White Matter Integrity Involvement in Preclinical Stage of Familial Creutzfeldt-Jakob Disease: A Diffusion Tensor Imaging Study

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Research

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Abstract

Background : To explore the patterns of white matter (WM) alterations using diffusion tensor imaging (DTI) in the preclinical stage of familial Creutzfeldt-Jakob disease (fCJD) .

Methods: 7 asymptomatic carriers of *PRNP* G114V mutation and 6 non-carriers from the same fCJD kindred were recruited at baseline. Follow-up was obtained in 7 asymptomatic carriers and 2 non-carriers 2 years later. We also included 10 symptomatic CJD patients and 10 age-and gender-matched healthy controls out of the kindred to observe the overlapping patterns of WM between asymptomatic carriers and symptomatic CJD patients. All subjects received clinical, neuropsychological assessments, electroencephalogram (EEG) tests, and DTI at baseline and follow-up. Tract-based spatial statistics (TBSS) was used in DTI study for whole-brain voxel wise analysis of fractional anisotropy (FA) and mean diffusivity (MD) in WM. Results were compared in three groups: baseline carriers against non-carriers (baseline analysis), changes after 2 years in carriers (follow-up analysis), and differences between symptomatic CJD patients and healthy controls (CJD patients analysis).

Results: Neither the carriers nor the non-carriers develop any neurological symptoms during 2 years follow-up. Baseline analysis showed no group differences between carriers and non-carriers in MD and FA. Follow-up analysis showed significant increased MD in left inferior fronto-occipital fasciculus, left uncinate fasciculus, bilateral superior longitudinal fasciculus, and bilateral corticospinal tract ($p < 0.05$), among which increased MD in bilateral superior longitudinal fasciculus and right corticospinal tract overlaps the pattern of CJD patients.

Conclusion: Integrity involvement within multiple WM tracts could be detected in preclinical stage of fCJD.

Background

Creutzfeldt-Jakob disease (CJD) is a rare, fatal neurodegenerative disorder which characterized by rapidly progressive dementia, motion disturbances, and akinetic mutism. Familial CJD (fCJD), which due to prion protein gene (*PRNP*) mutations, and sporadic CJD (sCJD) are two major forms of CJD, while previous studies have shown that they almost share the similar pathophysiological features[1]. By virtue of the completely dominant and fully penetrant inherited pattern of fCJD[2], the asymptomatic *PRNP* carriers provide an ideal preclinical model for research, while non-carriers from the same kindred would be the best control group with homogeneous nature for exploring the disease process. Up to now, a few studies have confirmed that the gray matter changes appeared prior to the symptomatic onset in preclinical CJD patients[3], but the WM changes in preclinical CJD is still unclear.

Diffusion tensor imaging (DTI), as a non-invasive MRI technique which can demonstrate the orientation and integrity of WM fibres in vivo, has been widely used to show WM changes in the early stage of CJD. Previous DTI studies in CJD cases demonstrated MD changes in multiple WM tracts[4, 5], which suggested

degeneration in WM as initial pathological alterations. Another pathological study in 26 CJD patients applying DTI and post-mortem analysis also showed reduced MD and reactive astrocytic gliolis in WM, which suggested possible primary involvement in WM[6]. However, few research has been done to investigate the WM integrity in the preclinical stage of CJD. Therefore, further observations of the WM changes in preclinical CJD is of great significance to study the pathogenesis of CJD.

In order to investigate these changes, we conducted a prospective DTI study in asymptomatic carriers of G114V mutation and non-carriers from the same fCJD kindred. The purpose of the current study was to investigate the patterns of WM changes in the brain of preclinical CJD patients.

Methods

Ethics statement

The study protocols outlined in this manuscript were approved by the Ethics Committee and local Institutional Review Board of Xuanwu Hospital, Capital Medical University, Beijing. All methods and experiments were performed in accordance with the relevant guidelines and regulations. All participants enrolled in the study or their guardians signed an informed written consent specifically approved for this study prior to the study commencement.

