1188T

The cerebral glucose transporter SLC45A1 is mutated in individuals with non-syndromic intellectual disability and epilepsy. *M. Srour[1,2], N. Shimokawa[3], F.F. Hamdan[1], S. Dobrzeniecka[4], G.A. Rouleau[5], C. Poulin[2], J.L. Michaud[1].* 1) Sainte-Justine Hospital Research Center, Montréal, H3T 1C5, Canada; 2) Division of Pediatric Neurology, Montreal Children's Hospital-McGill University Health Center, Montreal, H3H 1P3, Canada; 3) Department of Integrative Physiology, Gunma University Graduate School of Medicine, Gunma 371-8511, Japan; 4) CHUM Notre-Dame Hospital Research Center, Montreal, H2L 2W5, Canada; 5) Montreal Neurological Institute, McGill University, Montreal, H3A 2B4, Canada.

We have identified a consanguineous Lebanese family with two sisters affected with moderate non-syndromic intellectual disability and epilepsy of unknown etiology. SNP genotyping was performed in the two affected sisters as well as in their unaffected sibling. We identified 7 regions larger than 1Mb that were homozygous in the two affecteds but not in the unaffected sister. Whole exome sequencing was performed in one affected individual. The exome dataset was analyzed by looking for homozygous rare (<0.5% minor allele frequency) coding and splicing variants found in the candidate homozygous regions. We excluded variants that did not segregate with the phenotype in the family or that were found in 95 ethnically-matched controls. Of the remaining variants, only one missense variant in *SLC45A1* (c.C629T/p.A210V) was predicted damaging by Polyphen-2 and mutation taster. *SLC45A1* encodes a glucose transporter that has only recently been characterized. Slc45a1 is highly expressed in the brain of mice, is induced after hypercapnia and mediates glucose uptake along the pH gradient. We show that *Slc45a1*-transfected COS-7 cells carrying the same c.C629T (p.A210V) mutation exhibited a 40-50% decrease in intracellular glucose uptake, suggesting that the mutation affects the function of the Slc45a1 transporter. Mutations in another cerebral glucose transporter, *GLUT1*, are implicated in neurologic disease and are well known to result in epilepsy with variable degrees of intellectual disability, or movement disorders. Our results suggest the possibility of specific treatment in the form of a ketogenic diet for the family, and implicate for the first time *SLC45A1* in human disease. Identification of additional similarly affected families will be necessary to establish *SLC45A1* as a neurodevelopmental disease gene. Collaborations towards this effort are welcome.

1189F

Adducin function is essential for sustained changes in neuronal activity upon learning. *V. Vukojevic[1,2], F. Peter[1,2], P. Demougin[1,2], N. Hadziselimovic[1,2], J.-F de Quervain[2,3,4], A. Papassotiropoulos[1,3,4], A. Stetak[1,3,4].* 1) University of Basel, Department of Psychology, Division of Molecular Neuroscience, Birmannsgasse 8, 4055 Basel, Switzerland; 2) University of Basel, Department Biozentrum, Life Sciences Training Facility, Klingelbergstrasse 50/70, 4056 Basel, Switzerland; 3) University of Basel, Department of Psychology, Division of Cognitive Neuroscience, Birmannsgasse 8, 4055 Basel, Switzerland; 4) University of Basel, University Psychiatric Clinics, Wilhelm Klein-Strasse 27, 4055 Basel, Switzerland.

Identifying molecular mechanisms that underlie learning and memory is one of the major challenges in neuroscience. Previously, we have reported that genetic variability of the human ADD1 gene is significantly associated with episodic memory performance in healthy young subjects. Taken the advantages of the nematode Caenorhabditis elegans, we have shown that α-adducin is required for consolidation of synaptic plasticity, for sustained synaptic increase of AMPA-type glutamate receptor (GLR-1) content and altered GLR-1 turnover dynamics. ADD-1, in a splice- form- and tissue-specific manner, controlled the storage of memories presumably through actin-capping activity (Vukojevic et al, 2012). In the present work, we further investigated the effects of adducin dependent changes on neuronal activity during synaptic transmission. With the help of genetically encoded calcium indicators (GECIs) we visualized the neuronal activity in vivo in defined neuronal populations. Specifically, we monitored calcium currents in neurons crucial for avoidance behavior, especially in AVA and RIM neurons that controll activation and inhibition of reversals. Taken together, the method implemented enabled us to get the insight of function and integration at the level of a single neuron. Moreover, we were able to caught in vivo, a single neuronal cell in learning and memory formation. Remarkably, in add(lf) mutants the learning phase induced changes in AVA and RIM neuronal activity fail to be consolidated after 30 minutes. Therefore we were also capable to investigate in vivo the role of neurons in memory storage. These findings further support the role of ADD-1 in the stabilization of synapses, changes in GLR-1 dynamics and finally modulations of neuronal activity patterns. All together, our results suggest that the lack of adducin in AVA interneuron has consequences on synapse remodelling and changes of neuronal activity that are functionally reflected also in other members of the motor network.

