14 57. His affect was flat, his speech was effortful, and he was perseverative,

15 stimulus-bound and demonstrated poor insight. His neurological examination

16 showed jerky ocular pursuit, increased arm tone with cogwheeling in the left

17 greater than right, slowed finger taps, fasciculations throughout the arms and

18 legs, a fine postural tremor of the outstretched hands, and a slow stooped gait.

19 His exam was also notable for delayed response times, marked utilization

20 behavior, and inability to perform tasks. Neuropsychological testing showed

21 moderate impairments in episodic memory encoding and consolidation,

22 impaired language comprehension, verbal agility, and repetition, marked

23 executive impairment, and impaired abstract reasoning, with relatively spared

24 visuospatial skills (see Table 1).

25   His past medical history includes hypertension, ankylosing spondylitis, and

1 prostate resection. Regarding family history, his mother was diagnosed with

2 Parkinson's disease dementia and had a brain autopsy showing neuronal loss in

3 the substantia nigra without Lewy bodies. His medications included Donepezil

4 (10mg), Quetiapine (800mg), divalproex sodium (500mg), and Trazodone

5 (300mg). His MRI showed moderate bilateral lateral parietal atrophy as well as

6 bifrontal atrophy, vermian atrophy, and bilateral caudate atrophy.

7   He died at 58 years of age. The fresh brain weighed 1340 grams.

8 Neuropathological exam showed atrophy with most severe degenerative

9 changes involving the prefrontal and peri-rolandic cortices, substantia nigra

10 and lower motor neurons of the brainstem and spinal cord.

11 Immunohistochemical analysis showed an unclassifiable FTLD-TDP with

12 frequent granular or compact neuronal cytoplasmic inclusions, in superficial

13 and deep layers of affected cortices, subcortical and brainstem and spinal cord

14 structures. Although primary motor cortex showed TDP-43 pathology, no

15 corticospinal tract demyelination was observed, making motor neuron disease a

16 more appropriate pathological characterization than ALS. In addition, Lewy

17 body pathology was observed in the dorsal motor nucleus of the vagus,

18 corresponding a very early Parkinson's disease Braak stage I [24].

19

20   All the 17 cases fulfilled the most recent bvFTD clinical consensus criteria [2].

21 Among the remaining 13 cases lacking well-defined delusions, one case showed

22 confabulation that disappeared within 2 years from its appearance. The other

23 cases did not show any other psychotic symptoms. Seven cases had motor

24 neuron symptoms to variable extend, and one case had family history of ALS.

25 Two cases have Parkinsonism. Mean age at disease onset is 60.4 years old,

1 mean age at death is 68.2 years old. Neuropathologically, in addition to TDP-43

2 pathology, three non-delusional cases had additional non-AD tau pathology.

3

Neuroimaging Results

5 VBM analysis showed greater atrophy in left parietal precuneus area at the

6 level of uncorrected $p<0.005$ in the four cases with delusions compared with

7 other 13 cases without delusions (Figure 1). In the small volume correction

8 analysis for left parietal precuneus area, the atrophy was also significant at a

9 Family Wise Error (FWE)-corrected p level of <0.05.

10

Neuropathological analyses

12 p62 positive/TDP-43 negative characteristic inclusions in the amygdala

13 were seen in most of the 17 cases and no notable difference was found between

14 the two groups. Among the 13 patients without delusions, three showed

15 overlapping argyrophilic grain disease restricted to limbic areas and one

16 showed an atypical tauopathy.

17

Discussion

19 We report the clinical, neuropsychological, neuroimaging, and

20 neuropathological findings in four FTLD-TDP cases with delusions associated

21 with *C9ORF72* mutations. *C9ORF72* mutation cases account for 12% of familial

22 and 3% of sporadic FTD cases [3,6]. Pathologically, *C9ORF72* mutations are

23 associated with FTLD-TDP, type B [25], as well as type A [5], or a unclassifiable

24 type that features both type A and type B characteristics. Additionally,

25 depositions of ubiquitin or p62-positive/TDP-negative characteristic inclusions

1   are found in cerebellum, hippocampus and thalamus. These inclusions contain

2   dipeptide-repeat proteins translated in an ATG-independent fashion from the

3   hexanucleotide repeats and are pathognomonic of *C9ORF72* expansion. On

4   structural imaging, in addition to atrophy in frontal, insular, and anterior

5   temporal areas commonly affected in bvFTD, patients with *C9ORF72*

6   mutations show atrophy in parietal, occipital, cerebellar, and thalamus [6-8,26].

7   Psychotic features (particularly delusions) are seen in up to 50% of

8   *C9ORF72* mutation carriers [5,6], a much larger frequency than in other FTLD

9   types [15]. Therefore, the distinctive anatomical and neurochemical features of

10 *C9ORF72* may reveal insights into the neurobiological basis of psychosis [5-8,27].

