suppression of the zebrafish ortholog of *CHD1L* by CRISPR/Cas9 led to a significantly decreased head size at 5dpf. We further evaluated whether *CHD1L* could be implicated in the growth abnormalities observed in 1q21.1 CNV carriers; its overexpression indeed led to a significant increase of the total body length and inter-somites distance at 5dpf. We also showed that the combinatorial overexpression of *CHD1L* and *GJA8*, another 1q21.1 gene, exacerbates the neurodevelopmental alterations induced by *CHD1L* overexpression alone, but does not impact further the body growth, suggesting a genetic interaction between *CHD1L* and *GJA8* on some, but not all phenotypic components. Our results suggest that *CHD1L* is a major contributor of the 1q21.1 CNV-associated neurodevelopmental phenotypes and indicate that *CHD1L* has a potential role in the control of human growth via an epigenetic regulatory mechanism.

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Malformations of the cerebal cortex: from targeted next generation sequencing to whole exome sequencing

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Cortical brain malformations (rare disorders of proliferation, neuronal migration or cortical organization) have been associated with mutations in a rapidly growing number of genes. This complicates molecular diagnostic by Sanger sequencing. Until 2015, we used a targeted Next Generation Sequencing (NGS) based work flow with a panel of 103 genes for routine diagnostic. Nowadays our flow is based on whole exome sequencing (WES) using a filter for a panel of 175 relevant genes. This approach has the advantage that novel genes can be easily included and expansion to full exome analysis is possible.

The WES work-flow involved the DNA enrichment using the Agilent SureSelect CRE Capture. The detected variants are filtered and annotated with the Cartagenia software and classified with Alamut Visual

DNA samples of 108 individuals were tested with the WES based panel. Eight patients (7,4%) received a direct diagnosis and 12 (11.1%) patients were solved after additional investigations. With the previous used targeted NGS approach in total 192 patients were tested with a diagnostic yield of 12,5%.

However, most of the identified alterations are variants of unknown clinical relevance. Despite the use of in silico prediction programs, usage of frequencies, evaluation of the conservation among species they cannot be judged without additional clinical information and feedback from the specialist.

In conclusion, the WES approach for malformations of the cerebal cortex is a powerful tool for DNA diagnostics. In order to increase the diagnostic yield of cortical brain malformations, close collaboration between laboratory and referring specialist is mandatory.

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***CYP2C19* and *CYP3A4* gene variants and schizophrenia in Armenian patients**

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Introduction: Genetic variations play an important role in antipsychotic drug treatment response in several mental disorders, including schizophrenia. Clinical studies suggested that antipsychotic drug metabolizing enzymes of cytochrome P450 family contribute to reduction of disease symptoms and manifestation of side effects. In this study we aimed to investigate the potential of schizophrenia with two single nucleotide polymorphisms (SNPs) of genes, coding CYP2C19 and CYP3A4 enzymes (*CYP2C19* rs4244285 and *CYP3A4* rs2740574, respectively).

Materials and Methods: Here patients with paranoid form of schizophrenia and healthy subjects of Armenian population were enrolled. DNA was isolated using salting out method with a simple introduction of chloroform step. Genotyping was performed using PCR-SSP. Distribution of genotypes corresponded to Hardy-Weinberg equilibrium. Statistical analysis was performed using Pearson's Chi-squared test.

Results: We found that genotypes and allele frequency of the *CYP2C19* gene rs4244285 polymorphism was equally distributed among the study groups (*CYP2C19* 681A allele frequency in cases vs. controls: 0.11 vs. 0.17, $p = 0.46$). The same applies for the *CYP3A4* rs2740574*G allele frequency (0.017 vs. 0.019, $p = 0.96$). Interestingly, the minor allele frequencies obtained significantly differ from those in 1000 Genomes that might reflect ethnic differences in the populations enrolled.

Conclusion: Despite this pilot study identified no association between schizophrenia and genetic variants within the *CYP2C19* and *CYP3A4* genes, further studies in large sample size and independent research centers are required to clarify these findings.Funding: the basic part of the Ministry of education and science of the Russian Federation, state task project No. 6.6762.2017/BT.

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A missense variant in *PER2* is associated with delayed sleep-wake phase disorder

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Delayed sleep-wake phase disorder (DSWPD) is a circadian rhythm sleep disorder, and is characterized by an inability to fall asleep until very late at night and awaken at a socially acceptable morning time. The pathogenesis of DSWPD is poorly understood. Recently, several large scale GWASs of chronotype have reported genetic variants associated with variation in chronotype. Several associated variants were located in genes related to circadian rhythms. This study was performed to identify variants associated with DSWPD from known circadian genes. We focused on low-frequency missense variants. We utilized data obtained from databases of genetic variations (whole exome-/ genome- sequencing). Candidates were extracted by integrating the data and *in silico* assessment. DNA samples from 236 patients with DSWPD and 1,436 controls were genotyped to examine whether the candidates are associated with DSWPD. A missense variant (p.Val1205Met) in *PER2* showed a significant association with DSWPD (minor allele frequency (MAF) of 2.5% in cases and 1.1% in controls, P=0.026, odds ratio = 2.32). In addition, MAF of the variant in 222 patients with idiopathic hypersomnia was significantly higher than that in 3,554 controls (MAF of 2.3% in cases and 1.1% in controls, P=0.038, odds ratio = 2.07). PER2 is noted for its major role in circadian rhythms. PER2 forms a heterodimer with CRY, and the heterodimer plays an important role in the regulation of the circadian rhythm. The p.Val1205Met substitution was located in the PER2 CRY-binding domain. The substitution could be a potential genetic marker for circadian rhythms and sleep phenotypes. (Grants: KAKENHI and AMED)

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A novel role for DNAJC12, a gene recently associated with hyperphenylalaninemia and early-onset dopa-responsive parkinsonism, in brain development

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Introduction: We recently described biallelic null-mutations in the *DNAJC12* gene in two probands of unrelated families with early-onset, dopa-responsive, and non-progressive parkinsonism. This gene encodes a member of DNAJ/Hsp40 family. It was suggested that DNAC12 interacts with the aromatic amino acid hydroxylases involved in the dopamine and serotonin metabolism. Despite this hypothesis, its function is still unclear. Understanding DNAJC12 physiological role could shed light on new pathways potentially involved in Parkinson disease pathogenesis and progression.

Materials and Methods: Immunofluorescence experiments were performed in HepG2 and in differentiated SH-SY5Y cell lines to assess DNAJC12 cellular localization and co-localization with potential cellular partners. To better characterize its function, the *DNAJC12*-zebrafish orthologue *(dnajc12)* has been cloned and the expression analyzed during embryogenesis. Gene functional ablation assays were carried out in zebrafish embryos using mRNA-specific antisense morpholino oligonucleotides. Histological analyses were performed to evaluate the effects of the loss-of-function approach.

Results: Our immunofluorescence experiments showed that DNAJC12 does not present a specific cellular localization but is present both in the cytoplasmic and the nuclear compartments. Concerning the *in-vivo* experiments in zebrafish, the dnajc12-morphants were characterized by a severe brain developmental phenotype. In particular, the morpholino-injected embryos displayed a marked expansion of the cerebral ventricles.

Conclusion: Our results suggest the existence of other unknown functions for DNAJC12 beyond dopamine and serotonin metabolism. Further studies will help shedding light on the specific role of this gene during early brain development.