PROGRESSIVE WHITE MATTER
ABNORMALITIES IN AUTOSOMAL-DOMINANT
ALZHEIMER’S DISEASE: RESULTS OF THE DIAN
STUDY

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Background: DIAN (Dominantly Inherited Alzheimer’s Network) is an
international longitudinal study of autosomal dominant Alzheimer’s disease,
including individuals affected with, or at risk for, AD. In late onset
AD it is often difficult to separate white matter disease associated with
aging and diseases of aging (hypertension, diabetes, etc) from that of
AD. In this young cohort, we quantified WM pathology using volumetric
MRI and diffusion tensor imaging (DTI) in order to evaluate WM disease
in ADAD. Methods: 71 participants from the DIAN study underwent
DTI. Participants were classified into four groups based upon mutation
(M+ and M-) and dementia status (CDR, Table 1). DTI was acquired
using a 64 direction sequence at 3T. Image analysis was conducted
with Tract Based Spatial Statistics (TBSS), a part of FSL. Group-level
differences were assessed with a general linear model controlling for
age, gender, and education and corrected for multiple comparisons using
Threshold-Free Cluster Enhancement. Volumetric T1 (MPRAGE)
studies were processed with FreeSurfer to generate white matter volumes.
Results: White matter volumes decrease with carrier status and progressive
dementia (Figure 1). Associated loss of fractional anisotropy (FA,
Figure 2) and elevated mean diffusivity (MD, not shown) are widespread.
Periventricular white matter is particularly involved at very mild (CDR
0.5) and mild (CDR 1.0) dementia (Figure 2). Conclusions: These findings
support the hypothesis that widespread white matter abnormalities are associated
with dementia in ADAD, and that these abnormalities precede the
development of dementia.
<table>
<thead>
<tr>
<th></th>
<th>Non-carriers</th>
<th>Carriers</th>
<th>Carriers (M+)</th>
<th>Carriers (M+)</th>
<th>Carriers (M+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(M-)CDR 0</td>
<td>(M+)CDR 0</td>
<td>CDR 0</td>
<td>CDR 0.5</td>
<td>CDR &gt; 1</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>43</td>
<td>44</td>
<td>18</td>
<td>15</td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
<td>39.90 (9.02)</td>
<td>34.84 (9.08)</td>
<td>41.77 (10.95)</td>
<td>47.67 (8.63)</td>
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<tr>
<td><strong>Estimated time to dementia</strong></td>
<td>-5.48 (12.33)</td>
<td>-12.02 (8.47)</td>
<td>-1.72 (8.75)</td>
<td>+2.27 (0.02)</td>
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<tr>
<td><strong>Gender</strong></td>
<td>M—33%</td>
<td>M—36%</td>
<td>M—56%</td>
<td>M—60%</td>
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<tr>
<td><strong>Education</strong></td>
<td>15.05 (2.49)</td>
<td>14.61 (2.62)</td>
<td>13.50 (2.31)</td>
<td>12.27 (1.98)</td>
<td></td>
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</tbody>
</table>

*Mean (standard deviation) in years