11   Before the discovery of *C9ORF72* mutation, delusions were thought to be a

12 relatively rare symptom in FTD patients. Some of these reports show patients

13 with young-onset FTD who were diagnosed with psychotic disorders before the

14 dementia-onset [28,29]. Paranoid delusions were the most frequent symptoms in

15 these series. Other case reports showed complex delusions [30], grandiose

16 delusions [31], and Cotard delusions [32]. Snowden et al. reported that most of the

17 delusions with their *C9ORF72* mutation cases were somatic delusions such as

18 alterations in temperature perception, preoccupation with bowel movements,

19 and leg pain [5], which was different from our series showing various delusions.

20   Compared to FTD, delusions are a relatively common symptom in

21 Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB). A review

22 article reported a median prevalence of 36% (9.3–63%) for delusions in AD, most

23 involving delusion of theft, which can be included in the persecutory delusion

24 category [10,33]. Studies focusing on the underlying biological background of

25 delusions in AD have suggested that persecutory delusions occur early in the

1   disease course and are associated with neurochemical and neuropathological

2   changes in frontostriatal and temporal-limbic circuits [34]. On the other hand,

3   delusional misidentification in AD is associated with greater global cognitive

4   deficits and advanced limbic pathology [34]. In patients with DLB, hallucinations

5   are the most frequent psychotic symptoms, with a prevalence from 63 to 78%,

6   followed by misidentifications (56%) and paranoid delusions (25 to 28%) [35,36].

7   Paranoid or persecutory delusions in DLB subjects were hypothesized to be

8   associated with dysfunction in the frontal cortex in addition to occipital cortex

9   dysfunction [35].

10   Several studies on schizophrenia suggest that development of delusion is

11   associated with a dysfunction of dopamine regulation in the ventral striatum,

12   which leads to aberrant assignment of salience to stimuli [11,37]. Also, dysfunction

13   in brain areas associated with executive behavioral control such as the

14   prefrontal cortex (PFC) may lead to alterations in affective state, disinhibition,

15   and ways of thinking that might increase the risk of delusion formation [38]. PFC

16   was found to be implicated in prediction-error processing [39,40], and reality

17   monitoring tasks [41], structural volume loss in the PFC correlates with

18   symptoms of delusion [42]. Thalamic dysfunction may also result in reduced

19   ability to adjust sensory responsiveness to ongoing behaviors in patients with

20   schizophrenia [43]. Psychosis in schizophrenia is associated with

21   source-monitoring deficits whereby self-initiated behaviors become attributed to

22   outside sources, and one of the functions of the thalamus is to adjust sensory

23   responsiveness in accordance with the behavioral contextual cues. Lower

24   numbers of cerebellar Purkinje neurons also seen in association with psychosis

25   in patients with schizophrenia and bipolar disorder [44]. The decreased synthesis

1 and release of reelin from cerebellar granule cells could be associated with the

2 pathophysiologies that regulate GABAergic neuron dysfunction in the

3 cerebellum of these patients.

4 There are a variety of neurological disorders strongly associated with

5 psychosis. Often, psychosis occurs in association with temporal lobe dysfunction

6 and is seen in patients with temporal lobe epilepsy, herpes simplex encephalitis,

7 and autoimmune encephalitis that target the temporal lobes [45-47]. Disorders of

8 the basal ganglia and brain stem have a higher than expected prevalence of

9 delusions and psychosis as is seen with Huntington's disease, Fahr's syndrome,

10 and Wilson's disease [48-50]. These results suggest that variety neurobiological

11 substrates may predispose to delusions.

12

13 Why, then did the four FTD cases with *C9ORF72* mutations presented here

14 exhibit delusions? Mahoney et al. hypothesize that dysfunction of thalamic and

15 cerebellar projections could be related to the neuropsychiatric features

16 associated with this *C9ORF72* mutations cases, including hallucinations and

17 delusions [7]. This thalamic and cerebellar pathology is relatively unique to

18 *C9ORF72* mutation FTD cases. Although this hypothesis remains appealing, it

19 is important to note that the other 13 cases in our series without delusions also

20 showed changes in thalamus and cerebellar structures.

21 Thus, based on above-mentioned knowledge of delusions in other

22 neurodegenerative disorders and schizophrenia, we hypothesized that in

23 addition to PFC dysfunction that is common in patients with FTD, other regions

24 might have contributed to development of delusions in our series of patients[23].

