TUESDAY, JULY 16, 2013
POSTER PRESENTATIONS: P3

P3-001 MITOCHONDRIAL GENOME-WIDE ASSOCIATION STUDY OF ALZHEIMER'S DISEASE

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Background: Mitochondrial dysfunction may play a key role in the pathogenesis of Alzheimer's disease (AD) with progressive mitochondrial dysfunction reported in post-mortem AD brains (Devi et al. 2006). Genetic defects in the mitochondrial genome may result in mitochondrial dysfunction and increase AD susceptibility. Several studies have reported the association of specific mitochondrial DNA (mtDNA) single nucleotide polymorphisms (SNPs) with AD, with concordant and conflicting results. Also, investigation at the sub-haplogroup level has shown a positive association between AD and sub-haplogroup H5 (Santoro et al. 2010). Recently, we sort to replicate the mtDNA SNP associations reported with AD utilising a powerful cohort of 4,133 AD cases and 1,602 matched controls (the Genetic and Environmental Risk in AD1 (GERAD1) sample). However, no SNP showed consistent association (Hudson et al. 2012). This study investigates the role of mtDNA SNPs and sub-haplogroups in AD using a two stage analysis. Stage one analysed mitochondrial SNPs represented on the Illumina 610-quad chip in the GERAD1 sample. Stage 2 genotyped 123 mitochondrial variants in an additional 8,042 cases and 9,387 controls as part of the International Genomics of Alzheimer's Project (IGAP). **Methods:** This study comprised a total sample of 12175 Alzheimer's disease cases and 10989 controls. Stage 1 genotyping was performed on the Illumina 610-quad chip at the Sanger Institute, UK. Stage 2 genotyping was performed using a custom Illumina iSelect array at the Centre National de Génotypage (CNG), France. Variant frequencies were compared in case patients and controls: 1) on an individual SNP-by-SNP basis using Pearson's test (p) and 2) across the entire data set by permuting the disease status (p*), an approach that partially accounts for the phylogenetic structure of the data. All statistical analysis was carried out in PLINK (v2.050) using a single allele-based model. **Results:** Will be presented at AAIC 2013. **Conclusions:** A large body of evidence suggests that intervention at the mitochondrial level could ameliorate Aß triggered dysfunction and degeneration, and reduce or alleviate defects in glucose utilization and oxidative phosphorylation in the brains of AD patients. This study uses a powerful design to investigate mitochondrial genetic variation in a large AD case-control dataset.

P3-002 GWAS OF THE JOINT ADGC DATA SET IDENTIFIES NOVEL COMMON VARIANTS ASSOCIATED WITH LATE-ONSET ALZHEIMER'S DISEASE

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Background: Combined data sets produce more power to detect associations than meta-analysis of the same sample size. We prepared a combined-dataset from the 15 studies that make up the ADGC and performed a genome-wide association study (GWAS) for late-onset Alzheimer's disease (LOAD). **Methods:** We used directly genotyped SNPs in common across the 15 ADGC studies for principal components for population structure, and to identify cryptic relatedness using KING-ROBUST. We combined HapMap2 imputed data sets after excluding strand ambiguous SNPs. We performed a case-control association for LOAD on a) 19,692 individuals who were no more closely related than 3 rd degree relatives, and b) on 22,645 individuals which included known and cryptically related people. Initial models included terms for population stratification and each study site. Secondary models additionally adjusted for age, sex and APOE ε 4 dosage. **Results:** In the combined analysis, 20 different loci were associated with AD at a p- value $\leq$ 5.0x10 -6. The strongest signal from our primary analysis was in the APOE region. We confirmed previously identified loci. Additionally, we identified four novel suggestive/significant loci of interest at HBEGF-PFDN1 (rs6884244, p- value =1.75x10 -8; OR=1.13), AUTS2 (rs1686315, p- value =7.93x10 -8; OR=1.19), ANAPC1 (rs9308632, p- value =7.77x10 -7; OR=0.90)and ADAMTSL3 (rs12917432, p- value =3.25x10 -7; OR=0.88). There were 19 SNPs in the HBEGF-PFDN1 region with p values$<$1x10 -6. **Conclusions:** We identified some novel loci associated with AD with a combined ADGC HapMap2 data set. Subsequent work will include attempts to replicate these findings with other data sets.

