P1-211 WHOSE MUTATION IS IT?

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Background: For clinical research with First Nations, the marriage of cultural ideals and western medicine is dynamic. Many issues have arisen while working with a First Nation population in British Columbia who has EOFAD due to a unique mutation in the PS1 gene. This has led to an obligatory need for partnerships. The Nation members are close, interact regularly with one another through community activities on their traditional territory and have information access through various media. **Methods:** Qualitative evaluation of focus group sessions has revealed longstanding patterns of interactions with First Nations and western systems. In a follow-up community based research meeting, a member stated "I am not worried at all about stigmas because stereotyping has always been part of the First Nations." At the same time, another remarked that "we won't be acknowledged for the work we will be contributing if our nation remains anonymous." **Results:** Discussion includes ownership: Who has the right to benefit from discovery or to determine use of the discovery? How can a clinical discovery transition to a community benefit, even if the discovery has a potential difficult consequence (EOFAD)? Can the community prepare for this? Does the community want to prepare for this, especially in the face of other priorities? Above all, how can the western ethics norm of protection of individual rights be consistent with and part of communal rights? Keeping the name of participants and their community confidential could undermine the higher ethical principal of relational accountability. **Conclusions:** Shene (2002) argues that the existence of a mutation should be regarded as familial information, not capable of veto by one family member. Port et al (2008) suggest that in a hierarchical tribal context, rights of the individual may be relinquished in favour of the rights of the tribe. To date, Canadian researchers working with Indigenous peoples are encouraged to follow OCAP, which promotes collective **O**wnership, **C**ontrol, **A**ccess, **P**ossession of data. Reconciliation between OCAP and more usual academic and clinical structures needs a strong partnership. Bringing the groups to common ground reveals ongoing interactive thoughtful discussion.

P1-212 ALZHEIMER'S DISEASE HIPPOCAMPUS MICRO-RNA EXPRESSION

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Background: MicroRNAs play an essential role in gene regulation in the brain. However, little is known about their role in neurodegenerative diseases, such as late-onset Alzheimer's disease (AD). Characterizing expression profiles of microRNA in AD brain may help elucidate the role of microRNA in the pathophysiology of AD and may lead to identification of AD specific biomarkers. The aim of this exploratory investigation was to determine if AD hippocampus microRNAs are differentially expressed compared to AD cerebellum, control hippocampus or control cerebellum. **Methods:** First, post-mortem brain samples were pooled to measure multiple microRNA (n = 377) levels using microRNA arrays. Pooled samples consisted of AD hippocampus, AD cerebellum, control hippocampus, or control cerebellum (n = 21 each). Second, individual post-mortem brain AD and control samples, consisting of a subset of the pooled sample, were used in qRT-PCR assays to further explore differences in microRNA levels between subjects and according to *APOE* e4 genotype, gender, amyloid plaque score or Braak stage. In addition, *in silico* analyses were performed to predict target genes for differentially expressed microRNAs. **Results:** We found several microRNA (n = 20) to be differentially expressed in the AD hippocampus compared to controls using microRNA arrays. Many of these 20 microRNA are predicted to target AD relevant genes (i.e. *ADAM10, APP, BACE1, MAPT, PSEN1* and *PSEN2).* A subset of these 20 microRNA were measured using qRT-PCR, of which three microRNA; miR-15a, miR-330-3p, miR-501-5p, are strongly associated with hippocampus expression compared to cerebellum, independent of disease status. MiR-15a level is associated with *APOE* e4. MiR-330-3p level is associated with gender, amyloid plaque score and Braak stage. MiR-501-5p level is associated with *APOE* e4, gender and amyloid plaque score. **Conclusions:** In conclusion, this investigation demonstrates that microRNA levels are differentially expressed according to brain region and are associated with *APOE* e4, amyloid plaque score and Braak stage. MicroRNA identified in this exploratory study are predicted to target AD relevant genes and thus may warrant further investigation into their functional impact on expression and their utility as biomarkers of neurodegenerative disease.

