cognitive impairment defined by MMSE and TMT B time scores were eligible for the study.

There was no statistical difference in cognitive improvement as assessed by the primary efficacy measure, the V-ADAS-cog scores between donepezil and placebo after 18 weeks of treatment. There was a significant treatment effect favoring donepezil on several executive function tests (TMT B time, p=0.005; TMT A time, p=0.01; Exit25, p=0.02). Donepezil was well tolerated, with patients experiencing typical adverse events associated with cholinesterase inhibition and VaD. Discontinuation due to adverse events was 8.5% in placebo subjects and 11.6% in donepezil subjects.

Although donepezil had no effect on the V-ADAS-cog in CADASIL patients with cognitive impairment, improvements were noted on several scales associated with executive function. This suggests an involvement of cholinergic deficits in executive function, which fits with previous histopathologic data. Further, this trial illustrates the limitations of studies using ADAS-cog tests and similar tests used to study AD, as well as the need to incorporate executive function tests in future trials. The clinical relevance of these findings needs clarification, and further research is warranted.

Genome-Wide SNP Linkage Screen for Intracranial Aneurysm Susceptibility Genes: Results from 333 Multiplex IA Families

Genetic risk factors are considered important in the development, growth, and rupture of intracranial aneurysms (IAs). However, few of these risk factors have been identified. The Familial Intracranial Aneurysm (FIA) Study is a collaborative research effort of neurologists and neurosurgeons throughout the United States, Canada, Australia, and New Zealand that is studying genetic factors in 475 families with multiple IA-affected members.

Prof. Tatiana Foroud, Indiana University, Indianapolis, IN, discussed recent results from this collaboration, in which 6000 single nucleotide polymorphisms were screened in two independent groups of FIA families. This is the largest familial IA sample ever collected. It consisted of 333 families with 1895 members with both ruptured and unruptured IAs. All families had at least two members with an IA.

Subjects were classified using both a 'narrow' (n=705 definite IA cases) and 'broad' (n=866 definite or probable IA) disease definition. Multipoint model-free linkage analysis was performed. One analysis method was performed to identify genes that might have their greatest effect in those families with a high rate of smoking based on average pack-years. Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the 6K Illumina system.

A LOD score (logarithm base 10 of odds) was used to analyze linkage. By convention, a LOD score >3 indicates linkage.

Model-free linkage analyses detected modest evidence of linkage. Parametric analyses yielded an unadjusted LOD score of 2.5 on chromosome 4q (162 cM), with a rare disease allele (0.7%) and reduced penetrance for both heterozygotes and homozygotes. On chromosome 12p (50 cM), an unadjusted LOD score of 3.0 was obtained, under a recessive disease model with a more common disease allele (4% frequency). Significant evidence for a gene x smoking interaction was detected using both the narrow (LOD 4.1; p=0.001) and broad (LOD 3.2; p=0.01) disease definition detected on chromosomes 3, 7, and 12.

This study provides modest evidence of possible linkage of IA to several chromosomes. However, heritable risk for IA can be affected by age of diagnosis and demographic characteristics. Using smoking as a covariate in the linkage analyses allowed for the detection of additional genetic loci that appear to have a strong interaction with this important covariate. Though these data suggest it is unlikely that there is a single common variant with a strong effect in the majority of the IA families, parents, siblings, and children of an IA family member may be at increased risk for this condition.

Subsequent analyses were performed to test whether common susceptibility genes might contribute to the risk of intracranial as well as aortic aneurysms (AA). Analyses employing 29 families having members with either IA or AA confirmed a previously reported linkage to chromosome 11q24-25 and also detected linkage to chromosome 6p.