Subjects

Data used in this study were from a Chinese Han fCJD kindred with G114V mutation in *PRNP* which have been followed since 2008[7]. Details of the clinical findings and genetic analysis of this family have already been published[8]. Thirteen asymptomatic family members aged above 18 and one of whose parents should be fCJD patient or G114V mutation carrier were enrolled, We defined asymptomatic subjects as who did not report any neurological complaints and were normal upon neurological examinations. The exclusion criteria were as follows: (1) A main complaint of memory decline or objective memory impairment with cutoff points for Mini Mental State Examination (MMSE) score as 19 (no formal education), 22 (1 to 6 years of education), and 26 (seven or more years of education); cutoff points for Montreal Cognitive Assessment (MoCA) as 13 (no formal education), 19 (1 to 6 years of education), and 24 (seven or more years of education); a Clinical Dementia Rating (CDR) score ≥ 0.5; (2) Presence of abnormality waves in a 2-hour EEG; (3) Presence of psychiatric disorders (Neuropsychiatric Inventory Questionnaire [NPI-Q] ≥ 1); (4) A history of other neurologic disorders; (5) A history of traumatic brain injury; (6) A history of psychosis or congenital mental growth retardation; or (7) contraindications for MRI. The subjects were then divided into 2 groups as 7 asymptomatic carriers of the G114V mutation and 6 non-carriers. All subjects received clinical, neuropsychological assessments, EEG tests, and DTI at baseline. All evaluations were double-blind to genotypes, which means that neither physicians examining the subjects nor the subjects themselves aware of their gene pattern.

The follow-up evaluation was carried out on average 2 years after the baseline interview in 7 carriers and 2 non-carriers, it consisted of in-depth clinical, neuropsychological assessments, EEG tests, and DTI. Five

non-carriers failed to obtain follow-up due to refusal to further participate in the study. All carriers and non-carriers that obtained follow-up had received no treatment for cognitive impairment and neurological symptoms in 2 years.

To compare with the subset of carriers and non-carriers that obtained follow-up, from 2018 to 2019, 10 symptomatic CJD patients which are out of this G114V fCJD kindred were enrolled from clinic in Xuanwu Hospital and their age- and gender-matched healthy controls were enrolled from community. All symptomatic CJD patients were diagnosed according to the European probable CJD criteria[9]. Patients with other causes of cognitive impairment and those are incapable of cooperation were excluded. The controls were recruited for the absence of cognitive symptoms, normal general cognitive functioning, and no active neurological and psychiatric disease. The exclusion criteria for health controls were the same as those for the asymptomatic family members that was described in the preceding paragraph.

Neurological assessments

All subjects received standardized clinical and cognitive assessments including MMSE, MoCA, CDR, and NPI-Q assessments. Clinicians who performed the assessments were not aware of the mutation status of participants.

Genetic analysis for PRNP gene mutation

Blood samples were obtained from 10 symptomatic CJD patients. 5 ml venous blood was collected by EDTA anticoagulant vessel collection and stored at -20℃. Blood extraction kit was used to extract blood DNA. DNA concentration and purity were determined by NanoDrop2000. Specific primers were used to amplify DNA fragments in the region of the mutation site. Reaction system: 2 × Phanta Max Buffer 12.5 μL,Phanta Max Super-Fidelity DNA Polymerase (1 U/μL) 0.5 μL□dNTP Mix(10 mM each) 0.5 μL, Primer-F(10 μM) 1μL□Primer-R(10 μM) 1μL, DNA 1μL, Add water to 25μL. Reaction procedure: 95℃ denaturation 5 min; 95℃ denaturation for 30 s, 65℃ annealing for 30 s, 72℃ extension for 30 s, 25 cycles, each cycle reduced by 0.6; 95℃ denaturation for 30 s, 50℃ annealing for 30 s, 72℃ extension for 1 min, 20 cycles; 72℃ extended 10 min. After PCR, 3 μL products were taken for 2.5% agarose gel electrophoresis. PCR products were sequenced by ABI 3730XL DNA Analyzer.

