NEUROGENETICS

FP13

DE NOVO DIGENIC HETEROZYGOUS MUTATIONS IN EZR AND NR2E3 REVEALED BY EXOME SEQUENCING IN A PATIENT WITH CATARACT, RETINAL DEGENERATION, EPILEPSY AND LEUKODYSTROPHY

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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 iSyTE database which provides meta-analysis of expression profiles of photoreceptor and lens datasets. iSyTE identified EZR (Ezrin) and NR2E3 (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 asa 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. Nr2e3 is only expressed in the lens postnatally, but it has high expression in photoreceptors, and defects in NR2E3 (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 NR2E3 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 AUTOSOMAL RECESSIVE MICROCEPHALY BY WHOLE-EXOME SEQUENCING

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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*, *AP4M1*, *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.

FP15

OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANT (HCT) IN CHILDHOOD CEREBRAL ADRENOLEUKODYSTROPHY (CCALD): A MULTI-INSTITUTIONAL STUDY

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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, 4 in US and 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+/7Gad-). 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%).

MRI 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

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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

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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_1193del 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

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

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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 became 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 exome 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 DRP 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

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Introduction: Attention Deficit and Hyperactivity Disorder (ADHD) is a common condition of childhood characterized by symptoms of inattention, hyperactivity and/or impulsivity. Candidate genes involved in dopaminergic and serotoninergic 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 control and 86 trios (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 SNAP25). 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 ($p=0.0025$ 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 ($p\leq 0.01$) and processing speed index ($p<0.05$) 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 asDAT1 gene in ADHD.

FP20

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

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Megalencephalicleukoencephalopathy with subcortical cysts (MLC) is an autosomal inherited disease resulting from MLC1 or GLIALCAM mutations. MLC can befurther 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-upstudy were performed in twenty Chinese patients in this study. The clinicalcharacteristics of Chinese MLC patients were similar with reports abroadincluding early-onset macrocephaly, fast head growth rate, gross motordevelopmental delay and characteristic abnormalities on cranial MRI. TheChinese patients with MLC1- and GLIALCAM-related MLC were 80% and15%, respectively. Mutation spectrums were expended by the novel mutations of MLC1and GLIALCAM in these Chinese patients including 6 novel mutations of MLC1(c.803C>G (p.T268R); c.824C>A (p.A275T); c.858C>G(p.I286M);c.881C>T(p.P294L); c.596delCAgt(p.S199Cfs220X) and one splicing mutationc.895-1G>A in IVS11-1) 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 ahot spot mutation in present study or a founder mutation of Chinese MLCpatients. The disease progress from follow-up were analyzed systemically. Most demonstrated relative stable, while temporary deterioration induced by minor head trauma was common. No evident genotype-phenotype correlations in MLC1 patients, however the patient with homozygous c.772-1G>C mutation might be showed a severe phenotype. The results might provide the exact genetic counselling and future prenatal diagnosis for those MLC pedigrees and could be useful for understanding the natural history and the genotype-phenotype correlation of this disease.

FP21

EXPANDING THE GENETIC LANDSCAPE OF NEURODEVELOPMENTAL DISORDERS WITH WHOLE EXOME SEQUENCING

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The advent of whole exome sequencing (WES) represents a significant breakthrough in clinical genetics, providing physicians with a powerful tool for etiological discovery. In order to better characterize the genetic landscape of neurodevelopmental disorders, we analyzed 46 patients in our pediatric neurogenetics clinic who underwent WES, characterizing their clinical features and molecular diagnoses. This was a heterogeneous mix of patients with a spectrum of neurodevelopmental disabilities. With WES, the overall diagnostic rate was 41.3% (n = 19). Eleven patients had a single autosomal dominant disorder, while seven patients had a single autosomal recessive disorder. The remaining subject had both an autosomal dominant disorder and autosomal recessive disorder. Of the positive cases, n = 16 had intellectual disability/developmental delay; n = 6 had a CP-like syndrome; and n = 3 had autism. The 19 patients with positive mutations exhibited a variety of neurological issues, including microcephaly (n = 8), seizures/epilepsy (n = 6), hypotonia (n = 15), dystonia (n = 7), and stereotyped repetitive behaviors (n = 7). On neuroimaging, these 19 subjects demonstrated a wide range of deficits, including delayed myelination/hypomyelination (n = 6) and cerebellar abnormalities (n = 7). Interesting discoveries emerged from the use of WES. A patient was found to have a pathogenic *PANK2* mutation without an eye-of-the-tiger sign. Another individual with diagnosed with two rare genetic disorders. The high diagnostic yield of WES, and its role in elucidating nonspecific clinical presentations and atypical manifestations of disease, support the use of WES in pediatric neurology practices.

FP22

FOLLOW UP STUDY OF 34 CHINESE PATIENTS WITH VANISHING WHITE MATTER DISEASE AND ROLE OF UPR AND AUTOPHAGY IN THE PATHOGENESIS

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Introduction and Methods Vanishing whitematter disease (VWM) is one of the hereditary leukoencephalopathies inchildhood. Mutations in EIF2B1-5, encoding subunits of eukaryotic translation initiation factor 2B (eIF2B), are identified in > 90% of patients. In this study, an average 4 year follow-up was performed in 34 gene-confirmed Chinese VWM patients. And in vitro study was performed in patients' fibroblasts as well as in human oligodendrocyte lines to investigate the role of unfolded protein response (UPR) and autophagy in the pathogenesis.

