Association of Genetic Variation in the Electron Transport Chain and Alzheimer's Disease

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Background

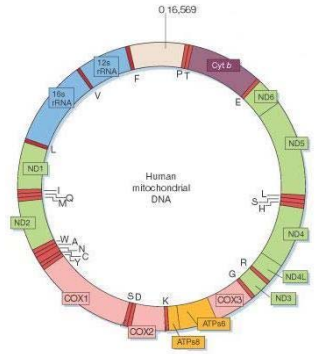
Alzheimer's disease is the most common form of age-related dementia and one of the most serious health problems in the industrialized world. Current theories suggest that genetics play a large role in the development and expression of Alzheimer's disease; however, non-genetic factors are also very important. To date there is a large literature documenting the role of cardiovascular disease and related factors as well as cerebral and systemic inflammation in the development and progression of Alzheimer's disease[1, 2]. Recent progress in the Human Genome Project, the HapMap Project, and Genome-wide Association studies have made it feasible, for the first time, to conduct allelic association studies for all common polymorphisms found in the human genome. Appropriate use of this technology requires large numbers of well-characterized subjects. The multi-site collaborative effort of the Texas Alzheimer's Disease Research Consortium (TARC) is currently investigating the simultaneous roles of genetics, inflammation, cardiovascular disease, and metabolic disorders (e.g., hyperlipidemia, hyperinsulinemia) in Alzheimer's disease. As part of this study, the TARC is conducting a longitudinal study of over 800 active patients (500 Alzheimer's disease and 300 cognitively normal individuals).

Genetics and Alzheimer's

- Genetically, Alzheimer's disease is heterogeneous and complex, with age of onset being one of the most evident dichotomies
- More than 160 highly penetrant but rare mutations have been described in three genes (*APP*, *PSEN1*, and *PSEN2*) that cause early-onset familial Alzheimer's disease
- Familial Alzheimer's, which is inherited in a Mendelian fashion, accounts for less than five percent of Alzheimer's disease burden
- Apolipoprotein E gene (APOE-ε4) has been associated with increased susceptibility to the more common, late-onset form of the disease [3, 4]
- APOE-ε4 accounts for less than half of the genetic variance in Alzheimer's disease, suggesting that additional Alzheimer's disease genes remain to be identified
- Data from two recent large GWAS studies support this contention.[5, 6]

Mitochondria and Alzheimer's Disease

- The Beta amyloid cascade hypothesis remains the most widely accepted pathogenic model of Alzheimer's[7]
- The overall role that Beta Amyloid plays in the majority of sporadic cases is unclear
- There is increasing evidence that oxidative stress and mitochondrial dysfunction occurs in the brain and peripheral tissues of Alzheimer's disease patients
- The proteins encoded by all three of the genes responsible for Familial Alzheimer's disease have been localized to the mitochondria
- Mitochondria play a central role in cellular energy metabolism, apoptosis, and steroidogenesis, all of which are critical processes for neural functioning
- The mitochondrial genome encodes 13 enzymatic subunits that comprise the enzymatic portion of the electron transport chain
- Previous studies examining DNA polymorphisms within the mitochondrial-encoded genes have provided contradicting evidence regarding their association with the development of Alzheimer's disease



Data Collection

In this study, 474 Alzheimer's disease and 247 cognitively normal individuals were genotyped with the Affymetrix® Genome-wide Human SNP Array 6.0. This SNP panel includes more than 906,600 single nucleotide polymorphisms (SNPs) and more than 946,000 probes for the detection of copy number variation. The array contains 109 mitochondrial polymorphisms that which were assessed for association with Alzheimer's disease.

Texas Alzheimer's Research Consortium Demographics

The Texas Alzheimer's Research Consortium (TARC) is a multi-center research effort comprised of five medical research institutions across the state of Texas. Researchers at the four initial TARC institutions have accrued a large longitudinal cohort for the multidisciplinary study of Alzheimer's disease. The current TARC study population contains 615 Alzheimer's disease patients and 350 cognitively normal controls. TARC subjects are primarily female (62%) and Caucasian (93%), with the mean age at baseline of 74 years. As part of the longitudinal study, neuropsychological and clinical data as well as samples of whole blood, plasma, serum, and DNA were collected from each patient at each annual visit.

Data Analysis

- Mitochondrial SNPs were excluded from the analysis which had a Minor Allele Frequency <1%
- Mitochondrial SNPs were analyzed individually with disease status by chi-square analysis
- SNPs were excluded from further analysis if chi-square analyses with disease status had a probability >0.05
- Remaining SNPs were tested with for significant linkage disequilibrium by chi-square analysis
- SNPs that exhibited significant linkage disequilibrium were excluded from further analyses
- SNPs were tested individually by Binary Logistic Regression for association with disease status
- Co-factors included in the Logistic Regression included Baseline Age, Education, Sex, and APOE e4 allele count
- SNPs were combined into a mitochondrial genetic load score
  - Genetic load was calculated by summing risk alleles
  - Genetic load loci were unweighted
- Genetic Load Score was tested by Binary Logistic Regression for association with disease status
- Co-factors included in the Logistic Regression included Baseline Age, Education, Sex, and APOE e4 allele count

Results

- Five SNPs were identified as associated with Alzheimer's disease from the chi-square analysis
- Two of these SNPs (rs2853501 and rs2853506) encoded non-synonymous mutations and were not significantly linked to each other P=0.15 (The remaining 3 mtSNPs were excluded from further analysis)

Results

- rs2853501 is found in ND5 (mt position 13106), is an T/C substitution and encodes an Isoleucine-Valine amino acid change
- rs2853506 is found in Cyt *b* (mt position 15219), is an A/G substitution and encodes a Threonine-Alanine amino acid change
- Individually, each SNP was associated with Alzheimer's
- rs2853501 (T allele) aOR 3.82 (95%CI 2.51-5.80; p<0.001)
- rs2853506 (A allele) aOR 2.94 (95%CI 1.14-7.60; p=0.026)
- Genetic Load Scores were calculated by summing risk alleles from rs2853501 (C=0;T=1) and rs2853506 (G=0;A=1) ; Risk scores ranged from 0 to 2

	Beta	95% Confidence Interval		Significance
Sex(M)	0.611	0.415	0.901	0.013
Baseline Age	1.094	1.069	1.118	>0.001
Education	0.981	0.95	1.013	0.25
APOE e4 count	3.961	2.84	5.525	>0.001
Genetic Load	3.514	2.392	5.161	>0.001

Summary and Conclusion

- Mitochondrial polymorphisms within ND5 and Cytochrome b were associated with Alzheimer's disease
- Combining mitochondrial risk alleles into a genetic load score allowed simultaneous screening of both SNPs
- Polymorphisms within the Electron Transport Chain may provide increased risk for the development of Alzheimer's disease.

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