Electroencephalogram

All subjects received a two-hour EEG at baseline and follow-up using 18 lead electroencephalographic transducer (Micromed, Italy). Electrodes were placed in accordance with the international standard 10–20 system. Conventional single lead, double lead and sphenoid lead were traced. Eyes closing and deep breathing experiments were performed.

MRI acquisition and imaging parameters

Magnetic resonance(MR) scanning was performed on a GE Signa PET/MR 3.0 T scanner (GE Healthcare, Milwaukee, WI) in Xuanwu Hospital, Capital Medical University. All 13 asymptomatic family members received their first PET/MR scans in 3/2017. 9 of them received follow-up scans in 3/2019. All 10

symptomatic CJD patients received their scans on the same scanner during their hospital stays from 2018 to 2020. DTI data were acquired using a spin echo-echo planar imaging sequence (TR/TE = 16500/97.6 ms) with a b-value of 1000s/mm2, applying diffusion gradients along 30 directions. 70 axial slices with no slice gap were acquired (FOV = 220 × 220mm2, matrix = 112 × 112, slice thickness = 2 mm, number of excitations = 1).

Diffusion Tensor Imaging processing

DTI data were preprocessed using PANDA software package (a pipeline tool for analyzing brain diffusion images, PANDA; http://www.nitrc.org/projects/panda/) independently developed by the state key laboratory of cognitive neuroscience and learning of Beijing Normal University. Briefly, the preprocessing involves correction of eddy current and head movement, creating a brain mask and fitting the diffusion tensor model. The output yielded voxel-wise maps of fractional anisotropy (FA) and mean diffusivity (MD). The FA index of DTI is a sensitive neuroimaging measure of the degeneration and describes overall white matter health, maturation, and organization. Another index, MD, represents the average dispersion level and dispersion resistance of the water molecule as a whole, which can reflect the changes of brain tissue. The higher the MD value is, the more free water molecules in the tissue, and the information transmission speed will be affected to some extent.

Tract-based spatial statistics analysis

In order to explore the influence of CJD pathology on white matter integrity, Tract-Based Spatial Statistics (TBSS) was performed in this study. TBSS projects all subjects' FA and MD data onto a mean FA tract skeleton before applying voxel-wise cross-subject statistics. Voxel-wise statistical analyses were performed using a nonparametric permutation-based inference tool ["randomize," part of FMRIB Software Library (FSL)] with the general linear model (GLM) as statistical modeling. Pairwise group comparisons based on voxels were performed between carriers versus non-carriers at baseline, carriers at baseline versus at follow up and CJD patients versus healthy control. The DTI parameters at each voxel were modeled as a linear combination of predictors (five grouping variables) and covariates (age and sex) stored in the columns of a "design matrix"; The significant thresholds were set at family-wise error (FWE) corrected $p < 0.05$ using the threshold-free cluster enhancement option.

Statistical analysis

In this study, SPSS 23.0 software was used to evaluate the statistical significance. Differences of age and education were assessed using student's t-test. Differences in sex were assessed using Chi-square test. Differences of cognitive scores were assessed using student's t-test. The results were considered statistically significant at $p < 0.05$.

The estimated years from expected symptom onset were calculated as the age of the participant at the time of the study assessment minus the age of the parent at symptom onset. And if the parent of the participant has not developed the symptom of CJD, the age of the grandparent would be used to calculate the estimated years from expected symptom onset. For example, if the participant's age was 35

years, and the parent's age at onset was 45 years, then the estimated years from expected symptom onset would be 10. The parental age at onset was determined by a semi-structured interview in which family members were asked about the age of first progressive cognitive decline.

Results

13 asymptomatic family members were recruited from the same kindred which was shown in Fig. 1. In this kindred, 9 family members (4 males and 5 females) have passed away due to CJD. The detailed data of the clinical features and examinations were summarized in Table S1 (See Additional file 1).

