RESULTS: We identified likely pathogenic mutations in known AR-MC genes in eight pedigrees (ASPM, WDR62, TRAPPC9, TUBGCP6, PNKP, APMI1, and ASNS). In six additional pedigrees, likely pathogenic mutations in genes not previously associated with human diseases emerged. These include two genes encoding centrosomal proteins, two genes encoding enzymes in amino acid metabolism and one gene encoding a synaptic protein. In total, we identified candidate pathogenic mutations in 14/40 pedigrees (35%).

Conclusions: This study confirms the highly heterogeneous nature of AR-MC, and highlights novel biological pathways involved in pathogenesis of AR-MC. We sequencing proved efficient in identifying mutations in known and novel AR-MC genes in consanguineous pedigrees, and holds great promise for its clinical application in outbred populations as well.

FP18
OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANT (HCT) IN CHILDHOOD CEREBRAL ADRENOLEUKODYSTROPHY (CCALD): A MULTI-INSTITUTIONAL STUDY
Asif M. Paker1, Patrick Aubourg2, Maria L. Escolar3, Joanne Kurtzberg4, Susan Paadre2, John J Bailer5, Paul Orchard6, Gerald V Raymond7, bluebird bio, Cambridge MA, United States; 2Hôpital Pité Salpétrière, Paris France, France; 3University of Pennsylvania, United States; 4University of Minnesota, United States

The combination of exome sequencing and bioinformatics analyses of large expression datasets can be highly effective in prioritization of candidate genes. In a young adult male with congenital cataract, retinal degeneration, epilepsy and leukodystrophy, routine studies were not informative. Exome sequencing of gDNA identified over 30 de novo heterozygous variants. To identify candidates for ocular phenotypes, we used the SIFT database which provides meta-analysis of expression profiles of photoreceptor and lens datasets. SIFT identified EZR (Ezrin) and NRZ2E3 (Nuclear Receptor Subfamily 2, Group E, Member 3) as top candidate genes in the lens and photoreceptors respectively. Expression of Ezr is enriched in the mouse lens pre and postnatally as well as the adult mouse retinal pigment epithelium, and is the best candidate to explain a congenital cataract phenotype. EZR functions as a protein-tyrosine kinase substrate in microvilli and plays a key role in cell surface structure adhesion, migration and organization. Recently, a few EZR variants in individuals with age related cataract and epilepsy had been reported. N2e3 is only expressed in the lens postnatally, but it has high expression in photoreceptors, and defects in NRZ2E3 (a nuclear transcription factor) cause retinitis pigmentosa as well as the enhanced S cone syndrome. The two de novo heterozygous variants found in this individual are predicted to be deleterious. The enriched expression of EZR in the developing lens and of NRZ2E3 in retinal photoreceptors, together with the reported human phenotypes, suggest that mutations in these two genes caused cataract and retinal degeneration in this individual.

FP14
IDENTIFICATION OF GENES FOR AUTSOMATIC RECESSIVE MICROCEPHALY BY WHOLE-EXOME SEQUENCING
Ganeshwaran H. Mochida1, Timothy W. Yu1, R. Sean Hill1, Khalil1, Klaus Schmitz-Abe2, Anna Rajab3, Samir individual. in these two genes caused cataract and retinal degeneration in this to together with the reported human phenotypes, suggest that mutations

Aim: Autosomal recessive microcephaly (AR-MC) is a highly heterogeneous group of disorders. Despite recent advances in genetic analysis of AR-MC, it is estimated that many causative genes are yet to be identified. In this study, we performed whole-exome (WE) sequencing of consanguineous pedigrees with AR-MC in order to identify its novel causative genes.

Methods: DNA samples from one or two affected individuals from 40 families with AR-MC were subjected to WE sequencing on Illumina HiSeq, and the results were annotated with ANNOVAR. Identified homozygous variants were filtered for their: 1) predicted effect on the protein product, 2) occurrence in public databases or other exomes sequenced in our lab, and 3) presence in a block of homozygosity within the family.

Results: We identified likely pathogenic mutations in known AR-MC genes in eight pedigrees (ASPM, WDR62, TRAPPC9, TUBGCP6, PNKP, APMI1, and ASNS). In six additional pedigrees, likely pathogenic mutations in genes not previously associated with human diseases emerged. These include two genes encoding centrosomal proteins, two genes encoding enzymes in amino acid metabolism and one gene encoding a synaptic protein. In total, we identified candidate pathogenic mutations in 14/40 pedigrees (35%).

