[1]Children's Hospital at Westmead, Sydney, Australia, [2]University of Sydney, Sydney, Australia, [3]Children's Hospital of Philadelphia, Philadelphia, United States, [4]Royal Children's Hospital, Melbourne, Australia, [5]University of Melbourne, Melbourne, Australia, [6]Chinese Academy of Science, Beijing, China, [7]BGI-Shenzhen, Shenzhen 518083, China

Background: Leigh syndrome (LS) is caused by mutations in one of more than 30 genes; most of which are associated with the mitochondrial respiratory chain (MRC). Aim: To identify the genetic cause of disease in a patient with an overall clinical picture of Leigh syndrome.
Patient & Methods: A girl with clinically suspected diagnosis of LS was first hospitalized at 2 years because of febrile seizures and partial left ptosis, with subsequent left-sided arm and leg weakness, scoliosis and worsening dystonia at 6 years. Brain MRI showed symmetrical putaminal abnormalities, raised lactate on brain magnetic MRS, but normal in blood and cerebrospinal fluid. Whole exome sequencing (WES) and functional studies were performed to identify the causative gene.
Results: WES uncovered compound heterozygous mutations in the NADH dehydrogenase ubiquinone flavoprotein 1 [NDUFV1](c.1162+4A>C, which causes skipping of exon 8, and c. G640A; p. Glu214Lys), both previously associated with complex I deficiency and LD. Despite normal complex I enzyme activity in patient muscle, liver and fibroblasts, the protein level of NDUFV1 was significantly reduced by 75 % on Western blotting.
Conclusion: WES can be used to provide a definitive diagnosis of a suspected MRC disorder even in cases where MRC enzyme activity is apparently normal.

P-269

Whole exome sequencing identifies novel compound heterozygous mutations in PNPT1 in affected siblings with a mitochondrial phenotype

Alodaib A[1 2 3], Sobreira N[4], Gold W A[1 2], Riley L[1 2], Wilson M[1 2], Bennetts B[1 2], Boehm C[4], Christodoulou J[1 2]

[1]Children's Hospital at Westmead, Sydney, Australia, [2]University of Sydney, Sydney, Australia, [3]King Faisal Specialist Hosp Res Cent, Riyadh, Saudi Arabia, [4]Johns Hopkins Univ School Med, Baltimore, United States

Background: We undertook a gene discovery project using whole exome sequencing (WES) in a non-consanguineous family with two affected boys with severe intellectual disability, sensorineural deafness, optic atrophy, an axonal neuropathy and chronic lung disease.
Methods: WES was performed using the Illumina HiSeq2000 platform. Target regions were captured using the Agilent SureSelect Human All Exon 50 Mb Kit.
Results: WES identified compound heterozygous missense variations in exons 9 (p. Gln254Lys) and 19 (p. Ala510Pro) of PNPT1 (Polyribonucleotide nucleotidyltransferase 1) in both boys. PNPT1 encodes for the protein PNPase, which is involved in the transport of small RNAs to mitochondria. Mutations in PNPT1 have previously been reported to affect RNA import into mitochondria, mitochondrial protein translation, combined oxidative phosphorylation defects (OMIM 614932) and autosomal recessive deafness (OMIM 614934). Our variations were predicted to be damaging and in vitro studies revealed a clear reduction in PNPT1 protein and mRNA expression in patient fibroblasts. Furthermore, patient fibroblasts showed reduced mitochondrial respiratory chain complexes I and IV protein levels and enzyme activities, and a reduction in total mitochondrial protein synthesis.
Conclusion: Using WES, we have identified novel, probably pathogenic variations in PNPT1 in this family. Lentiviral rescue studies are being undertaken to provide further evidence of pathogenicity.

P-270

An early manifestation of LBSL (leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation) syndrome, case description

Grechanina E Y[1], Zdubskaya E P[1]

[1]Kharkiv Specialized Medical Genetic Cent, Kharkiv, Ukraine

Background: In leukoencephalopathy, mutation in gene DARS2 is associated with this syndrome. The gene is located on the long arm of chromosome 1 (1q 25.1), the disease is associated with deficiency of mitochondrial aspartyl - tRNA synthetase.
Case report: 1 year and 5 month old boy, with static kinetic and psychospeech development delay, excess body weight (16 kg). The child, from a first pregnancy complicated by a threatened miscarriage, was delivered at 36–37 weeks by caesarean section. Birth weight was 3300 g. Examination revealed decreased muscle tone, muscle strength, and absent tendon and periosteal reflexes, nystagmus, ataxia. ENMG – the neuropathic type of changes, myopathic syndrome. MRI of the brain - using T1, T2 and FLAIR- modes - white matter lesions of the brain and cerebellum. The karyotype - 46,XY. Phosphorylation rate was decreased - 111.8 mmol/min/mg of protein. Amino acid levels, blood lactate were normal. GC-MS analysis showed no evidence of an organic aciduria or a disorder of fatty acid oxidation. Partial analysis of the DARS gene by sequencing: in 5 gene locus - mutation c492+2 T-C in the heterozygous state.
Conclusion: In our case, the disease manifested in a child in whom we were only able to find a single mutation and who developed obesity by one year of life.

P-271

A new case with resistant hypoglycemia, hypertrophic cardiomyopathy, and encephalopathy due to mitochondrial TSFM gene defect

Dursun A[1], Gerdan C F[6], Kızılkan-Pehlivantürk M[3], Yılmaz-Yücel D[1], Yuceturk B[6], Topcu M[2], Yalnızoglu D[2], Yigit S[4], Orhan D[5], Sagiroglu M[6], Ozgul R K[1]

[1]Hacettepe Univ, Div Metab Dis, Ankara, Turkey, [2]Div Pediat Neurol, Hacettepe Univ, Ankara, Turkey, [3]Dep of Pediatrics, Hacettepe Univ, Ankara, Turkey, [4]Div Newborn, Hacettepe Univ, Ankara, Turkey, [5]Dep Ped Pathology, Hacettepe Univ, Ankara, Turkey, [6]TÜBİTAK, BİLGEM, Kocaeli, Turkey

The TSFM gene encodes the mitochondrial translation elongation factor Ts (EF- Ts). Our patient was diagnosed prenatally with hypertrophic cardiomyopathy and developed severe lactic acidosis and hypoglycemia at age 24 hours. Fatty acid oxidation defect (FAOD) was initially suspected and it was excluded as repeated investigations of acylcarnitine profiles that were found to be normal. He developed generalized muscle hypotonia, seizures, encephalopathy at age six days and one day later died due to respiratory failure. With these findings mitochondrial disease was clinically suspected and autopsy revealed cytochrome c oxidase deficiency in myocardial fibers, smooth muscle fibers and hepatocytes. A homozygous mutation c.997C>T; p. Arg333Trp in TSFM gene was detected by whole exome sequencing. Previously three cases were reported with the same mutation presenting different clinical features, one with hypertrophic cardiomyopathy, one with encephalopathy and one with liver dysfunction. Our case had an additional finding, resistant hypoglycemia. These findings suggest a broad clinical spectrum associated with mitochondrial translational deficiencies and that in the presence of such symptoms, if consanguinity exists, next-generation sequencing will be a