P3-003 GENOME-WIDE SNP ANALYSIS FINDS EXECUTIVE-PROMINENT LATE-ONSET ALZHEIMER'S DISEASE IS HIGHLY HERITABLE

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Background: Literature suggests 10-15% of people early in the course of late-onset Alzheimer's disease (LOAD) present with a prominent executive functioning deficit. Imaging and neuropathological studies have found differences between these individuals and those with more typical memory-prominent LOAD. We sought to use genome-wide single nucleotide polymorphism (SNP) data to estimate the heritability of differences between memory and executive functioning among people with early stage LOAD. **Methods:** Participants were from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and from the Uniform Data Set (UDS) subset of genotyped participants from the National Alzheimer's Coordinating Center (NACC) in the Alzheimer's Disease Genetics Consortium (ADGC). Phenotype data were derived from cross-sectional neuropsychological data at the first visit with Clinical Dementia Rating Scale 0.5 or 1.0 or at the time of initial conversion to LOAD. We used parameter estimates from published analyses of memory and executive functioning composite scores (ADNI-Mem and ADNI-Exec) to generate memory and executive functioning scores on the same metric from the two datasetss. Our phenotype was the difference between these scores. We used standard quality control steps with genome-wide genotype data imputed to 1000 Genomes.We used Genome-wide Complex Trait Analysis (GCTA; J Yang et al. 2010) to estimate heritability (the proportion of phenotypic variance explained) with the genome-wide SNP data. **Results:** There were 624 participants from NACC and 302 from ADNI (total n = 926) who met our entry criteria. Our

phenotype was approximately normally distributed, with mean (SD) of 0.62 (1.4). The heritability estimate h 2 (and its standard error) were 0.69 (0.12), p- value (compared to h 2 = 0) =0.0008. While sample size limited statistical power to detect genome-wide associations, preliminary association testing identified several SNPs with large effect sizes (standardized $\beta >$ 0.30). **Conclusions:** We co-calibrated neuropsychological data across two studies with different neuropsychological batteries to develop a unified phenotype of executive-prominent LOAD, which demonstrated high heritability. Future directions include adding additional datasets and identifying particular genetic loci associated with this phenotype.

P3-004 NOVEL RARE VARIANTS ASSOCIATED WITH LATE-ONSET ALZHEIMER'S DISEASE CANDIDATE GENES IN CARIBBEAN HISPANIC FAMILIES

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Background: Common variants associated identified by Genome-Wide Association Studies (GWAS) explain a small proportion of the substantial heritability attributed to Late Onset Alzheimer's Disease (LOAD). In this experiment, we conducted whole exome sequencing in a sample of 183 patients of Caribbean Hispanic ancestry targeting 24 LOAD susceptibility genes identified through GWAS. **Methods:** We studies 183 Caribbean Hispanic LOAD cases (54% of the patients come from large families with multiple affected) for 25 candidate genes (ABCA7, APP, BIN1, CD2AP, CLU, CR1, EPHA1, EXOC3L2, GRN, MAPT, MS4A4E, MS4A6A, MTHFD1L, PICALM, PION, PSAPL1, PSEN1, PSEN2, SORCS1, SORCS2, SORCS3, SORL1, TARDBP, VCP and WASF1). Sequencing was carried out on Illumina HiSeq 2000 sequencer. The reads were aligned to the human reference build 37.1 using the Burrows-Wheeler Aligner. The GATK pipeline was used to recalibrate the BAM files, call variants and downstream quality control of the variants. Variants were filtered for base, mapping and variant calling quality levels to identify potentially pathogenic mutations. **Results:** We achieved over 100 fold mean sequence coverage for the samples. We identified 373 high quality exonic variants. Variant filtering of these exonic variants (Figure 1) yielded two coding non-synonymous new variants segregating with LOAD families (present in at least 2 affected siblings). Two siblings from the same LOAD family carried a new variant in WASF1 gene (chr6:110423394bp, G>A, Arg307Cys). One of the siblings appeared to be homozygous for the mutation (GG).The other variant in EPHA1 gene (chr7:143095499bp G>A, Pro460Leu) was present in two siblings (both heterozygous AG) from a LOAD family where the other members did not carry the mutation. EPHA1 gene is a member of the ephrin receptor subfamily with suggested roles in apoptosis and inflammation. WASF1 encodes a protein part of the Wiskott-Aldrich syndrome protein (WASP)-family, that has been implicated in the disturbance of actin assembly in AD brains. **Conclusions:** Our results demonstrate that rare variants in these candidate genes could explain an important proportion of genetic heritability of LOAD. Work in progress includes the validation of the variants by further genotyping of carriers and unrelated controls.