Conclusions: This study confirms the highly heterogeneous nature of AR-MC, and highlights novel biological pathways involved in pathogenesis of AR-MC. We sequencing proved efficient in identifying mutations in known and novel AR-MC genes in consanguineous pedigrees, and holds great promise for its clinical application in outbred populations as well.

HCT is the only currently available therapy for CCALD, but there is limited multi-institutional outcome data. We conducted a retrospective study to characterize the natural history of untreated CCALD and the efficacy and safety of HCT. Data were collected from 5 centers, in 4 in US and in 1 in France on 136 cases (72 untreated/65 HCT) from diagnosis until either 2 years post-diagnosis or death. Key efficacy measures were neurologic-function-score (NFS) and MRI (Loes).

In the untreated, 70 of 72 (97%) had at least one NFS score and an MRI; 31 (43%) with gadolinium (24 Gad+/7 Gad-). Gadolinium enhancement was highly predictive of rapid progression. Of the Gad+, the majority showed significant decline in NFS and Loes scores during the follow-up period. In the 65 HCT-treated boys, all were evaluated with NFS and MRI with contrast. Majority (93%) had resolution of enhancement (median 3.4 months). In a subset of 22 HCT-treated patients with early CCALD (NFS ≤ 1, Loes ≤ 9), 73% had stabilization of NFS (NFS≤ 4 or change in NFS≤3) at 24 months post-transplant. Engraftment failure occurred in 18.5%, and severe acute and chronic GVHD in 11% and 5%, respectively. The highest incidence of death during the follow-up period occurred in HLA mismatched, non-related transplants (12/32, 37.5%). These subjects also had the highest incidence of overall (23/32, 72%) and serious GVHD (6/32, 19%).

MR enhancement is predictive of progression, and it rapidly resolves following HCT. Successful HCT improved all outcomes versus untreated. There is a clear unmet need for novel therapies for patients without an HLA-matched sibling donor.

FP16
PATIENT-DERIVED STEM CELLS AS MODELS FOR FAMILIAL BRAIN DISORDERS
Alan Mackay-Sim1. National Centre for Adult Stem Cell Research, Eskitis Institute for Drug Discovery Griffith University, Brisbane, QLD, Australia

The usual approach to understanding Mendelian disorders is based on identifying the gene mutation responsible and expressing it in mouse. While productive for understanding gene functions this has led to many drugs effective in mouse but not in human. Why does this happen? For many patients with apparently Mendelian brain disorders the causative gene mutations are not known so that drugs aimed at an identified gene miss the target for most patients. Additionally, mouse models lack the genetic background upon which human gene mutations operate. We have developed a new technology for understanding brain disorders; patient-derived stem cells from the olfactory mucosa, the organ of smell in the nose that regenerates through the human lifespan. We use the heterogeneity among cells from multiple patients and controls to understand how gene mutations affect cell signalling
pathways and cell functions, rather than concentrating on single genes and proteins. We derived olfactory stem cells from children with Ataxia Telangiectasia. These cells are metabolically normal until stressed by irradiation when they show expected deficits in DNA damage repair, which were abolished after correcting the genetic mutation. The AT patient-derived cells show deficits in neuronal differentiation. Hereditary Spastic Paraplegia is another familial disorder with multiple gene mutations causing similar clinical signs affecting upper motor neurons to the lower limbs. Olfactory stem cells from HSP patients with similar clinical phenotypes but different causative genetics had similar cellular phenotypes affecting intracellular organelle trafficking. These cells can be grown at sufficient scale for high throughput drug discovery.

**FP17 AN APPROACH TO GENOTYPE-PHENOTYPE CORRELATION IN RETT SYNDROME**

M. Paulina Carullo, Elana Cavassa, Pablo Jorat, Mario Massaro, Rita Valdez, Mercedes Villanueva, Angeles Schteinschneider. FLENI, Raul Carrea Instituto de Investigaciones Neurologicas, Argentina

**Introduction:** Rett Syndrome (RTT) is a genetic disease caused primarily by mutations in MECP2. There are more than 200 MECP2 mutations but 7 recurrent mutations are associated with 70% of cases. Diagnosis is based on clinical criteria and confirmed by molecular analysis.

