A genomic scan for age at onset of Alzheimer's disease in 437 families from the NIMH Genetic Initiative.

We performed linkage analysis for age at onset (AAO) in the total Alzheimer's disease (AD) NIMH sample (N = 437 families). Families were subset as late-onset (320 families, AAO ≥ 65) and early/mixed (117 families, at least 1 member with 50 < AAO < 65). Treating AAO as a censored trait, we obtained the gender and APOE adjusted residuals in a parametric survival model and analyzed the residuals as the quantitative trait (QT) in variance-component linkage analysis. For comparison, AAO-age at exam (AAE) was analyzed as the QT adjusting for affection status, gender, and APOE. Heritabilities for residual and AAO-AAE outcomes were 66.3% and 74.0%, respectively for the total sample, 56.0% and 57.0% in the late-onset sample, and 33.0% for both models in the early/mixed sample. The residual model yielded the largest peaks on chromosome 1 with LOD = 2.0 at 190 cM in the total set, LOD = 1.7 at 116 cM on chromosome 3 in the early/mixed subset, and LOD = 1.4 at 71 and 86 cM, respectively, on chromosome 6 in the late-onset subset. For the AAO-AAE outcome model the largest peaks were identified on chromosome 1 at 137 cM (LOD = 2.8) and chromosome 6 at 69 cM (LOD = 2.3) and 86 cM (LOD = 2.2) all in the late-onset subset. Additional peaks with LOD > 1 were identified on chromosomes 1, 2, 3, 6, 8, 9, 10, and 12 for the total sample and each subset. Results replicate previous findings, but identify additional suggestive peaks indicating the...
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Genetics of AAO in AD is complex with many chromosomal regions potentially containing modifying genes.

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