25 VBM analysis showed more atrophy in left parietal precuneus area in

1   delusional patients compared to the non-delusional patients. Although the

2   result is significant even after correction, our sample is small and the time gap

3   latency between delusion onset and MRI acquisition should be taken into

4   consideration. This parietal involvement has also been reported in other

5   *C9ORF72* mutation series [3,6]. Precuneus is involved in discriminating

6   self-relevant information from self- irrelevant information and in retrieving

7   source memories [54]. Therefore, in addition to executive dysfunction, failing to

8   discriminate between self-relevant and self-irrelevant information and to

9   retrieve the information source must make the patients hypersensitive to all

10   information. Although the precuneus is very vulnerable to AD and to associate

11   with delusions in patients with AD[51-53], such delusions are typically delusions of

12   theft, rather than bizarre delusions as observed in our C9orf72 mutation series.

13   Thus, we speculate that degree of frontal involvement may contribute to the

14   variety of delusions in our cases.

15   Downey et al. suggested a distributed anatomical correlate in

16   thalamo-cerebello-cortical circuitry including parietal cortex as a key terminus

17   to explain altered body schema processing in C9orf72 related FTD patients [55].

18   Our findings corroborate their observations. In fact, their results provide a

19   useful framework for interpreting our findings, in particular the candidate

20   mechanism of self / non-self regulation. However, as they point out, the

21   spectrum of neuropsychiatric phenomena attributable to altered body schema

22   processing is potentially much wider than delusions and hallucinations. Thus,

23   our results have to be interpreted causally. Although precuneus changes may be

24   neuroanatomical basis underlying delusions in C9orf72 related FTD patients, it

25   is not possible to rule out a broader change in network vulnerable to this

1 disease.

2

3 Neuropathological information revealed that 3 out of 4 delusional patients

4 presented an overlapping tauopathy (2 AGD and 1 atypical tauopathy). This

5 75% frequency is significantly higher that frequency of tauopathies in

6 non-delusional cases 23% (3/13) and may indicate an association. Patients with

7 AGD are prone to present persecutory delusions [56,57]. Thus, the mixture of tau

8 pathology and FTLD-TDP pathology especially in frontal cortex and ventral

9 striatum, may have contributed to the clinical picture of delusions. In case 4,

10 there was an additional Lewy body pathology. Lewy body pathology is

11 associated with visual hallucinations, which were present in this patient, but

12 the link is weakened because Lewy body pathology was restricted to the dorsal

13 motor nucleus of the vagus nerve. None of the previous three subjects showed

14 hallucinations in any modality. This may indicate a difference in pathological

15 background between delusions and hallucinations. However, Snowden et al.

16 reported that among 4 pathological confirmed cases with psychosis, 1 had tau

17 pathology without TDP-43 pathology and the others had TDP-43 pathology

18 without accompanying pathology [5]. Synergistic effects of FTLD-TDP and certain

19 tauopathies in causing delusions deserve investigation in a larger cohort, once it

20 becomes available.

21 Although postmortem examination can potentially identify the underlying

22 basis of neuropsychiatric symptoms, its power is limited by the long lag between

23 the onset of delusions and expiration. It is possible that the advance stage of the

24 disease by the time of passing precludes identification of more subtle differences

25 between patients with specific symptoms. It might explain why we could not

1 find any distinctive pathological findings in parietal and precuneus in the

2 delusional group. This also supports the hypothesis that precuneus can be a

3 component of a network that may show differential vulnerability.

4

5 Interestingly, all of our four delusional cases had Parkinsonism, compared

6 to 2/13 non-delusional cases. However, iatrogenic Parkinsonism cannot be

7 discarded as two delusional cases (case 1 and case 4) and one non-delusional

8 subject were treated with atypical antipsychotics. This may indicate higher

9 sensibility of delusional subjects to dopamine dysfunction, both associated to

10 delusions and to Parkinsonism. Association between delusions and

11 Parkinsonism in *C9ORF72* mutation cases suggests an overlapping

12 vulnerability of certain brain areas to both Lewy body disease and *C9ORF72*

13 mutation-related pathology, even though both have different abnormal protein

14 deposition signatures. One clinico-pathological study with 68 patients shows a

15 greater loss of dopaminergic neurons in the substantia nigra of patients with

16 *C9ORF72* mutations than those without [58]. Parkinson disease itself is not

17 associated with *C9ORF72* mutations [59].

18

19 Finally, delusions in our series often preceded the behavioral and cognitive

20 disabilities. This observation may increase the likelihood of misdiagnosis and

21 delayed appropriate treatment. FTD cases are often diagnosed as having

22 atypical psychosis such as late-onset schizophrenia or late-life depression with

23 psychotic features[60]. Indeed, patients with FTD receive a prior psychiatric

24 diagnosis significantly more often than patients with AD (FTD, 50.7% vs. AD,

25 23.1%) [61]. Clinicians need to consider the possibility of this mutation and assess

1 the family history when a patient presents with middle age onset delusions.