Results 34 patients were consisted of 21 early childhood, 10 infantile and 3 juvenile types. All showed progressively rapid motor regression. The median survival time was 8.83±1.51years. 71% showed episodic aggravation during febrile diseases. Seizures occurred in 50%. In the in vitro study, UPR was over activated under baseline conditions and persisted after ER stress in human oligodendrocytes with mutant EIF2B3, which led to increased apoptosis and decreased cell viability. Meanwhile, the autophagy level was decreased in oligodendrocytes lines but not in patients' fibroblasts. The cell viability decreased, and apoptosis increased, even more after autophagy inhibition or UPR enhancement in the mutant oligodendrocytes. It is suggested that excessive UPR and depressed autophagy after ERS may play important roles in the pathogenesis, especially in episodic aggravations in the case of stress.

Conclusions This is the largest long-term follow-up study in VWM, which is helpful for better understanding of the natural history of this rare disease. Study on UPR and autophagy may provide evidence for future therapeutic targets.

FP23

PROTEOLIPID PROTEIN 1 AND GAP JUNCTION A12 GENE MUTATIONS IN 72 CHINESE PATIENTS WITH PELIZAEUS-MERZBACHER DISEASE/ PELIZAEUS-MERZBACHER LIKE DISEASE AND PRENATAL DIAGNOSIS OF 15 FOETUSES IN TWELVE CHINESE FAMILIES WITH PMD PROBANDS

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Aim: The object of this study was to identify PLP1 and GJC2 mutations in 72 Chinesepatients (P1-72) with Pelizaeus-Merzbacher disease (PMD) / PMLD and prenataldiagnosis of fifteen fetuses in twelve Chinese families with PMD probands.

Methods: Genomic DNA was extracted from peripheral bloodssamples. Amniotic fluid/chorionic villus sampling was performed. Gene dosage was determined by MLPA. All 7 exons and exon-intron boundaries of PLP1gene were amplified and analysed by direct DNA sequencing. Results Of these 72 patients, there were 18 transitional, 45 classical, and 9 congenital PMD according to the clinical and radiological presentation. PLP1 duplications were identified in patients 1-52 with PMD, account for 72.2% (52/72). Their mothers were PLP1 duplications carriers except P52'mother was wild type. 15 hemizygous missense mutations including eight novel mutations and one reported splicing mutation were found in 17 Patients (P53-69) with PMD 23.6% . For three patients without PLP1 mutation, we then tested GJC2 mutations with c.925_938del(p.A309Pfs342X), c.201C>G(p.C67T),c.689delG (p.G230Afs), c.735C>A (p.C245X), and c.1199C>A (p.A400E). For the results of prenatal diagnosis (male 9 and female 6), 9 fetuses werePLP1 wild type, 1 was with PLP1 duplication carrier, and 5 found PLP1duplication and 1 with c.623G>T (G208V).

Conclusions: We identified 52 genomic duplications and fifteen missense/splicing mutation of PLP1gene in 69 Chinese patients with PMD and five missense/frameshift mutations in three patients with PMLD. Prenatal diagnoses for fifteen fetuses in twelve PMD proband families were performed, which is useful and helpful for those families.

FP24

THE 9P13 DELETION SYNDROME: CONFIRMATION AND EXPANSION OF THE PHENOTYPE

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Introduction: The 9p13 microdeletion syndrome was recently reported in two unrelated young children with facial dysmorphism, developmental delay, short stature, and precocious puberty (Niemi et al, 2012). Autosomal dominant (*VCP, TPM2)* and autosomal recessive (*GALT*, *ILIIRA*) genes map within this 5 Mb region of 9p13.13. Associated phenotypes include: IBMPFD1-inclusion body myopathy with Paget disease of bone and frontotemporal dementia (*VCP*), distal arthrogryposis type 1/type 2B Nemaline myopathy (*TPM2*), galactosemia (*GALT*), craniosynostosis, delayed tooth eruption, and supernumerary teeth (*ILIIRA*). *GALT* and *FANCG* are the only two genes known to be dosage sensitive. Protein under-wrapping predicts gene dosage sensitivity.

Aim: Describe the clinical, molecular findings in 2 children with the 9p13 microdeletion syndrome and in silico prediction of gene dosage sensitivity using protein under-wrapping analysis.

Methods: Two unrelated young (6.5 and 10 years old) children underwent a comprehensive clinical genetic evaluation and array comparative genomic hybridization analysis.

Results: A 5 Mb de novo heterozygous deletion at 9p13.3p13.1 with similar breakpoints was identified in both children on aCGH analysis. They have developmental delays, autism, overlapping facial dysmorphism, panhypopituarism, short stature and metopic suture synostosis.

Conclusion: *GALT* and *IL11RA* are dosage sensitive genes since their haplosufficiency causes low GALT enzyme activity identifiable on routine metabolic newborn screening and metopic suture synostosis respectively. However, haploinsufficiency of *VCP* and *TPM2*genes was not sufficient to produce related phenotypes suggesting that they are dosage insensitive. We also propose that a hypopituitarism related gene maps within this region.