laboratory findings such as hypoglycaemia, hyperammonemia, lactic acidosis and elevated CK levels. With the progression of the disease epilepsy, developmental delay, cognitive impairment, global brain atrophy and pyramidal signs appear.

Materials and Methods: We report a 4-year-old child with developmental delay. From 21 months of age he showed episodes of suddenly onset hypotonia, gait instability, ataxia, and distortion of the head and upper body. During these paroxysm plasma creatinine kinase and lactate was elevated. He has seizures from 2-years-of-age: grand mal and spasms also occurred. He has hypothyreoidism.

Results: A pathogenic apparently homozygous TANGO2:c.385C>T variant was identified in exon 4 of the TANGO2 gene by Whole Exome Sequencing. We examined the parents for the above mentioned variant, but we could only detect the variant in the mother. Based on that further examinations were needed to distinguish in between homozygosity versus heterozygosity with a deletion. With quantitative PCR assay by using 3 gene-specific amplicons encompassing the coding exons 3,4,5 of the TANGO2 gene a large deletion encompassing exons 3-5 was detected.

Conclusions: The above mentioned compound heterozygous state in our patient confirms the diagnosis of TANGO2-associated biallelic disorder. The disease might be very underdiagnosed, whole exome sequencing is still a clue to find the alterations in TANGO2 gene.

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P06.57D
Adult form of Tay-Sachs disease: main symptoms, enzyme and genetic diagnostics in Czech patients

H. Vlaskova, H. Jahnova, E. Kostalova, M. Magner, J. Jireckova, H. Poupetova, K. Peskova, V. Kozich

Department of Pediatrics and Adolescent Medicine, General University Hospital and First Faculty of Medicine, Charles University in Prague, Prague 2, Czech Republic

Tay-Sachs disease (TSD) is a rare neurodegenerative disorder caused by lysosomal β-hexosaminidase A deficiency due to mutations in the *HEXA* gene. Phenotypic spectrum of TSD is diverse and differs between infantile and adult form. No effective treatment for TSD is available and genetic counselling (DNA analysis) is thus important for prenatal diagnosis. Our cohort includes 14 patients with adult form of TSD (surprisingly twice more than infantile form) diagnosed in the Czech Republic between 2002 and 2018 yielding an estimated birth prevalence of 1:325,000. Median age of first symptoms and of diagnosis were 21 years and 35 years, respectively. The main clinical symptoms were problems with mild dysarthria, rapid speech, proximal weakness of lower extremities, balance disturbances and/or psychiatric disorders. Cerebellar atrophy in brain MRI was a constant feature. Leukocyte hexosaminidaseA activity was decreased to 1.8 - 4.1% of controls. All patients carried at least one allele with the mild variant p.Gly269Ser; a novel variant p.Arg252Cys was detected in one family. Adult form of TSD seems to be an underdiagnosed although an enzyme assay in serum/plasma is a fast, inexpensive and reliable tool to detect patients with this form of TSD and genetic confirmation is routine.

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P06.58A
TRMU-related transient liver failure of infancy presents with microcephaly and neurodevelopmental delay

H. Azaklı[1], E. Yücel[2], Ç. Arıkan[3], A. Armutlu[4], S. Eraslan[2], H. Kayserili[1,2]

[1]Institute of Health Sciences, Koç University School of Medicine (KUSoM), İstanbul, Turkey, [2]Medical Genetics Department, Koç University School of Medicine (KUSoM), İstanbul, Turkey, [3]Gastroenterology Department, Koç University School of Medicine (KUSoM), İstanbul, Turkey, [4]Pathology Department, Koç University School of Medicine (KUSoM), İstanbul, Turkey

21 months-old girl presented at genetics outpatient clinics due to microcephaly, mild neurodevelopmental delay and facial dysmorphism. She was born to healthy non-consanguineous couple. Prenatal and perinatal history was uneventful. She was followed up at metabolism& gastroenterology clinics for vomiting attacks, elevated liver enzymes/ lactate levels during 3-to-12 month-of-age. Mitochondrial work-up had not revealed the underlying pathology. SNParray showed 16q23.1 deletion encompassing two genes, *WWOX* and *LSM3P5*, which is associated with bilateral cataracts, iris coloboma and autistic behaviour. Paternal transmission of the microdeletion was conclusive for its possibly benign nature. Clinical Exome Sequencing(CES) revealed homozygous *TRMU gene* c. G835A(c.V279M) pathogenic change explanatory for the history of transient liver failure of infancy. FibroScan at $2^{1/2}$ years revealed stage2 hepatosteatosis with mild fibrosis and liver biopsy was performed for histopathological evaluation. *TRMU* (tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase) gene mutations were identified as responsible from transient liver failure of infancy at 2009.

