

meta-analysis of existing genome-wide association studies on AD performed by the International Genomics of Alzheimer's Project (IGAP), an in-tronic variant in SQSTM1 (rs72807343) showed sub-genome wide association with AD. We hypothesized that SQSTM1 variants could act as risk factors for AD. **Methods:** We systematically screened the coding SQSTM1 region in a Belgian cohort of 435 early onset-onset AD patients and 872 control individuals. To test association between rare SQSTM1 variants (MAF<0.01) and early onset AD, we performed a rare variant burden analysis. **Results:** The analysis revealed 30 coding variants of which 12 were non-synonymous: 2 in AD and 9 in controls only. Significant allelic association with AD was observed for both common synonymous variants p.D292= (OR=0.82 [95%CI 0.68-0.99]; allelic p-value 0.035) and p.R312= (OR=0.81 [95%CI 0.68-0.98]; allelic p-value 0.03). We identified 2 rare variants in the ubiquitin-associated (UBA) domain of the p62 protein, which were reported in patients with PDB. Further research of these pathogenic variants in context of AD is needed. Rare variant meta-analysis did not show association with AD. **Conclusions:** To extend our findings, we currently are screening the coding SQSTM1 region in a large AD cohort ascertained within the European Early-Onset Dementia (EOD) consortium and originating from Italia, Spain, Sweden, Germany and Portugal. Sequencing is performed on a MiSeq-platform (Illumina) after MASTR-assay target enrichment.

O1-04-05 NOVEL CODING VARIANTS IN TREM2 INCREASE RISK FOR ALZHEIMER'S DISEASE

Carlos Cruchaga¹, Sheng Chih Jin², Bruno A. Benitez³, Celeste Karch⁴, Alison Goate², ¹Washington University School of Medicine, Saint Louis, Missouri, United States; ²Washington University in St. Louis, St. Louis, Missouri, United States; ³Washington University in Saint Louis, Saint Louis, Missouri, United States; ⁴Washington University, St Louis, Missouri, United States. Contact e-mail: jin810@wustl.edu

Background: The triggering receptor expressed on myeloid 2 (TREM2) variant c.140G>A (p.Arg47His) was previously shown to increase Alzheimer's disease (AD) risk. We hypothesized that there are additional rare variants in TREM2 that substantially affect AD risk. **Methods:** Therefore, we performed pooled sequencing of TREM2 coding regions in 2,082 AD cases and 1,648 cognitively normal elderly controls of European American (EA) descent and compared genotypes in 878 cases and 556 controls with both exome array and sequencing data to assess the concordance percentage and statistical power in detecting rare-variant association. **Results:** We identified 16 non-synonymous variants, 7 of which were novel in the sequence data. Gene-based tests demonstrate these variants are significantly associated with AD (OR = 2.55; P SKAT-O = 5.96×10^{-7}). The association of TREM2 variants with AD is retained after excluding p.Arg47His (OR = 2.48; P SKAT-O = 7.72×10^{-5}), indicating that additional TREM2 variants affect AD risk. c.185G>A (p.Arg62His) was also associated with disease risk ($p=2.36 \times 10^{-4}$, OR = 2.36 [1.47-3.80]). Comparison of genotypes from exome arrays and deep re-sequencing shows a concordance rate of 88% among heterozygotes and rare homozygotes of overlapping variants that passed quality controls. Furthermore, 52% of heterozygotes and rare homozygotes identified by pooled sequencing were missing in exome arrays. **Conclusions:** Our results also suggest that sequencing-based methods have more power to detect rare-variant association and only require a 5-fold smaller sample size compared to exome arrays to achieve comparable power. Additionally, analysis of our sequencing data across different algorithms demonstrated that SKAT-O outperformed other rare-variant association methods.