**Methods:** Clinical severity and phenotypic characteristics of patients with a clinical diagnosis of Rett syndrome and MECP2 gene mutations were analyzed using the Rett Syndrome Severity Scale (RSSS). Type of sequence change in MECP2 gene was considered individually.

**Results:** 16 patients (age: 2-19 years) were assessed. The mean RSSS corresponded to the intermediate range of severity, which reflected that the majority of participants were in the moderate severity category. All of the patients in the sample had speech, hand use and gait abnormalities; 81% had sleep irregularities; 69% epilepsy; 50% breathing abnormalities and only 31% suffered scoliosis (which might be related to a young average sample age). Truncating mutations were related to more severe phenotypes of patients with Rett syndrome and the missense mutation T158M mutation and c.820_1190del associated with milder phenotypes.

**Conclusions:** While it is not possible to establish a genotype-phenotype correlation due to the small number of patients and variability of genotypes in our sample, we can say that the general genotype-phenotype relationships were confirmed. The clinical severity was found to be very variable even between individuals with the same mutation, which may be influenced by X chromosome inactivation.

**FP18 EPIDEMIC WEAKNESS, CEREBELLAR ATAXIA, DEAFNESS AND OPTIC ATROPHY - A NEW PHENOTYPE OF A NOVEL ATP1A3 MUTATION**

Bruna Ben-Zeev, Gali Heimer, Lorri Israelian, Yair Zadaka, Alessandra Ruggieri, Christian Marshall, Stephen Walter Scherer, Yair Aniketis, Andrea Nissenkom, Berge A. Minassian. 1Pediatric neurology unit, Edmonds and Lilly Safra Pediatric hospital; Sheba med ctr; Ramat Gan, Israel; 2Division of Neurology, Department of Paediatrics, The Hospital for Sick Children, Canada; 3Pediatric neurology unit, Soroka Med ctr; Beer-Sheva, Israel; 4Ped. Metabolic unit, Emondand Lila Safra Pediatric hospital Sheba Med Ctr; Ramat-Gan, Israel; 5Ped. Neurology unit, Emondand Lila Safra Pediatric hospital Sheba Med Ctr; 6Ped. Neurology unit, Emondand Lila Safra Pediatric hospital Sheba Med Ctr. Ramat-Gan, Israel; 7Program in Genetics and Genome Biology, The Hospital for Sick Children Division of Neurology, Department of Paediatrics, The Hospital for Sick Children, Canada

**Introduction:** To delineate the molecular basis for a novel genetic syndrome in a mother and her two children. The syndrome is characterized by infantile acute onset severe muscle weakness episodes, ataxia, remitting gradually but recur and become permanent in adulthood associated with acquired permanent areflexia, progressive sensorineural hearing loss and optic atrophy.

**Methods:** Sequencing the mitochondrial DNA and sequencing and MLPA of the OPA1 gene were applied to exclude mitochondrial disease in general and OPA1 plus related disease specifically which were suggestive by inheritance pattern and the involved systems. Whole exon sequencing was performed on all patients and Sanger sequencing was subsequently used to verify the mutation in the patients and assess segregation within the family.

**Results:** Whole exome sequencing revealed a previously unreported E818K mutation in the ATP1A3gene in all three patients. Sanger sequencing confirmed mutation presence in the patients and its absence in all nine unaffected family members that were checked.

**Conclusion:** ATP1A3 gene was implicated in the last decade as the causative gene of two distinct diseases - rapid onset dystonia parkinsonism (RDP) and alternating hemiplegia of childhood (AHC). The clinical presentation in the family described in here differs significantly from these two diseases by the predominance of ataxia rather than extrapyramidal movement disorder that prevail in RDP and AHC and by the peripheral neural system involvement (e.g. weakness; areflexia, hearing loss and optic nerve pallor).We conclude that ATP1A3 mutation is the cause of a novel distinct AD genetic syndrome.