Twenty-two patients have been reported uptill now and clinical variability ranges from early death(6/22) to normal development. Although no systematic follow-up is available, microcephaly and mild neurodevelopmental delay has been reported. The case we reported herein presented with microcephaly and psychomotor retardation and diagnostic work-up revealed the etiopathogenesis of transient liver failure in infancy. CES as the leading diagnostic technology for single gene disorders, enables clinical management, counselling also for TRMU-related hepatic failure which has a relatively benign course. *TRMU* gene sequencing is highly recommended in infants with unexplained liver failure not only in Yemenite Jewish but in all Middle East populations and Turkey.

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P06.59B
Genetics meets Metabolomics in Type 2 Diabetes in a Middle Eastern Population

N. A. Yousri[1], K. A. Fakhro[2], K. Suhre[1], R. G. Crystal[3]

[1]Weill Cornell Medical College- Qatar, Doha, Qatar, [2]Sidra Medical Research, Doha, Qatar, [3]Weill Cornell Medical College- NY, New York, NY, United States

T2D and its complications are a major concern for its high prevalence in Qataris, and both genetic risk and lifestyle/environmental factors play a role in T2D. We investigate: Polygenic Risk Scores (PRS) of T2D in Qataris, genetically Determined Metabotypes (GDM) of T2D and gene-metabolic networks. Polygenic risk scores highlight the role of genetics in early diagnosis, compared to other risk factors. Identifying gene-metabolite associations is important for understanding the genetic factors affecting metabolic pathways. 1000 Qatari samples (57% T2D), with whole exome sequence and genotype array data were used. All samples were profiled for more than 1000 metabolites. We constructed a PRS using those SNPs that replicated from 81 published loci, in the array data, and computed the accuracy of PRS in individuals with whole exome data. For determining GDMs in T2D, we first identified metabolites significantly associated with T2D, and then the associations of those metabolites with 1.6 million common variants. We found 229 metabolites associated with T2D, among which 6 metabolites are significantly associated with SNPs in 5 loci. We identified a gene-metabolic network containing 21 unique loci and 33 unique metabolic pathways. In this study we show genes that contribute to the polygenic risk score of T2D, genetically determined metabotypes and gene-metabolic networks in T2D. We believe these results will help improve the understanding of T2D mechanisms and in early diagnosis of the disease.Acknowledgement: This work was supported by Biomedical Research Program in WCM-Q, and by Qatar National Research Funds grants numbers: 09-740-3-192 and 09-741-3-793.

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P06.60C
High-throughput metabolomics for early detection of individuals at increased risk for type 2 diabetes

J. Hällfors, S. Ruosaari, P. Würtz, N. Tertipis

Nightingale Health Ltd., Helsinki, Finland

Introduction: Advances in metabolomics now allows for profiling of large-scale cohorts. We identified circulating blood biomarkers predictive of T2D. Also, metabolic signatures were generated for risk stratification and tracking the health of the individuals.

Materials and Methods: NMR metabolomics was used to quantify 228 metabolic measures in 11,896 individuals from four Finnish cohorts (mean age 35 years, range 24-45).

Results: Associations between baseline metabolites and diabetes onset during the 7-15 years of follow-up (392 incident cases) were assessed by logistic regression. Altogether 113 metabolites were associated with incident diabetes ($P<0.0009$; range of odds ratios (OR) per 1-SD: 0.59-1.50) after adjusting for sex, baseline age, glucose and BMI. Among the strongest predictors of increased risk of diabetes were higher concentrations of branched-chained and aromatic amino acids (OR: 1.33), triglycerides in very-low-density lipoproteins (VLDL; OR 1.50), and lower levels of omega-6 fatty acids (OR 0.75). A biomarker signature comprised of phenylalanine, free cholesterol in large HDL, and the ratio of cholesteryl esters to total lipids in large VLDL was predictive of incident diabetes in an independent validation cohort after adjusting for baseline glucose and BMI (OR 10.1 comparing 5th vs 1st quintile of the biomarker score).

Conclusions: Individuals at risk for T2D display a distinct metabolic signature even years before the disease develops. Using the signature, both early risk stratification and personalised follow-up of the disease progression is enabled. High-throughput metabolomics therefore provides a powerful tool for population-wide diabetes prevention and control programs. Metabolomics is already used for health tracking in Finland.

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