P1-213 RARE GENETIC VARIANTS IN APP, PSEN1, PSEN2, GRN, APOE AND MAPT ASSOCIATED WITH CSF Aß AND TAU/PTAU181 LEVELS IN PATIENTS WITH LATE-ONSET ALZHEIMER'S DISEASE

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Background: To date the genetic variations identified by several genome-wide association studies have explained only a small fraction of the heritable risk for Late-Onset Alzheimer's diseases. Rare variants are predicted to be playing an important role in the genetic of complex traits. The cerebrospinal fluid (CSF) Aß and tau levels have proven to be the most cost-effective endophenotype for research purposes. **Methods:** 224 individuals from the WU-ADRC study were included. We used two DNA pools; a "high-risk" is formed by people at the bottom 30% of CSF Aß42 levels and at the top 30% of CSF tau and ptau181 levels. The "low-risk" pool consisted of people at the top 30% of CSF Aß42 and at the bottom 30% of tau and ptau181 levels. The targeted genomic regions were amplified by high-fidelity PCR. The PCR products were pooled and sequenced using the Illumina sequencing technology. The SPLINTER was used for calling and estimating the frequency of the variants. SIFT2 was used to predict the effect of variants on protein structure and function. The Sequenon was used for validation. **Results:** A total of 97 significant variants were identified in both groups. Of all those, 60% had a minor allele frequency $< 5\%$. Non-synonymous (nSv) (36), synonymous (19) and splice-site sequence (3)variants were found along all six genes. To date we have validated 13 of all nSv; seven have been previously reported but none have a clear clinical interpretation, and six are novel variants. 15 variants have resulted to be non-polymorphic and seven we are validating by using another technology. Five variants were common to both pools. Only two nSv in MAPT2 were found to be specific for the high risk pool. On the other hand, one nSv in PSEN2, GRN, APOE, respectively and three in MAPT were found in the low risk pool. **Conclusions:** In the present study, we have identified novel rare variants in the genes encoding APP, PSEN1, PSEN2, GRN, APOE and MAPT genes in subsets of individuals estimated to have the highest and lowest AD risk based on the combined CSF Aß and tau levels.

P1-214 FALSE REASSURANCE FOLLOWING GENETIC SUSCEPTIBILITY TESTING FOR ALZHEIMER'S DISEASE: EVIDENCE FROM THE REVEAL STUDY

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Background: False reassurance has been hypothesized to occur when persons receiving negative genetic test results inappropriately under-estimate their disease risk. Few studies have examined this empirically. We utilized self-reported risk for Alzheimer's disease (AD) to see if false reassurance could be observed in cognitively normal individuals following genetic risk assessment. **Methods:** The REVEAL Study is a series of multisite randomized controlled trials assessing the impact of Apolipoprotein E (*APOE*) disclosure and genetic risk assessment for AD. This analysis used 6-week post-disclosure data from participants in the second and third REVEAL trials with a family history of AD (n = 434; mean age 58.2yrs±10.8;66% female; 16% African American). We tested whether those who learned that they were e4-were more likely to underestimate their actual AD risk compared to those who learned that they were e4+ using logistic regression and controlling for age, gender, education, number of affected relatives and REVEAL trial. Since all participants had a first degree relative with AD, and since all educational materials in the study stressed the importance of heritable risk regardless of APOE genotype, false reassurance was defined as occurring in participants who reported a perceived risk that was lower, or equal, to someone who did *not* have a family history of AD (eg. 10-15% lifetime risk of AD). **Results:** Twenty-six percent of participants underestimated their risk of developing AD (defined above). Participants who were e4- (37%) had greater odds of underestimating their AD risk compared to e4+ participants (10%) (OR = 5.17, 95% CI: 2.84-9.41, $p < 0.001$). Participants who were younger than 60 years or who were African American also showed a risk underestimation (OR = 2.81,95% CI: 1.72-4.56, $p < 0.001$ and OR = 2.70, 95% CI: 1.44-5.04, $p = 0.002$, respectively). **Conclusions:** These results demonstrate that false reassurance occurs following genetic susceptibility testing for AD among individuals who learn that they are APOE e4-. As researchers begin stratifying AD intervention trials by including genetic testing and clinicians begin using genetic testing for risk estimation, they should be aware that false reassurance among individuals who learn negative genetic test results may make them less likely to participate in research trials, behavior modifications or other interventions.

