Copy Number Variations in the Human Genome - A New Page in Psychiatric Genetics: The Collaborative Project Psychcnvs

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ABSTRACT

Variations in the human genome associated with changes in the copy number of individual fragments have always been an object of close attention of medical geneticists. In the second half of the twentieth century, they were detected using cytogenetic methods. Chromosome aneuploidy, i.e., the actual change in copy number of all genes located on a dropped out or extra chromosome, is known to have critical consequences for the phenotype (the classical example is Down syndrome or trisomy 21).

Keywords: molecular genetics, psychiatry, international projects

Introduction. At the end of the twentieth century, a major international research programmer, the *Human Genome Project*, resulted in the discovery of another type of genetic variation. The goal was to completely decipher the nucleotide sequence of the genome. One of the major achievements of the project was the discovery of gene polymorphism, i.e., interindividual differences in DNA sequencing that occurred at the level of individual nucleotides[1] and were also due to small insertions or deletions of several nucleotides organized as adjacent (tandem) repeats. The proportion of interindividual variations due to such substitutions[2] was significant (up to 10%). Data on polymorphisms in individual genes proved to be very valuable for medical genetics. It has become possible to identify molecular genetic markers for various diseases, mostly widespread ones, in the development of which several genes are involved. During the period 2017-2022 another project has been implemented.

In 2006, the results of R. Redon's work were published in Nature. Redon et al. which mapped the genomes of 270 people belonging to different races using a specially developed method (it can be considered as submicroscopic compared to microscopic chromosome study). The authors detected a new type of variation in the human genome, CNVs. Approximately 1500 sites were identified in which significant lengths (from several thousand to several million pairs of nucleotides) of duplications (doublings) and deletions of DNA fragments were present. These fragments can comprise individual genes, in which case a duplication results in an extra copy of the gene, while a deletion, in turn, results in one less copy of the gene. They can also be incorporated into the nucleotide

sequence of a gene or dropped out of it, causing a gap. In general, the authors estimate the length of these sites to be as much as 12% of the genome, i.e., the contribution of CNVs to genome variation is comparable to or even greater than that of single nucleotide polymorphisms. Describing the importance of his discovery for future of genomics, R. Radon et al. figuratively compared the genome with the text of a book containing a unique for each individual information about his own life: if single nucleotide polymorphisms and short DNA sequences are letters and sentences, then gene copy variations are paragraphs or even entire pages. The text fragments may contain crucial information in the field of evolution and medicine. The text fragments can also contain crucial information on evolution and medicine.

It has been suggested that the detected genome regions contain a large number of genes[4] as well as loci associated with various diseases and functional elements. It has been shown that a number of mutations caused by CNVs can not only be inherited but also occur *de novo*. This fact was detected by comparing the genomes of the parents and the child. Although we inherit one copy of each gene from the father and one from the mother, it was found that the number of copies may vary from person to person and that the percentage of such variation is much higher than expected. The reasons for copy number variations are not yet clear. It is possible that CNVs occur in genome regions that include repetitive sequences or that these sequences are adjacent to them as duplicate or multiple copies. Such regions can often fail when parental chromosomes converge during the exchange of genetic material.

Copy number variation has been studied from the perspective of human evolution and medical genetics. To date, it has been discovered that CNVs may be the cause of several dozen sporadic diseases caused by genomic rearrangements . They have also been found in families with monogenic inherited diseases . As for widespread diseases, in the short period since the discovery of CNVs, there have been reports of their association with 17 human diseases, including systemic autoimmune and psychiatric diseases Full genomic studies of CNVs have now been carried out and a database is being created, as has been done previously for polymorphisms in the HapMap project.

Endogenous mental illnesses (schizophrenia, autism spectrum disorders, bipolar affective disorder) were among the first to come into the focus of research looking for copy number variations, as earlier findings indicated that karyotypic abnormalities may be critical to their development.

For example, patients with DiGeorge syndrome, an X- linked disorder in which one of the hemizygotes has a deletion of site 22q11.2, have been found to have psychotic disorders in 25% of cases. Mapping of this site to identify possible candidate genes for schizophrenia revealed two promising genes, catechol-O-methyltransferase (COMT) and proline dehydrogenase (PRODH). The association of allelic variants of these genes with schizophrenia has subsequently been found in several studies. Associated with the study of chromosomal aberrations was the discovery of another gene, DISC1[5], whose function is impaired in schizophrenia. It was first identified by D. Blackwood et al. in a Scottish family where mental disorders were combined with a chromosomal translocation . The two genes damaged as a result of the disruption were DISC1 and DISC2. In autism, the detection of cytogenetic abnormalities associated with the chromosome region 15q11-q13, made it possible to identify candidate genes that may be involved in the pathogenesis of this disease. These are genes encoding receptors for γ-aminobutyric acid (GABA), an important neurotransmitter associated with inhibition in the brain, and the UBE3A gene (ubiquitin E3A ligase), whose activity is expressed mainly in the brain. Recently, J. Glessner et al. found that this gene and others related to ubiquitin metabolism contain CNVs, which are present only in patients and not in a control group of mentally healthy people.