**FP19 MOLECULAR CHARACTERIZATION IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER**

Alberto Velez van Meerbeke, 1 Lubby M Galvez, 2 Claudia Talera-Guzman, 2 Heidy Mateus, 3 Dora J Fonseca, 1 NEUROS, School of Medicine and Health Sciences. Universidad Colegio Mayor de Nuestra Señora del Rosario, Bogota, Colombia; 2School of Medicine and Health Sciences. Universidad Colegio Mayor de Nuestra Señora del Rosario, Bogota, Colombia.

**Introduction:** Attention Deficit and Hyperactivity Disorder (ADHD) is a common condition of childhood characterized by symptoms of inattention, hyperactivity and/or impulsivity. Candidate or implicated genes involved in dopaminergic and serotonergic pathways and neuroplasticity have been proposed for the etiological study of ADHD.

**Methods:** DSM IV checklist and Multidimensional Behavior Assessment System for Children (BASC) criteria were applied to 250 children to evaluate the presence of ADHD. 117 cases and 80 controls were selected. DNA from blood samples was obtained from all cases and controls and 7 SNPs (case and his/her parents). Subsequent PCR, PCR-RFLP or STR analysis were performed to genotype eight polymorphisms located in seven genes (DRD4, DRD5, DAT1, DBH, HTR1B, 5HTT and SNAP23). A Transmission Disequilibrium Test (TDT) and a case-control analysis were used to evaluate possible association to ADHD.

**Results:** TDT analysis did not show evidence of preferential allelic transmission in any of the studied polymorphisms. Case-control study identified an association between ADHD and the genotype of T1065G and T1069C variants located in SNAP25 gene (p value 0.0025 and p=0.009). Also there was an association of ADHD to the haplotype of these variants. An endophenotype analysis showed a correlation between the genotype of a variable number tandem repeat (VNTR) located in DAT1 gene and subtests of cognitive flexibility (p=0.01) and processing speed index (p=0.03) deficit.

**Conclusions:** SNAP25 gene is associated to ADHD susceptibility. Endophenotype studies in highly heterogeneous disorders can be useful in the identification of susceptibility factors such as DAT1 gene in ADHD.

**FP20 NOVEL MLC1 AND GLIACAM MUTATIONS ANALYSIS AND FOLLOW-UP STUDY IN CHINESE PATIENTS WITH MEGALENCEPHALIC LEUKOENCEPHALOTATHY WITH SUBCORTICAL CYSTS**

Jingmin Wang, 1 Mangmang Guo, 1 Ye Wu, 1 Jiangxi Xiao, 1 Qiang Gu, 1 Xiru Wu, 1 Peking University First Hospital, China

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an autosomal inherited disease resulting from MLC1 or GLIACAM mutations. MLC can be further classified to three types: MLC1, MLC2A, MLC2B due to different clinicalfindings and prognosis caused by different genotypes in different inheritedmanner. The analysis of clinical features, mutation screening and follow-up study were performed in twenty Chinese patients in this study. The clinicalcharacteristics of Chinese MLC patients were similar with reports abroadicluding young-onset macrocephaly, fast head growth rate, gross motordelvelopmental delay and characteristic abnormalities on cranial MRI. These Chinese patients with MLC1- and GLIACAM-related MLC were 80% and15%, respectively. Mutation spectrums were expanded by the novel mutations of MLC1and GLIACAM in these Chinese patients including 6 novel mutations of MLC1:c.803C>G (p.T268R); c.824C>A (p.A275T); c.838C>G (p.I286M); c.881C>T (p.P294L); c.596delCAgt (p.S199Cfs220X) and one splicing mutation:c.895-1G>A in M511-1 and 2 novel mutations
of GLIALCAM (c.203A>T(p.K68M);c.395C>A(p.T132N)). Mutation c.772-1G>C in IVS9-1 was supposed to be a hot spot mutation in present study of GLIALCAM (c.203A>T(p.K68M);c.395C>A(p.T132N)). Mutation c.772-1G>C in IVS9-1 was supposed to be a hot spot mutation in present study of GLIALCAM (c.203A>T(p.K68M);c.395C>A(p.T132N)). Mutation c.772-1G>C in IVS9-1 was supposed to be a hot spot mutation in present study of GLIALCAM (c.203A>T(p.K68M);c.395C>A(p.T132N)). Mutation c.772-1G>C in IVS9-1 was supposed to be a hot spot mutation in present study.