At baseline, 7 asymptomatic carriers and 6 non-carriers from this kindred were examined. The demographic data and neurological assessments scores are summarized in Table 1. There was no significant difference in age, gender, years of education, MMSE or MoCA score between 7 asymptomatic carriers and 6 non-carriers. NPI-Q scores were 0 in all subjects. The clinical features and examinations were shown in Table S2 (See Additional file 2).

Table 1
Demographic data of non-carriers and carriers at baseline

	Non-carriers	Carriers	p value
Numbers of subject	6	7	-
Age	32 ± 8.0	33 ± 10.4	0.77
Gender (Male/Female)	4/2	2/5	0.29
Years of education	11 ± 3.3	10 ± 2.9	0.80
MMSE	29 ± 1.2	29 ± 0.8	1.00
MoCA	27 ± 2.7	26 ± 5.1	0.77
NPI-Q	0	0	-
Key: data are presented as mean ± standard			
MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; NPI-Q: Neuropsychiatric Inventory Questionnaire			

All 7 carriers and 2 out of the 6 non-carriers obtained follow-up. Neither the carriers nor the non-carriers developed any neurological symptoms during the 2-year follow-up. No signs of lesion were found in EEG and regular MRI. Comparing between baseline and follow-up, MMSE, and MoCA scores of the 7 carriers demonstrated no statistical difference. NPI-Q and CDR scores were 0 in all subjects. Detailed clinical features were shown in Table S2 (See Additional file 2).

Among 10 symptomatic CJD patients, 3 of them are familial cases with *PRNP* E200K mutation and the other 7 patients are sporadic cases without mutation detected. The demographic data and neurological

assessments scores are summarized in Table 2. There was no significant difference between CJD patients and controls in terms of age, gender, and years of education. The detail of the clinical features and examinations of 10 symptomatic CJD patients could be found in Table S3 (See Additional file 3).

Table 2
Demographic data of CJD patients and healthy controls

	CJD patients	Healthy controls	p value
Numbers of subject	10	10	-
Age	61 ± 7.7	56 ± 5.2	0.146
Gender (Male/Female)	4/6	5/5	0.661
Years of education	10 ± 4.8	11 ± 3.2	0.394
MMSE	4.4 ± 7.5	28 ± 0.8	< 0.001
MoCA	1.7 ± 3.9	26 ± 2.7	< 0.001
NPI-Q	N.A	0	-
Key: data are presented as mean ± standard			
MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI-Q, Neuropsychiatric Inventory Questionnaire; N.A: Not available			

Group Differences in WM Diffusion Metrics Among the Groups

At baseline, TBSS result showed that there was no significant difference in MD and FA between asymptomatic carriers of G114V mutation and non-carriers (FWE correction, $p < 0.05$).

After 2 years, TBSS result showed that asymptomatic carriers had increased MD across multiple WM tracts, including left inferior fronto-occipital fasciculus,left uncinate fasciculus□bilateral superior longitudinal fasciculus, and bilateral corticospinal tract (FWE correction, $p < 0.05$) (Fig. 2). No reduced FA was observed in any WM tracts.

There was also a significant difference between symptomatic CJD patients and their matched controls (FWE correction, $p < 0.05$) (Fig. 3). TBSS result showed that CJD patients had increased MD across multiple WM tracts, including left cingulate gyrus, forceps major, bilateral superior longitudinal fasciculus, and right corticospinal tract. No reduced FA was observed in any WM tracts.

Among those WM tracts with increased MD in symptomatic CJD patients, asymptomatic carriers showed overlapping patterns in bilateral superior longitudinal fasciculus and right corticospinal tract.

Discussion

In this prospective study applying DTI, we detected global WM involvement in asymptomatic G114V mutation carriers, characterized by increased MD accompanied with FA within normal range. These alterations mainly focused on several WM tracts in asymptomatic carriers, among which also shared overlapping patterns with symptomatic CJD patients. To our knowledge, our findings describe WM abnormalities in the preclinical stage of fCJD for the first time.

