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ABSTRACTS COLLECTION

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e-Posters

E-P01 Reproductive Genetics/Prenatal Genetics

E-P01.07
Epidemiological monitoring of congenital malformations in Yakutia from 2007 to 2018

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Introduction: Congenital malformations represent an urgent problem that affects the structure of infant and child mortality. In Yakutia, the prevalence of congenital malformations is recording in Register of Medical Genetic Center, Republican Hospital №1 - "National Medical Center". The purpose of epidemiological monitoring is to improve the prevention and treatment of congenital malformations.

Material and methods: The data from Medical Genetic Center Register was analyzing by the MedCalc 15.8 program.

Results: The incidence rate of congenital malformations over a 12-year period averaged 29.4 cases per 1000 newborns with a standard deviation of 2.9. It's high indicator In Russia (>20 ‰). At this period, the average annual number of births was 15725.7 (SD 1174.3). The high frequencies of malformations in 2012, 2017 and 2018 was observing (Table 1). The observed differences are statistically significantly ($p < 0.05$).

Table 1. Congenital malformations prevalence

Years	Incidences with 95% CI
2007	0.0296 (0.02694-0.03246)
2008	0.02734 (0.02479-0.03008)
2009	0.02743 (0.02492-0.03012)
2010	0.02893 (0.02636-0.03168)
2011	0.02981 (0.02723-0.03258)
2012	0.03336 (0.03067-0.03622)

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One family was referred to genetic counseling center because of multiple disabilities. They had three involved children resulting from consanguineous marriage with inbreeding coefficient about 6.25%. A 10 months boy and a 8 years old girl suffering from delayed development, high crying, irritability, decreased head circumference, visual and hearing impairment and finally quadriplegic mental retardation. Another girl was dead in 11 years old with similar manifestations. This family had three normal children and was pregnant too.

Chromosomal study and CGH array were normal. Whole Exome Sequencing were used to enrich all exons of protein-coding genes as well as some important other genomic regions. Next generation sequencing was performed to sequence close to 100 million reads on Illumina Sequencer. In this test, point mutations and micro-insertion/deletions and duplication (<20bp) can be simultaneously detected. A large homozygous deletion around following region was predicted: chr11:653904-710516, about 56600 bp, including genes: TMEM80, EPS8L2, DEAF1. DEAF1 gene acts as a regulator of transcription. Activity of this protein is important in the regulation of embryonic development. Mutations in this gene have been found in individuals with cognitive disability. EPS8L2 is a Protein Coding gene. Diseases associated with EPS8L2 include Deafness. TMEM80 is target gene of DEAF*1* and decreased mRNA levels were observed for Tmem80 throughout the brain of DEAF1 knockout mice. Clinical manifestations were seen in involved sibs appeared as a result of dysfunction of deleted genes individually and interaction with other related genes. Prenatal diagnosis was done and fetus born in normal condition.

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E-P11.037

Recessive inheritance of DISP1 variants in holoprosencephaly spectrum patients

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Holoprosencephaly (HPE; MIM# 236100) is the most frequent congenital brain malformation (1 in 10,000 live births, 1 in 250 conceptuses). It results from incomplete midline division of the prosencephalon between 18th and 28th day of gestation, affecting both the forebrain and the face. The clinical spectrum is very wide, ranging from severe HPE with a single cerebral ventricle and cyclopia to clinically unaffected carriers in familial HPE. The full spectrum of HPE includes also microforms characterized by midline defects, with cleft lip/palate, hypotelorism, coloboma and/or single maxillary median incisor (SMMI). HPE is phenotypically and genetically heterogenous and was previously considered as a dominant disease with variable expression and incomplete penetrance. From the use of High Throughput Sequencing Technologies, it emerges that the penetrance and the phenotypic variability have digenic or oligogenic origin. To date, at least 18 genes are implicated in HPE and are all associated with key pathways of forebrain development including sonic hedgehog (SHH) pathway. Interestingly, among these genes, *DISP1* appears to have a specific mode of inheritance. DISP1 is a positive factor necessary for efficient secretion of the SHH morphogen and thus the establishment of its concentration gradient along the midline of the neural tube. We describe the clinical characteristics of three families with severe HPE or microform associated to compound heterozygous variants in *DISP1*. We will review the literature and discuss the genotype-phenotype correlations.