O1-04-06 NEXT-GENERATION SEQUENCING GENE DISCOVERY STUDIES IN EARLY-ONSET DEMENTIA

Julie van der Zee¹, Lubina Dillen², Nicole Ziliotto³, William Deschamps³, Christine Van Broeckhoven³ BELNEU CONSORTIUM³ EU EOD Consortium³, ¹Neurodegenerative Brain Diseases Group, VIB and Institute

Bron-Bunge, University of Antwerp, Antwerpen, Belgium; ²Neurodegenerative Brain Diseases Group, VIB and Institute Bron-Bunge, University of Antwerp, Antwerpen, Belgium; ³Neurodegenerative Brain Diseases Group, VIB and Institute Bron-Bunge, University of Antwerp, Antwerp, Belgium. Contact e-mail: julie.vanderzee@molgen.vib-ua.be

Background: Major breakthroughs in dementia research were realized in studying large families with an early disease onset. Although early-onset dementia (EOD) is relatively rare, these findings are at the basis of our current understanding of the disease biology of neurodegenerative dementias and at the foundation of current drug development strategies. **Methods:** To further elucidate the missing heritability in dementia we apply whole exome sequencing (WES) on selected EOD patients with high genetic load. This project builds on an impressive collection of EOD patients (> 5000)/families ascertained within the framework of the European Early-Onset Dementia consortium. Patients of all dementia phenotypes are selected based on onset age < 65 years. We prioritize the WES studies on families with DNA for 2-5 affected relatives and isolated patients with onset age < 55 years and, particularly for Alzheimer patients, APOE E4 minus carriers. Selected patients are profiled for mutations in known genes using a NGS gene panel of 30 genes associated with neurodegenerative dementia and related diseases. **Results:** At present we selected 11 families with DNA of 2-3 patients. Except for one recessive pedigree all families were consistent with dominant inheritance. Further, we included 272 familial or sporadic isolated patients with disease onset below 55 years. Phenotypes include AD, FTLN, FTLN-ALS, ALS, CBD and ANCL. In one family WES we already identified a genetic variant that most probably explains disease. The pedigree includes a sibship of 5 of whom 4 patients and 2 unaffected parents, consistent with recessive disease. The patients suffer from a mixed phenotype of cognitive deterioration, speech problems, extrapyramidal symptoms and epilepsy presenting at age 50-60 years. The candidate variant is homozygous in the 3 tested patients and heterozygous in the unaffected mother. The unaffected sib is homozygous for the wild-type allele. **Conclusions:** A better understanding of the genetics and biology of dementia will improve classification of patients based on their molecular profile rather than on clinico-pathological symptomatology, which is expected to drastically improve development of effective diagnostic tools, biomarkers and targeted therapies, both for early- and the more common late-onset forms of dementia.

SUNDAY, JULY 13, 2014

ORAL SESSIONS

O1-05

CLINICAL TRIALS I: TRIAL DESIGN AND OUTCOME MEASURES

O1-05-01 MODELING HOW THE INTENSITY OF THE INITIAL TREATMENT RESPONSE FORECASTS DEMENTIA PROGRESSION IN ALZHEIMER'S DISEASE

Kenneth Rockwood, Matthew Richard, Arnold Mitnitski, DGI Clinical, Halifax, Nova Scotia, Canada. Contact e-mail: asimpson@dgiclinical.com

Background: Cholinesterase inhibitors and memantine remain the main stays of treatment for people with Alzheimer's disease (AD). Not everyone responds, and of those who do, not all show a uniform treatment effect. Our objective was to investigate how the intensity of the initial treatment response forecasts dementia progression in AD. **Methods:** Memory Clinic patients who were diagnosed with AD and treated with a cholinesterase inhibitor were evaluated. The initial treatment response (~6 months) was related to long term changes (>12 months). SymptomGuide tm tracking score and cognitive test scores were used to assay treatment effects. Logistic regression was used to model long-term AD state-change, with separate models for subjects initially showing worsening and subjects showing initial improvement. Modeling was performed separately for each measurement. **Results:** Of the 94 patients with SymptomGuide tm tracking, 44 (47%) showed