In our study, increased MD and normal FA were detected in WM of both asymptomatic carriers and CJD patients. Our results differ from what was usually reported in CJD patients[5, 6], but are consistent with changes caused by demyelination[4]. Notably, Previous studies have suggested dymelination in WM of CJD patients. A histopathological study in 6 CJD cases found pathcy foci of demyelination in WM, which was accompanied by reactive astrocytic gliosis performing similar pathological changes with the second stage of Braak hypothesis in CJD[6, 10]. Other histological studies and have also found demyelination in WM as well[11–13]. To date, the only previous DTI study in familial CJD patients showed increased MD in several WM tracts suggesting that the increases in MD could be mainly contributed by the changes in radial diffusion due to demyelination, which in consistent with our findings[4, 14]. Other DTI researches in sCJD patients also found increased MD in WM as well[15]. Elevated MD usually appears in demyelination or axonal degeneration as the water movement is less restricted[4, 5, 16]. Therefore, it's assumed that increased MD in both asymptomatic carriers and symptomatic patients could be explained by demyelination in WM. As for FA, it reflects the ratio of axial to radial diffusivity[5]. We hypothesized that, considering the WM changes may impair the water diffusion in all directions[5, 12], similar alterations in both axial and radial diffusion could lead to a relative preservation in FA. Previous study in CJD patients has also showed FA within normal range that are consistent with ours[5].

In asymptomatic carriers, WM changes were found at follow-up in left inferior fronto-occipital fasciculus,left uncinate fasciculus□bilateral superior longitudinal fasciculus, and bilateral corticospinal tract. Among those changes, bilateral superior longitudinal fasciculus and right corticospinal tract overlapped the pattern of CJD patients which suggests that it may be pathological alterations detected in preclinical stage rather than changes secondary to neuronal degeneration. Additionally, previous researches have also detected WM alterations in correlated areas which are similar with our pattern. A DTI study in 26 CJD patients detected MD changes in WM including corticospinal tracts[6]. Another study applying DTI in 21 CJD patients showed increased MD in corticospinal tract as well[4]. However, alterations in superior longitudinal fasciculus have not been reported in CJD patients. AS superior longitudinal fasciculus often associates with spatial working memory[17, 18], its impairment may contribute to cognitive dysfunction. In current study, symptomatic CJD patients showed cognitive deficits, MMSE and MoCA score decline which in consistent with the presentation of superior longitudinal fasciculus impairment[17, 18]. These findings suggest that pathological changes in WM may appear in preclinical CJD patients and could be correlated with the onset of CJD.

A strength of this study is that it shows the earliest known brain changes of DTI in the asymptomatic stage of fCJD. However, interpretations of the results still need to be enhanced and were limited by the

small sample size since fCJD is a very rare disease. Additionally, the symptomatic patients were not included from the same kindred. Considering that our data was from an ongoing research project, further analyses should be conducted, to investigate the dynamic changes of indices from asymptomatic to clinical stage.

Conclusion

In conclusion, these preliminary results of TBSS analysis represented MD increment in several WM tracts and indicated WM integrity involvement in the preclinical stage of fCJD. This study could provide new insights into the pathogenesis of CJD.

Abbreviations

WM, white matter; DTI, diffusion tensor imaging; CJD, Creutzfeldt-Jakob disease; fCJD, familial Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease; PRNP, prion protein gene; EEG, electroencephalogram; TBSS, Tract based spatial statistics; FA, fractional anisotropy; MD, mean diffusivity; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; NPI-Q, Neuropsychiatric Inventory Questionnaire; FWE, family-wise error; MR, magnetic resonance; FSL, FMRIB Software Library; GLM, general linear model;

Declarations

Ethics approval and consent to participate: The study protocols outlined in this manuscript were approved by the Ethics Committee and local Institutional Review Board of Xuanwu Hospital, Capital Medical University, Beijing. All methods and experiments were performed in accordance with the relevant guidelines and regulations. All participants enrolled in the study or their guardians signed an informed written consent specifically approved for this study prior to the study commencement.

