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ABSTRACTS COLLECTION

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Interactive e-Posters

P01 Reproductive Genetics/Prenatal Genetics

P01.001.A
Prenatal diagnostics of 15q11.2 microdeletion syndrome - the possibilities and challenges

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Microdeletion in 15q11.2 has been described as a distinct syndrome encompassing an area between two fragile sites in 15q (BP1 and BP2), with approximately 500 bp size, containing *NIPA1, NIPA2, TUBGCP5*, and *CYFIP1* genes. It is a multisystemic disease affecting mostly the nervous system (intellectual deficits, delayed psychomotor development, ataxia, epilepsy, behavioral problems, etc.), followed by congenital heart defects and various dysmorphisms. This microdeletion was found in 0.57-1.27% of pediatric patients targeted for microarray analysis, mainly with developmental delay and intellectual deficits. However, not all of the deletion carriers have a clinical manifestation - it is found in 0.25% of the population of healthy controls. The penetrance of 15q11.2 microdelection syndrome is estimated at 10.4%, which is significantly higher in de novo occurrence. We report 4 cases of prenatally established 15q11.2 microdeletion, in 3 of the cases the microdeletion was inherited from clinically healthy mothers. The indications for aCGH prenatal diagnosis were: 1) ultrasound data for unilateral cleft lip and palate in combination with an increased nuchal translucency of 3.3 mm- mother was the carrier; 2) second pregnancy after the first case; 3) increased risk from the biochemical screening (1:6) and tricuspid regurgitation, brother with neuropsychiatric disability - mother was a carrier; 4) Increased NT of 7.3 mm. Our results highlight the importance of microarray analysis in the diagnostic refinement of

Background: Hearing loss (HL) can be divided into syndromic and non-syndromic hearing loss (NSHL, approximately 70 %). While pathogenic variants affecting the gene *GJB2* account for roughly 10-30 % of NSHL, the majority of NSHL is distributed among more than 100 other genes. For many patients who do not benefit sufficiently from hearing aids, cochlear implants (CIs) are the device of choice. Performance of CI recipients is expected to depend on genetic background and a favorable outcome has been associated with pathogenic variants in genes affecting the function of the cochlear sensory organ (CSO); a negative outcome was reported for patients with variants in genes associated with spiral ganglion neuron (SGN) function.

Patients: 129 unrelated hearing impaired children and adults without pathogenic variants in *GJB2* and without evidence for acquired HL.

Methods: Whole exome sequencing was performed analyzing 148 genes associated with HL listed in the Deafness Variation Database and additional 681 genes listed in the Human Phenotype Ontology database based on hearing impairment.

Results: In 33 of 129 patients we identified pathogenic or likely pathogenic variants in 30 different genes, confirming the genetic heterogeneity of hereditary HL. Among these was one patient with a (homozygous) pathogenic variant in a gene proven to affect SGN function (*DFNB59*).

Conclusions: For meaningful results, a significantly higher number of cases is required. In addition, a further functional subdivision of patients with gene alterations influencing CSO function should be considered.

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P02.22.C

In silico *and* in vivo analyses of novel variants identified by Whole Exome Sequencing in Argentinean deaf patients: to be or not be pathogenic

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Hereditary hearing loss (HHL) is the most common sensory disorder affecting 1 in 500 newborn children. Since HHL is related to more than 150 target genes, we designed a diagnosis strategy in order to identify pathogenic variants. A total of 1250 patients were analyzed for frequent mutations in *GJB2* and *GJB6* genes by Sanger Sequencing, genotyping 25% of them. From undiagnosed patients, 29 families were selected to perform Whole exome sequencing. After filtering and analysis process, 45% of patients were genotyped, identifying 23 causative mutations (11 novel, 12 reported) classified according to ACMG Standards. Some of the novel variants were further studied *in silico* by structural and stability studies of the mutated proteins. In addition, datasets from deafness and specific variant databases were correlated with different protein motifs in order to predict the theoretical pathogenicity effect of the aminoacid changes. Furthermore, knock-down phenotype rescue assays in zebrafish are underway to accomplish in vivo validation. In some cases, extensive analysis reinforced the pathogenicity prediction effect of variants and surprisingly, in one case, discouraged the deleterious effect of a genetic variant to the protein. Preliminary results in zebrafish confirmed the pathogenicity of one novel variant in the hair cell function and auditory system. This study shows that our algorithm is successful for the genetic diagnosis of deafness. Comprehensive analysis is crucial to strengthen prediction of variant pathogenicity. These findings highlight the importance of genetic studies followed by *in silico* and in vivo validation to better understand the genetic basis of HHL.

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P02.23.A

Genetic spectrum of hereditary hearing loss in multigenerational families with autosomal dominant mode of inheritance

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