SQSTM1 mutations in frontotemporal dementia are associated with asymmetrical focal temporal lobe atrophy

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Background

FTD is a common cause of young onset dementia and in around a third of cases is genetic. Recently mutations in SQSTM1 have been shown to be a rare cause of familial FTD. Little is known about the clinical or neuroanatomical phenotype at present. In this study, we investigated the pattern of grey matter atrophy in a group of patients with SQSTM1-associated FTD.

Methods

From the UCL FTD DNA cohort (n=440), we investigated four patients with the SQSTM1 mutation variant: two P392L, one E155K and one E396fameshift mutation. The clinical diagnoses in the patients were behavioural variant FTD; FTD with motor neurone disease, corticobasal syndrome and primary progressive aphasia. The mean (standard deviation) age at onset was 59.9 (5.9).

All patients had undergone a T1-weighted magnetic resonance imaging scan acquired on a 3T Siemens Trio scanner: age at scan 65.8 (6.4). Their imaging was compared with 24 age- and gender-matched healthy controls (age: 66.9 (5.2)). We undertook a voxel-based morphometry (VBM) analysis comparing the SQSTM1 mutations carriers and the controls, correcting for age, gender and total intracranial volume. Statistical parametric maps were thresholded at p<0.05 after family-wise error correction and rendered on a study-specific average group T1-weighted MRI template image in MNI space.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Gender (male)</th>
<th>Age</th>
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<tbody>
<tr>
<td>SQSTM1</td>
<td>4</td>
<td>50 %</td>
<td>65.8 (6.4)</td>
</tr>
<tr>
<td>Controls</td>
<td>24</td>
<td>50 %</td>
<td>66.6 (5.2)</td>
</tr>
</tbody>
</table>

Table 1. Demographic and clinical variables for SQSTM1 patients and controls.

Results

Grey matter atrophy was asymmetrical with three patients having right-sided dominant atrophy and one left-sided. For the analysis we flipped the scan in the midsagittal plane of the patient with left-sided atrophy so that the hemisphere in which there was predominant atrophy was the same in all four cases.

The VBM analysis showed evidence of focal involvement of the antero-inferior-medial temporal lobe, particularly affecting the temporal pole, amygdala, hippocampus, entorhinal cortex, parahippocampal gyrus, and fusiform gyrus. There was an anterior-posterior gradient of atrophy as well as inferior-superior and medial-lateral gradients.

Conclusions

Patients with SQSTM1 mutations can have a varied clinical phenotype but appear to be particularly associated with focal temporal lobe atrophy that can predominantly affect the right or left hemisphere.

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