Consent for publication: Not applicable

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributionsDLJ, YJC, ZJZ and LYW were responsible for study concept and design. CLC, HL, LL, JY, ZGL, RG and LW were responsible for clinical data collection. YJC and ZJZ analyzed image results. DLJ, KXX and YC were the major contributors in writing the manuscript. ZJZ and LYW were

responsible for critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

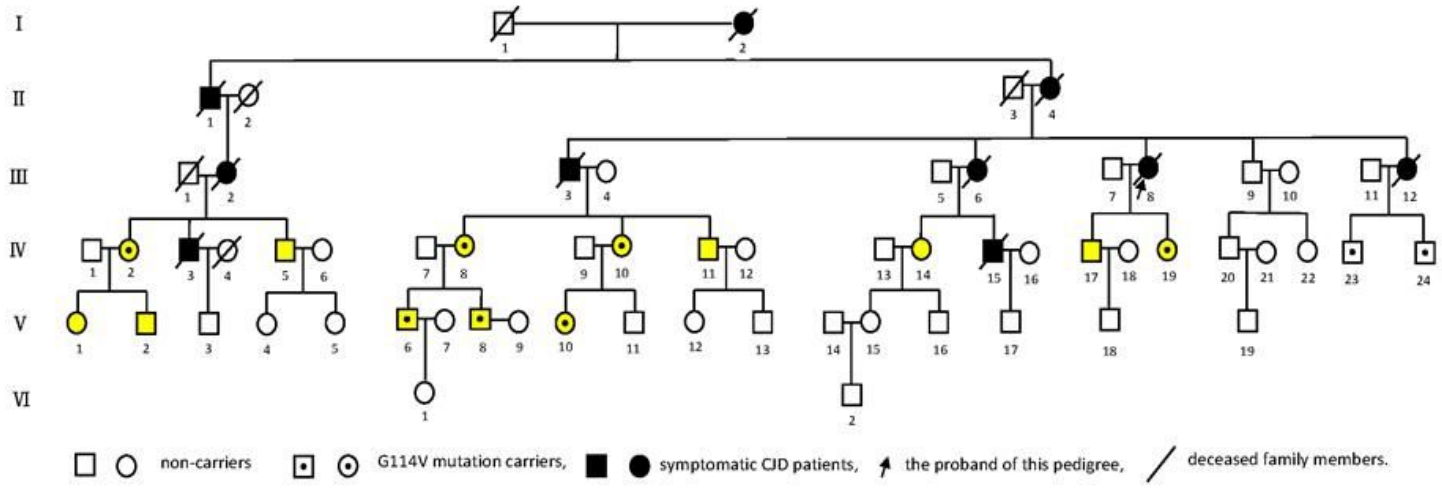

Figure 1

The family tree of the enrolled G114V kindred. Participants in this study were highlighted in yellow.

