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Combined whole exome sequencing and chromosomal microarray analysis improve clinical interpretation of genomic variants in patients with intellectual disability

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Introduction: aCGH determines pathogenic copy number variations (CNVs) in about 10% of patients with intellectual disability (ID). In another 20% of patients, probably pathogenic CNVs or variants with uncertain clinical significance are detected. It may be variants that do not fully explain the patient's symptoms, aberrations with reduced penetrance or inherited from healthy parents. The use of a sequencing method for such cases is advisable.
Objectives: Improvement of diagnosis of intellectual disability.
Methods: aCGH with 60K Agilent microarrays, qPCR, targeted sequencing, whole exome sequencing (WES).
Results: Six patients with ID and inherited deletions/duplications detected by aCGH and their parents if available were further examined by sequencing. Four patients had maternal CNVs: (1) del1q41 (*SPATA17, LINC00210, RRP15*), (2) del7q35 (*TCAF2*, exon 8), (3) dup8p22p21.3 (*PSD3,* exons 1-11), and (4) del12p11.1 (*SYT10,* exons 1-2). Two patients had paternal CNVs: (5) dup1q44 (*SMYD3*, exons 2-5) and (6) del15q11.2 (*TUBGCP5, CYFIP1, NIPA1, NIPA2, LOC283683*). The severe phenotype of patient (5) with dup1q44 could not be explained by the paternally inherited disruption of the single *SMYD3* gene. WES determined probably pathogenic SNV in the *MID1* gene associated with Opitz GBBB syndrome (OMIM 300000), which corresponds better to the patient's phenotype and is likely to be the cause of the disease. Although del1q41 is included in the region of chromosome 1q41-q42 deletion syndrome (OMIM 612530) the phenotype of the patient (1) is much milder; WES in the patient detected two pathogenic (*MPO, MAN2C1*) and one probably pathogenic (*ARID1B*) SNVs. In patient (6) with del15q11.2 pat WES detected additional pathogenic SNV in exon 7 of the *ARSE* gene. In patient (3) with dup8p22p21.3 WES determined two SNVs with uncertain significance in the *KIDINS220, FOXG1* genes. No SNVs were detected by WES in patient (2) with del7q35. For patient (4) with del12p11.1 targeted *SYT10* sequencing revealed no pathogenic SNVs as well.
Conclusions: Sometimes aCGH-analysis is sufficient to identify the causes of ID, however, in the case of detection of CNVs with uncertain clinical significance and/or inherited from healthy parents, it may be necessary to further examine the patient using sequencing methods. So, the accurate diagnosis was made by WES for one patient of eight. For another two patients the combination of CNVs and SNPs should be considered. For the last three patients the described aberrations could not explain the phenotype and whole genome sequencing may be the solution.This study was supported by the Russian Science Foundation, grant 21-65-00017, https://rscf.ru/project/21-65-00017/

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Diagnostic yield of chromosomal microarray and trio whole exome sequencing in congenital brain anomalies

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Introduction: The deductive method: from karyotyping to aCGH and WES is an important aspect in the diagnosis and search for the causes of intellectual disability due to congenital brain anomalies. There is recommendation to exclude the presence of CNV or monogenic variants for patients with a normal karyotype, but with a clinical picture of syndromic disease.
Objectives: Improvement of diagnosis of intellectual disability.
Methods: aCGH with 60K Agilent microarrays, WES with SureSelect Human All Exon V8
Results: Pathogenic or potentially pathogenic CNVs were excluded previously by aCGH for 10 families (total 32 people, 2 families had 2 children) with intellectual disability and congenital brain anomalies (for example, polymicrogyria, pachygyria, lissencephaly). The WES identified candidate variants for all families that can lead to impaired neurodevelopment, including 3 pathogenic variants in 3 families, 3 likely pathogenic in three other families, and 10 variants with uncertain clinical significance for 4 families. Almost all of these variants were identified *de novo*, except for one family, where the proband has been a compound heterozygous for two variants in the *RELN* gene. The first case of pathogenic mutation *de novo* was detected in a girl with agenesis of the corpus callosum. It was a missense mutation DYNC1H1 (NM_001376.5): c.4868G>A (p. Arg1623Gln), which leads to impaired intellectual development in autosomal dominant type 13 (OMIM 614563). The second variant was detected in a boy with corpus callosum agenesis, pontine hypogenesis, pachygyria in the frontal lobes. It was a missense variant MACF1 (ENST00000567887.5): c.21989A>G(p. Asp7330Gly), which leads to lissencephaly 9 with complex brainstem malformation (OMIM 614563). The third variant was found in a girl with epilepsy and impaired myelination of the white matter of the parietal-occipital areas of the cerebral hemispheres. It was a missense variant CDKL5 (NM_001323289.2):c.404-1G>A that leads to developmental and epileptic encephalopathy 2 (OMIM 300672).
Conclusions: Sixteen candidate variants potentially responsible for mental health were reported in this study. Most of these variants were missense changes in genes. All except one anomalies arisen *de novo.* Trio-based WES has been shown to be an important step in making a genetic diagnosis if other chromosomal and subchromosomal abnormalities had been excluded. The clinical description of the patient is the most important step for the correct interpretation of WES results, which allows to establish the exact genetic cause of the disease if several variants with unclear clinical significance were previously identified.
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