



Sample: Psychology - Review Article

In the article titled “Genomics, intellectual disability and autism”, the authors investigated whether chromosome microarrays and next-generation sequencing could be the powerful tools for identification of causative chromosomal copy-number changes and single-nucleotide changes for intellectual disability, autism and developmental delays.

The article is divided into two parts. In the first part, the scientists investigated the role of copy-number changes in the diagnostic workup for intellectual disability, autism, and developmental delays. Such new technique as array comparative genomic hybridization (CGH) was used for the discovery of copy-number changes. In the second part of the article, the scientists described three strategies for exome sequencing and the importance of these approaches for etiologic genes identification. These two parts of the article will be summarized separately.

I. The role of copy-number changes in intellectual disability

1. If copy-number changes in genomes of affected persons are identified by chromosome microarray, then these genomic rearrangements are causative for the investigated diseases.

The null hypothesis can be defined as the absence of causative relationship between copy-number changes in genomes and observed disorders.

2. The authors investigated the relationship between genomic rearrangements and their causal role in intellectual disabilities. Thus, I identified copy-number changes as independent variables and intellectual disabilities as dependent variables.
3. The authors reviewed two studies where 21.698 patients in the first one and 15.767 patients in the second were tested for copy-number variants. The scientists used array CGH analysis as an effective technique for identifying chromosomal microdeletions and microduplications. Array CGH can be used to quickly scan the entire genome for



subchromosomal alterations. This modern technique has a higher diagnostic yield than the karyotyping.

4. In the reviewed studies, the rate of positive genetic diagnosis was approximately 12% (data from 21.698 patients) and 14% (data from 15.767 patients). From these results, I made a conclusion that the hypothesis is true and chromosomal rearrangements are etiologic for intellectual disabilities, but only in 13% of cases on average.
5. Thus, identifying copy-number changes through array CGH analysis should be used as the primary step in the diagnostic workup for intellectual disability of unknown cause. It will help to diagnose autism and a large number of developmental delays and congenital anomalies.
6. I think that 13% is an insufficient diagnostic yield. Thus, scientists should continue the research aimed to provide a deeper understanding of the molecular mechanisms of intellectual disabilities. This will simplify these disorders diagnosis.

II. Exome sequencing is a powerful tool for causative genes discovery

Recently, the scientists have revealed mutations causing intellectual disability in a large number of single genes. Genome sequencing is an indispensable technique for identifying single-genes mutations. However, the whole genome sequencing is a highly expensive (\$700 000) and time consuming procedure nowadays. That is why sequencing of the protein-coding parts of the genome (exome sequencing) seems to be a more suitable approach. Proof-of-principle experiment was conducted to investigate whether exome sequencing can be successfully used for single gene disease identification.

The authors have described three approaches to exome sequencing. In the first one, the DNA sequence data from several unrelated and similarly affected subjects are compared in order to identify genes in which some or all of the subjects have a causative mutation. The second approach is the so-called trio analysis. It can be used when unaffected parents have a child with



intellectual disability. There is a chance that the cause of the disorder is the de novo mutated gene. The mutation that will be identified only in the child's DNA is likely to be disease-causing. If there are several affected children in the family, it suggests that their intellectual disability is inherited in a recessive way. In this case, recessive analysis should be used. If parents heterozygous for a deleterious mutation have children homozygous for the same mutation, it is probably a causative mutation.

Chromosome microarrays and next-generation sequencing have revolutionized gene discovery in intellectual disability, autism, and other disorders. However, there is still a long road before scientists make genome sequencing widely used in clinical diagnostic laboratories.



References

Mefford, H.C., Batshaw, M.L., & Hoffman, E.P. (2012). Genomics, Intellectual Disability, and Autism. *National English Journal of Medicine*, 366, 733-743.