# Parental History of Alzheimer Disease Predicts Abnormal White Matter in Cognitively Normal Elderly Individuals

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**Background**: Alzheimer Disease is characterized by the onset of dementia with associated cerebral atrophy and deposition of cerebral amyloid plaques. In addition, diffusion tensor MRI has characterized white matter abnormalities in individuals with Alzheimer Disease in the left anterior temporal lobe (1), as well as in the temporal lobe, splenium and cingulum (2), when compared to healthy, elderly controls. These white matter abnormalities may precede atrophy and clinically apparent dementia, and may represent some of the earliest changes apparent by imaging.

Greater interest in identifying individuals at risk for Alzheimer Disease is driving the search for earlier biochemical (3) and imaging biomarkers (4), which may predict onset of dementia and describe early pathophysiological changes prior to the onset of dementia. Although genes such as the APP, PS and APOE genes are well known to confer increased risk of Alzheimer Disease, there are likely a number of additional poorly understood genetic risk factors.

**Methods:** In order to determine if a parental history of Alzheimer Disease predicts early, pre-dementia changes in white matter, healthy, cognitively normal elderly subjects (CDR=0, n=30) were screened for a history of Alzheimer Disease in one or both biological parents. Healthy elderly controls (CDR=0, n=33) were also carefully screened for healthy, elderly biological parents without dementia. These participants underwent T1 and T2 anatomic, 25 direction echo planar diffusion tensor MR imaging with a 3.0 T Siemens scanner. Hand-drawn regions of interest were generated for evaluation of white matter diffusion measurements in each of the regions detailed below, for each participant following registration to an age-appropriate atlas. One-way ANOVA group analyses of the diffusion measurements were performed between the controls and subjects, controlling for age and gender. No significant group differences were noted between the subject and control groups in age, education, CSF $Abeta_{42}$ levels or global cerebral atrophy.

**Results**: Statistically significant differences in diffusion tensor measurements in the corpus callosum and the right parietal lobe were identified (Table 1).

**Conclusions**: These findings support the hypothesis that white matter abnormalities precede the clinically apparent onset of dementia, representing either early pathophysiological changes or fundamental differences in white matter integrity. These changes may place individuals at risk for subsequent development of Alzheimer Disease.

| | FA | MD | AxD | RaD |
|---|---|---|---|---|
| AD History | - / + | - / + | - / + | - / + |
| Genu | **0.84 / 0.87**** | 0.51 / 0.52 | 1.25 / 1.22 | **0.15 / 0.18*** |
| Splenium | 0.89 / 0.89 | 0.48 / 0.46 | **1.21 / 1.16*** | 0.12 / 0.11 |
| Precuneus | 0.40 / 0.40 | 0.60 / 0.59 | 0.86 / 0.86 | 0.46 / 0.46 |
| Temporal | 0.52 / 0.51 | 0.62 /0.62 | 1.01 / 1.02 | 0.42 / 0.43 |
| Parietal | **0.60 / 0.56**** | 0.53 / 0.54 | **0.97 / 0.92*** | 0.33 / 0.35 |
| Ant Cingulate | 0.58 / 0.58 | 0.57 / 0.58 | 1.01 / 0.99 | 0.37 / 0.37 |

Table 1. **Diffusion Tensor Measurements by region**. Fractional anisotropy (FA), mean (MD), radial (RaD) and axial (AxD) diffusivity measurements show regional differences between individuals with or without a parental history of Alzheimer Disease. *indicates $p < 0.05$. ** indicates $p < 0.02$ by one-way ANOVA controlling for age and gender.

Of note are the different patterns of diffusion tensor abnormalities depending on the region of interest. Whereas loss of fractional anisotropy in the genu was associated with a significant increase in radial diffusivity, a loss of anisotropy in the parietal lobe was associated with a significant loss of axial diffusivity in individuals with a parental history of Alzheimer Disease. A loss of axial diffusivity in the splenium was associated with no change in fractional anisotropy. These findings represent potential imaging biomarkers for future onset of dementia, and suggest disparate behavior of regional white matter. The present data establish a baseline for future longitudinal study.

**References**:
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