Chromosomal analysis revealed a de novo "apparently" balanced double rearrangement: a balanced translocation between chromosomes 2 and 3 at breakpoints 2q22 and 3q13.2 and a pericentric 8p23.1q24.1 inversion, both of which were confirmed by FISH analysis. Subsequently, array-CGH analysis revealed a novel heterozygous deletion within the EXT1 gene at the inversion breakpoints, rendering the inversion as unbalanced. The inheritance mode as well as the size of the deletion was further investigated by qRT-PCR and the deletion was characterized as a de novo 3.1kb deletion removing exon 10. The inversion in combination with the 8p23.1 deletion most likely abolishes the transcription of EXT1 downstream of exon 10 hence resulting in a truncated protein.
To conclude, a rare and novel pathogenic cause of HME is presented in this study, highlighting the importance of additional comprehensive cytogenetic investigation when EXT1 and EXT2 mutation analysis is negative.

1.P5

High occurrence of chromosomal rearrangements among genetic causes of congenital aniridia in Russia

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11p13 deletions are associated either with isolated congenital aniridia (OMIM #106210) (AN) or with WAGR syndrome (OMIM #194072) where aniridia is one of pathognomonic signs. If the deletion encompasses the WT1 gene Wilms tumor develops (in ~70% cases). Early nephroblastoma development poses the urgency of DNA diagnostics in all patients with clinical signs of congenital aniridia.
Materials and methods.
DNA diagnostics was performed in 195 patients from 163 unrelated families from Russia: 184 patients from 152 unrelated families with AN and 11 patients from 11 families with WAGR. Screening for mutations was carried out by Sanger sequencing, MLPA, and FISH analysis if the WT1 gene was affected.
Results.
A total of 149 different mutations: 107 small PAX6 intragenic variants and 42 large deletions were found in patients with AN. In all WAGR patients deletions encompassing the PAX6 and WT1 genes were defined. 3 patients showed neither small PAX6 mutations nor microdeletions of 11p13.
The proportion of chromosome rearrangements was about one third of all genetic causes of AN (42/149). The localization of chromosome breakpoints and the length of the deleted regions varied (0.1÷7.5Mb). The same deletion affecting PAX6 downstream regulatory regions (0.5÷1.5Mb) occurred especially frequent (17/42). One deletion (1/42) was found to be the result of pericentric inversion of chromosome 11 inv(11)(p13q14).
Conclusion.
Analysis of chromosomal imbalance of the 11p13 region is an important step of the DNA diagnostics in patients with AN in Russia, not only due to the importance of early detection of WAGR deletions, but also by the high frequency of large chromosome rearrangements among genetic causes of AN in the Russian population.
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1.P6

Susceptibility loci CNVs with incomplete penetrance accurate diagnosis with uncertain prognosis

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Chromosomal microarray analysis (CMA) is the first-tier test for developmental delay, autism spectrum disorders, and congenital abnormalities in postnatal diagnosis and for ultrasound abnormalities in prenatal diagnosis.
The detection of variants with clinical significance by CMA, when compared to karyotype, can increase up to 10-20% in postnatal diagnosis and up to 5-18% in prenatal diagnosis. Nevertheless CMA also detects incomplete penetrance neuro-Susceptibility Loci Copy Number Variants (SL-CNV), which although having clinical significance have an uncertain prognosis.
The aim of this study is to identify from the literature a set of SL-CNV, and the corresponding penetrance for each variant, determining their occurrence in our cohort of postnatal samples ran between January 2012 and August 2018 and prenatal samples ran between January 2015 and August 2018.
We have established a 21 SL-CNV set, and from a total of 835 postnatal samples and 317 prenatal samples we have identified 36 and 11 cases, respectively, with a variant in one of the 21 established SL-CNV.
The percentage of cases with a SL-CNV is relatively similar between postnatal samples (4.5%) and prenatal samples (3.5%), although the reason of referral for the two groups is not completely overlapping and also the total number of prenatal samples represents about half of the time span of the postnatal samples, which might have underestimated their occurrence. The estimated penetrance for each of the established SL-CNV present some inter-publication variability, especially concerning samples with different phenotypes. Nevertheless some variants show concordance.
Estimating the penetrance for SL-CNV, and their clinical impact for the patient or carriers in the family, is a complex task. Only time, analysis of larger cohorts, and future knowledge of genotype-environment-phenotype interactions will overcome this difficulty, decreasing uncertainty for the around 4% of patients diagnosed by CMA.

1.P7

19q13.32 microdeletion syndrome further delineation of the clinical phenotype

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Background
Interstitial 19q13.32 microdeletions are rare and have been reported in only five patients so far. Common features mentioned in the literature include intellectual disability/developmental delay, facial asymmetry, ptosis, oculomotor paralysis, orofacial clefting, micrognathia, kyphoscoliosis, cardiac abnormalities and constipation,. Since only a few patients have been reported, little is known about the phenotypic spectrum of these deletions.