2

3 **Conclusion**

4   All of our FTD series with the *C9ORF72* mutation presenting delusions had

5 some additional pathology and Parkinsonism, which suggests a common

6 anatomy or neurochemistry underlying these delusions. <u>VBM analysis suggests</u>

7 <u>relationship between precuneus and appearance of delusions, although the</u>

8 <u>number of cases is small to draw conclusions.</u> Further work with larger cohorts

9 will be required to investigate the biological correlates of delusions in this

10 genetic FTD group. Their presentations of this mutation carrier are

11 heterogeneous and may be at higher risk of being misdiagnosed with primary

12 psychosis. Clinicians need to consider the possibility of this mutation and assess

13 the family history when a patient presents with middle age onset delusions.

14

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18

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22

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7

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Table 1

Clinical, neuropsychological, and brain imaging features of 4 cases

	Right handed Male	Right handed Male	Right handed Male	Right handed Male
Clinical diagnosis	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 roaming	reduction in motivation increase in appetite	apathy / lack of interest rigid inflexible in schedule	hyperorality apathy
	stereotypy loss of personal hygiene		irritable environmental dependent	utilization behavior loss of personal hygiene
	preference for sweets		preference for sweets	
family history	negative	unknown (adaption)	mother/ maternal family	mother
neuropsychological examination				
Mini Mental State Exam	17/30	20/30	28/30	19/30
CVLT Short Form*	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
<u>Digit span Forward/Backward</u>	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 (sec)	unable	62sec	unable	unable
Boston Naming Test	11/15	11/15	13/15	15/15
Phonemic and Category	3 and 5	2 and 6	6 and 13	2 and 2

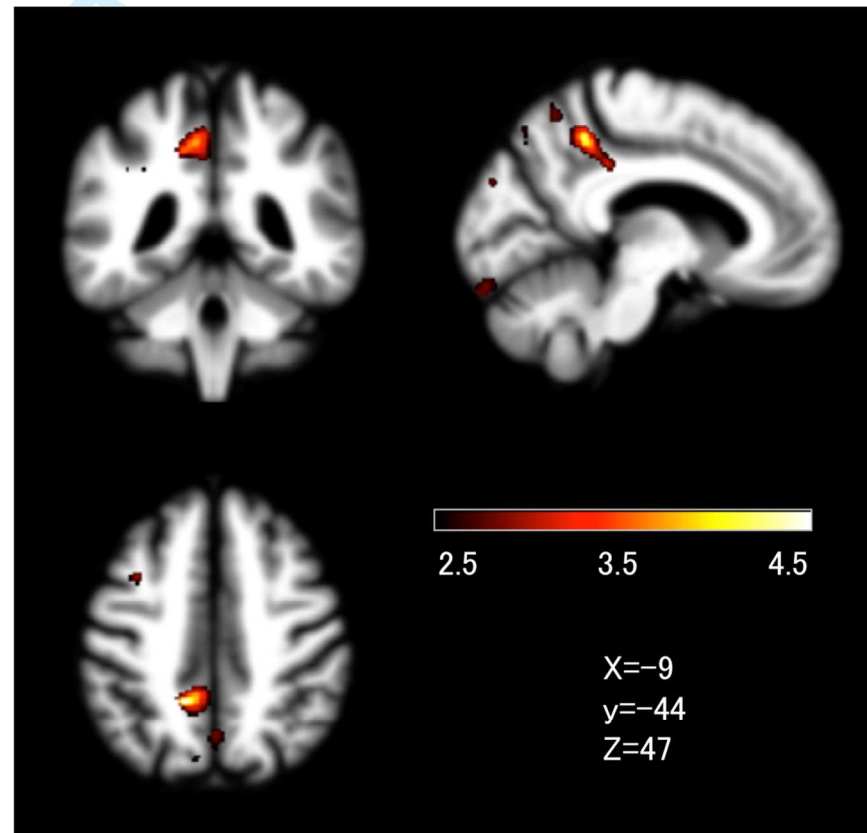|				
fluency				
Geriatric Depression Scale	12	4	0	15
Neuropsychiatric Inventory	45	8	20	52
(delusion scale)	8	2	2	12
Unified Parkinoson's Disease Rating Scale	9	10	-	6
MRI imaging**				
dorsolateral frontal atrophy	+ +	+	+	+
medial frontal atrophy	+ +	+	−	+ +
orbitofrontal atrophy	+ +	−	+	+
striatum atrophy	+	+	+	+
<u>parietal atrophy</u>	+ +	+	+	+ +
cerebellum atrophy	+	−	−	−
age at death	64	69	60	58
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

* California Verbal Learning Test, 4 time registration, 30 second recall, and 10 minutes recall of 9 words

**(+) means mild atrophy and (++)means severe atrophy, based on expert neurologist who is blind to patients'

clinical information

FTLD-TDP: frontotemporal lobar degeneration with TAR DNA-binding protein inclusions

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)