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E-P11.038

Detection of the pathogenic CNVs in the Macedonian patient with profound developmental delay

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Introduction: The array Comparative Genomic Hybridization (aCGH) is now recognised as a first tier diagnostic test for patients with wideranging phenotypes and has led to greater sensitivity in the detection of sub-microscopic genomic changes and pathogenic copy number variants (CNVs).

Materials and methods: aCGH was performed in the Macedonian patient with clinical signs of dysmorphia and developmental delay using the Affymetrix® CytoScan™ 750K Array (Applied Biosystems), that comprises 550 k non-polymorphic and 200 k SNP markers. The data was analysed using Chromosome Analysis Suite (ChAS) Software (v4.0).

Results: We describe a 2.5-year-old girl with dysmorphia and developmental delay. She has midfacial hypoplasia, facial asymmetry, prominent cheeks, deep set eyes, narrow rima oculi, short bulbous nose, simple and lop ears, round face and brachydactyly. Congenital hypothyroidism was detected at newborn screening, therefore she was on continuous l-thyroxine therapy. At the age of 2 weeks the baby developed hemolytic crises, followed by apnoic episodes. Developmental delay was noticed at 6 months of age, both for global and fine motor skills. She started to walk at 2 years of age, and no speech development so far. Her height and weight are below 3 percentile. Karyotype was 46,XX, del18p (11.1-pter). aCGH analysis was showed pathogenic 3 copies of the chromosomes 6q13q14.1 (4.081 kb) and 19p13.3 (650 kb) and one copy of chromosome 18p11.32p11.21 (14.919 kb), according to aDGV and ClinVar databases.

Conclusions: The array CGH analysis has become a widely accepted tool that supplements conventional karyotyping in patients with an unexplained phenotype.

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E-P11.039
EBF3-related neurodevelopmental disorder - case report of female with phenotypic expansion and review of the literature

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EBF3-related disorders were first described in 2017 (Sleven et al, Harms et al, Chao et al, Tanaka et al, Blackburn et al). Commonly reported features include global delays, mild-severe intellectual disability, ataxia, hypotonia, and mild facial dysmorphisms. Additional findings include high pain tolerance, febrile seizures, brain malformations, strabismus, feeding difficulties, scoliosis, genitourinary anomalies, short stature, perseverative social behaviours and motor stereotypies.

Herein, we report on a 19-year old female patient with a de novo likely pathogenic heterozygous variant in EBF3, c.487C>T, p.(Arg163Trp). Our patient shows many symptoms of EBF3-related disorders, including cognitive delay, mental health concerns, hypotonia, strabismus, autonomic dysfunction, poor feeding, complex renal anomaly, neurogenic bladder, febrile seizures, unstable gait, and an unusual coronal pattern of sulcation in the cerebellar tonsils. Additionally, she had two unexplained episodes of significant elevation in AST and ALT (4000-6000 U/L), not previously reported.

Our report provides further expansion of the phenotypic spectrum of EBF3- related disorders. Long term outcomes are not well described; our patient represents the third oldest individual in the literature. The elevated liver transaminases remain unexplained and could be related to her EBF3-related disorder, but the possible underlying mechanism is unknown. EBF3 encodes a member of the early B-cell factor transcription factor family. Haploinsufficiency has been proposed as a mechanism of EBF3-related disease (Lopes et al. 2017). This report contributes to the understanding of the long-term outcomes and health surveillance for affected individuals, and further supports the finding of multiple pleiotropic effects seen in EBF3-related disorders.

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E-P11.040
Expansion of phenotypic spectrum of *EP300* mutations

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Rubinstein-Taybi syndrome (RSTS) is a congenital malformation syndrome characterized by typical facial appearance, broad thumbs and halluces, and intellectual disability. Heterozygous mutations in *CREBBP* (50-60%) or *EP300* (8-10%) have been detected. Recently, a heterogeneous group of patients with *CREBBP* or *EP300*

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