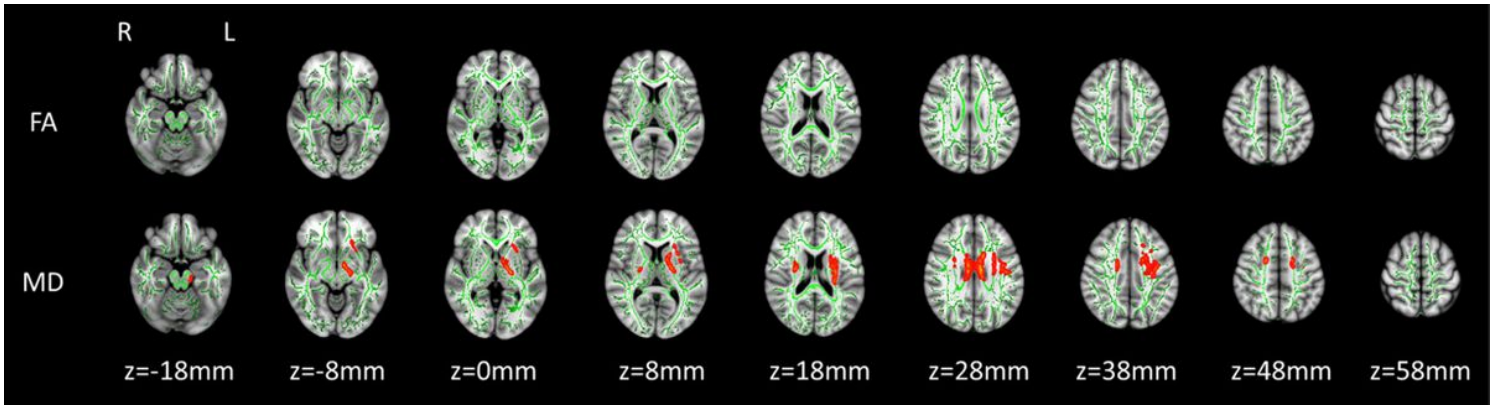

Figure 2

TBSS analysis of asymptomatic carriers at baseline against at follow-up. Increased MD were found in the asymptomatic G114V carriers at follow-up against baseline (FWE correction, P<0.05). Significant areas (red code) of increased MD in asymptomatic carriers at follow-up against baseline are shown in the skeleton (green).

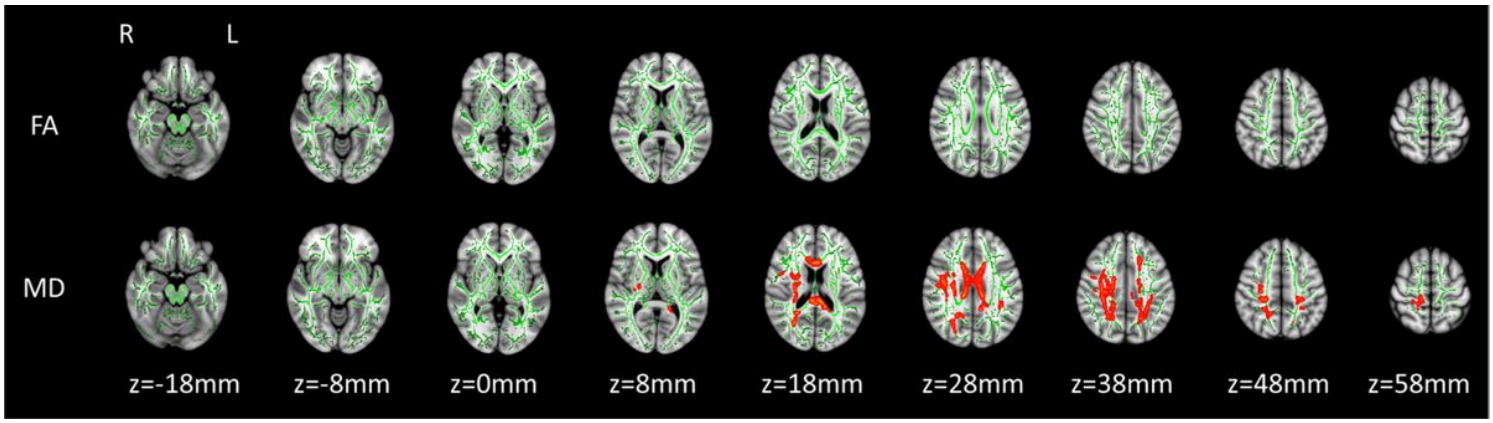

Figure 3

TBSS analysis of symptomatic CJD patients compared with healthy controls. Increased MD were found in the CJD patients compared with healthy controls (FWE correction, P<0.05). Significant areas (red code) of increased MD in CJD patients versus healthy controls are shown in the skeleton (green).

Supplementary Files

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