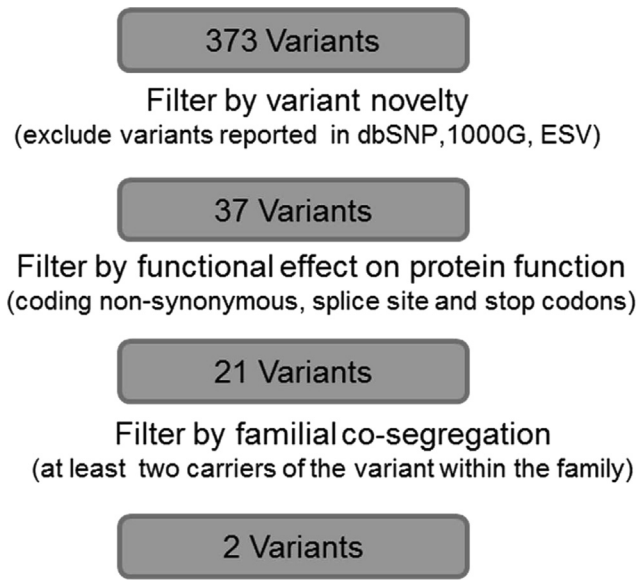

Figure 1. Filtering steps in WES data analysis of LOAD

P3-005 POPULATION-BASED ANALYSIS OF LATE-ONSET ALZHEIMER'S DISEASE RISK ALLELES IDENTIFIES CANDIDATE GENE-GENE INTERACTIONS

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Background: Researchers have implicated several genes associated with late-onset Alzheimer's disease including APOE where APOE ε4 increases risk and APOE ε2 reduces risk. Nine additional genes found on AlzGene.org significantly affect risk; BIN1 (rs744373), ABCA7 (rs3764650), CR1 (rs3818361), MS4A4E (rs670139), and CD2AP (rs9349407) are associated with increased risk while PICALM (rs3851179), MS4A6A (rs610932), CD33 (rs3865444), and CLU (rs11136000) are associated with decreased risk. While these loci have been studied in various combinations, no study has reported the combined population attributable fraction (PAF) for all risk alleles. Previously reported PAFs are also from clinically ascertained samples rather than a population-based sample. The latter may more reliably measure population risk. Additionally, the contribution of these nine risk alleles to case-control classification performance has been evaluated in just one paper by Verhaaren et al. **Methods:** Exactly 5,092 samples from the Cache County Memory Study were genotyped for APOE and the nine Alzheimer's risk alleles listed on AlzGene.org's "ALZGENE TOP RESULTS" list. We used logistic regression and ROC analysis to assess case-control predictive performance of the nine non- APOE alleles under additive and non-additive models. Specifically, we tested whether the non-APOE alleles significantly improved case-control classification over models excluding the non-APOE alleles. All models were adjusted for age and gender. We also compared odds ratios and PAFs between data from AlzGene.org and the Cache County study. **Results:** Odds ratios from Cache County were comparable in direction and magnitude to odds ratios from AlzGene.org except for ABCA7 and CR1. PAFs as calculated from AlzGene.org data ranged from 2.25% to 37.27% while those from Cache County ranged from 0.05% to 20.13%. The non- APOE alleles significantly improved case-control classification (AUC = 0.82) over APOE alone (AUC = 0.78) when allelic interactions were permitted ($p < 8.39e-07$). We identified significant allelic interactions: CD33-MS4A4E (SF = 5.31; $p < 0.003$) and CLU-MS4A4E (SF = 3.81; $p < 0.016$). **Conclusions:** While the nine non- APOE alleles contribute significantly to case-control classification, the improvement is marginal and does not reach the desired sensitivity or specificity for clinical use. The results suggest, however, that gene-gene interactions are important to solving Alzheimer's etiology.

P3-006 LATE-ONSET ALZHEIMER'S DISEASE GENETIC RISK FACTORS IN TWO CANADIAN COHORTS: CSHA AND ACCORD

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