1190W

Influence of Alzheimer's disease genes on cognitive decline: the Guangzhou Biobank Cohort Study. *S.S. Cherny[1], H.S. Gui[1], L. Xu[2], P.C. Sham[1], C.Q. Jiang[3], T.H. Lam[2], B. Liu[3], Y.L. Jin[3], T. Zhu[3], W.S. Zhang[3], G.N. Thomas[4], K.K. Cheng[4].* 1) Psychiatry & Centre for Genomic Sciences, Univ Hong Kong, Pokfulam, Hong Kong; 2) Department of Community Medicine, School of Public Health, University of Hong Kong, Hong Kong; 3) Guangzhou No. 12 Hospital, Guangzhou, China; 4) Public Health, Epidemiology, and Biostatistics, University of Birmingham, Birmingham, UK.

Mild cogntive impairment is a reliable predictor of the future onset of clinical dementia. In Hong Kong, the prevalences of very mild dementia and mild dementia in people aged 70 years and older were estimated to be 8.5% and 8.9%, respectively, in a population-based sample. For those subjects with a clinical diagnosis of dementia, Alzheimer's disease (AD) was the most common likely cause (73.5%), with 22.4% having vascular dementia (VaD), and 3.9% dementia with symptoms of Parkinson's disease. In addition to the impact on the patient and their family members, the economic cost of AD has been estimated to range from around $48,000 to $585,000 per patient per year around the world. To identify risk factors involved in cognitive decline, we selected 1325 extreme cognitive decline subjects and 1083 matched controls from Guangzhou Biobank Cohort Study (GBCS) for DNA genotyping at 30 known AD associated SNPs. Full information maximum likelihood (FIML) regression was adopted to analyse quantitative cognitive change scores, while multiple logistic regression was used to investigate the genetic effect of those variants on dichotomous phenotype. No allelic association was found by individual variant analysis. At the level of genotypic association, not only did we confirm that the APOE ε4 homozygote can significantly predict cognitive decline ($p < 0.05$), but also revealed carriers of the ACE rs1800764_C allele are more likely suffer decline than non-carriers, especially in the samples without college education. However, these effects together only explain 1.3% of the phenotypic variance, and suggest that AD risk variants/genes are only minor predictors of cognitive decline in these Chinese samples.

1191T

Fine Mapping and Association Analysis of Candidate Genes for Autism Spectrum Disorder and Language Impairment in the NJLAGS Sample. *A. Hare[1], A. Seto[1], J. Flax[1], M. Azaro[1], S. Buyske[2], C. Bartlett[3], L. Brzustowicz[1].* 1) Department of Genetics, Rutgers University, Piscataway, NJ; 2) Department of Statistics, Rutgers University, Piscataway, NJ; 3) Battelle Center for Mathematical Medicine, The Research Institute at Nationwide Children's Hospital and The Ohio State University, Columbus, OH.

Over the past decade, the New Jersey Language and Autism Study (NJLAGS) has collected families that contain one individual with autism and another individual with Specific Language Impairment (SLI) but not autism. This is the first study of its kind to investigate the share genetics between autism and SLI. Using a comprehensive neuropsychological testing battery, three categorical phenotypes: language impairment (LI), reading impairment (RI), and social impairment (SRS-DT), and two quantitative phenotypes: social impairment (SRS-QT) and obsessive-compulsive behaviors (YBOCS) were developed. Autism proband scores were included in the quantitative phenotypes and all categorical phenotypes included autism diagnosis as impaired for language, reading, or social skills, respectively. A previous study identified linkage in these families to 13q21.2 (YBOCS), 14q32.31 (SRS-QT), 15q25.1 (LI), 15q26.2 (SRS-DT), and 16p12.3 (RI). As genome-wide association did not reveal strong evidence for association, Ingenuity Pathway Analysis (IPA) was used to select candidate genes for fine mapping analysis. Four groups were analyzed in IPA: communication impairment (LI + RI), social impairment (SRS-DT + SRS-QT), restricted/repetitive behaviors (YBOCS), and an overall autism model (LI + RI + SRS-DT + SRS-QT + YBOCS). Genes in each analysis group were given a score that corresponded to the number of relevant functions identified by IPA. Seven of the highest-ranking genes were selected for association analysis from the LI, RI, and SRS-DT linkage regions: AKT1, JAG2, PTPN9A, SEMA7A, NTRK3, FES, and SCCN1B. Each gene was fine mapped using an oligonucleotide ligation assay and was analyzed for association using the KELVIN framework. Each gene was analyzed for association to its respective phenotype with and without the inclusion of autism diagnosis and for autism diagnosis only. JAG2 yielded the strongest evidence for association (PPLD|L = 5%) when autism diagnosis was included. When autism diagnosis was excluded, NTRK3 yielded the strongest evidence for association (PPLD|L =7%). For autism diagnosis only, no evidence for association was detected. The lack of strong evidence for association provides support for a role of rare variants in autism susceptibility and their role in the shared genetics between autism and SLI.