Further study of sites with copy number variations in patients with mental illness may contribute to the discovery of new candidate

genes. The first studies in this direction have been carried out G. Wilson et al. who found that copy number variation in patients with schizophrenia was observed in genes associated with the glutamatergic system (GRIK3, EFNA5, AKAP5 and CACNG2). However, these results were not confirmed by S. Sutrala et al. H. Moon et al. Moon reported that schizophrenic patients have insertion or loss of DNA fragments at several chromosomal sites: insertions are most frequent on chromosome Xq23 (52%) and losses on 3q13.12 (32%). N. Lachman et al. suggested another approach to studying copy number variations, suggesting that polymorphic CNVs can break the DNA sequence of the coding elements of candidate genes and thus directly participate in disease pathogenesis. In this case, a particular variant of CNVs may be a marker of the disease. In particular, the glycogen synthase kinase 3 β (GSK3β) gene located at chromosomal site 3q13.3, which targets lithium salts, was studied in patients with bipolar psychosis. Duplication can occur in the 3'-coding elements of the gene. The frequency of genetic variants carrying the duplication was found to be significantly higher in the group of patients compared to controls . Two chromosomal aberrations were found in schizophrenic patients by G. Kirov et al., one was a deletion in the 2p16.3 region that breaks the sequence of the neurexin 1 gene (NRXN1), the other was a newly formed duplication in the amyloid A2 precursor binding protein (APBA2). Both genes play an important role in synapse formation and function.

Of interest is the search for rare variants of CNVs, which are essentially mutations that may be responsible for the development of mental illness. Finding such variants requires a substantial research effort that is beyond the capacity of individual research teams. For this reason, scientists have come together to form the Schizophrenia Consortium. The first findings were published in J. Stone et al. Stone et al. That publication reported a full genome-wide study of rare CNVs variants in 3391 schizophrenia patients and 3181 controls. Areas of CNVs longer than 100,000 base pairs were found in 1% of all examined patients. However, they were more frequent in patients than in controls. Differences were more pronounced for rare, single CNVs or those CNVs that included individual genes. Deletions in schizophrenic patients were found on chromosome 22q Larger deletions were found at sites 15q13.3 and 1q21.1. In a study by Stefansson et al. screened 1,433 patients and 33,250 mentally healthy individuals and identified 66 newly formed mutations. Of these, 3 mutations, represented by deletions at sites 1q21.1, 15q11.2 and 15q13.3, were associated with schizophrenia and schizophrenic spectrum disorders.

In 2018, another international group was established, comprising teams of researchers from seven countries (UK, Iceland, Russia, Ukraine, Georgia, Macedonia and Serbia). The aim of the project proposed by this group (abbreviated as "PsychCNVs") is to search for copy number variations in patients with autism and early-onset psychoses. The research is to be carried out on a large sample of at least 4,000 patients and 30,000 controls. The project received financial support from the European Union's Seventh Framework Programme for Research and Technological Development (FP7) in 2009. The ability to search for rare and highly variable sequences was enabled by the development of the HumanCNV370 microarray, which allows detecting tens of thousands of DNA sequences, by deCODE genetics, the project coordinator. This unique development, including highly sophisticated software (including robots), is one of the world's most effective for the analysis of variable DNA sequences. At In this study participants will be required to use unified set of diagnostic tools: the Autism Diagnostic Interview Interview - ADI-R), adaptive behavior scale (Vineland Adaptive Behavior Scale), an interview for the diagnosis of schizophrenia and affective disorders in children and adults (Schizophrenia and Affective Disorders Scale - K-SADS-L, SADS-L, etc.). All diagnostic tools will be translated into the languages of the participating countries, and researchers from these countries will receive training in the use of the diagnostic tools. The next step will be large- scale

genotyping of DNA samples from patients and people in the control group using microarray technology. This will identify 40,000 rare CNV variants potentially at high risk for the psychopathologies in question, as well as 5,000 common CNVs and 320,000 single nucleotide polymorphisms associated with moderate risk. Further, 1% of all variant sequences studied will be selected for a more detailed study using state-of-the-art molecular and cytogenetic methods. Finally, an attempt will be made to establish a causal relationship between high-risk variants and phenotypic manifestations. Further studies are envisaged to investigate the expression of the identified genes, as well as studies in animals with deactivated function of these genes.

Conclusions: In terms of the size of the study group and molecular genetic methods, the latest study is unparalleled worldwide. It will enable the discovery of new genetic variants associated with the risk of early-onset autism and endogenous psychosis, which is of great importance for the early diagnosis of these disorders and the development of new medicines for their treatment, as well as for understanding the biological basis of the origin of mental disorders associated with early brain development disorders.

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