P1-215 GRADING THE CREDIBILITY OF GENETIC ASSOCIATIONS IN ALZHEIMER'S DISEASE USING THE INTERIM VENICE CRITERIA

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Background: The Alzgene database is a valuable resource for researchers working in Alzheimer's disease (AD). In the database, the credibility of genetic associations is graded using the interim Venice Criteria but these criteria have never been formally evaluated. **Methods:** We evaluated the robustness of the Venice grades in Alzgene data in a simulation study by adding hypothetical results of simulated studies to the meta-analyses in the top list. We further conducted a follow-up study of the interim grades of the top list. **Results:** The Alzgene 'top list' changed considerably (40%) over the course of one year. A total of 3 genes with strong credibility were graded to weak within this short period. When evaluating the question whether this is due to a high type 1 error (p-values) or type 2 error (low power), we found that increasing power had very little effect on the positive predictive value of a finding, but the impact of testing with a lower p-value is major. Based on a data-freeze of December 2009 our simulations show that many genes could drop due to a low OR (< 1.15; bias criterion), except for APOE and ACE. Our simulation studies show it is impossible to change the credibility of ACE based on the heterogeneity (I2). However, the credibility for ACE altered empirically due to first study bias. **Conclusions:** Based on our finding we propose evidence criterion by a criterion based on the p-values and to replace the low summary OR criterion for bias by a criterion based on the presence of replication.

P1-216 IDENTIFICATION OF ALZHEIMER'S DISEASE HAPLOTYPE THAT PREDICTS EFFICIENCY OF SORL1/SORLA EXPRESSION IN THE BRAIN

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Background: SORLA is an intracellular sorting receptor for amyloid precursor protein (APP) that prevents processing of this precursor into amyloidogenic products. Loss of receptor expression has been documented in patients suffering from sporadic Alzheimer disease (AD). Also, genetic variants in SORL1 (the gene encoding SORLA) have been associated with late-onset AD in the human population. However, a direct link between distinct SORL1 variants and receptor protein expression is lacking. **Methods:** Brain autopsy material from 88 confirmed cases of AD and 85 matched unaffected individuals were obtained from the Netherlands Brain Bank and London Brain Bank. DNA, RNA, and proteins were extracted from brain autopsies of AD cases and controls and used for *SORL1* genotyping, RNA profiling, and SORLA protein quantification, respectively. **Results:** Our studies identified a novel SORL1 haplotype consisting of two SNPs in the 3' gene region that is associated with poor receptor expression in the brain of AD cases. The gene variation alters the SORL1 transcript sequence, resulting in a change from frequent to rare codon usage in the minor risk haplotype. Studies in cultured cells confirm less efficient translation of the minor receptor transcripts into protein. **Conclusions:** Our findings suggest a functional mechanism that correlates SORL1 genotype with efficiency of receptor expression in the human brain.

P1-217 REPLICATION OF LOAD GWAS ASSOCIATIONS

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Background: Three large-scale late-onset Alzheimer's disease (LOAD) genome-wide association studies (GWAS) published to date have reported associations meeting genome-wide significance in 5 genes (CLU, CR1, PICALM, BIN1 and EXOC3L2). We have previously reported replication of the association with CLU, CR1 and PICALM. Here we evaluate the SNPs from the most recent LOAD GWAS which reported association with rs744373 near *BIN1* ($p = 1.6x10^{-11}$) and rs597668 near EXOC3L2/BLOC1S3/MARK4 ($p = 6.5x10^{-9}$). Replication of associations meeting genome-wide significance from more recent GWAS will also be presented. **Methods:** We have genotyped these variants in a large (3,287 LOAD, 4,396 controls), independent dataset comprising eleven case-control series from the USA and Europe. We performed meta-analyses of the association of these variants with LOAD and tested for association using logistic regression adjusted by age-at-diagnosis, sex and *APOE* e*4* status. **Results:** Meta-analysis results showed no evidence of series heterogeneity and logistic regression analysis replicated the association of BIN1 (rs744373) with LOAD with an odds ratio (OR = 1.17, $p = 1.1x10^{-4}$) comparable to that previously reported (OR = 1.15). The variant near EXOC3L2 (rs597668) showed only suggestive association with LOAD ($p = 0.09$) after correcting for the presence *APOE* e4. Addition of our follow-up data to the results previously reported increased the strength of evidence for association with rs744373 (Fisher combined $p = 3.8x10^{-20}$). We also tested for epistatic interaction between these variants and *APOE* e4 as well as with the previously replicated LOAD GWAS genes