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FACULTY OF SPECIAL EDUCATION
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12. MEĐUNARODNI NAUČNI SKUP „SPECIJALNA EDUKACIJA I REHABILITACIJA DANAS”

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APPLICATION OF MODERN METHODS OF MOLECULAR GENETICS IN PRACTICE

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Introduction: *The development of new methods of molecular genetics, especially in the last two decades, has led to enormous progress in the field of medicine and enabled more comprehensive prenatal and postnatal diagnosis of hereditary diseases and other disorders, as well as preimplantation testing.*

Aim: *The aim of the work is to present modern methods of molecular genetics and their application in the diagnosis of hereditary diseases and developmental disorders.*

Methods: *Having reviewed the relevant literature, insight was gained into the current development of molecular genetic methods and their practical application.*

Results: *Chromosome microarray is an analysis of all chromosomes in the genome, which, thanks to microchip technology, enables the detection of chromosomal microdeletions and microduplications, as well as changes in the number of copies, in just one reaction. This method has found application in all areas of clinical genetics, and especially in the detection of genomic changes in patients with intellectual disabilities, developmental delays, autism spectrum disorders and congenital anomalies. The gene microarray is also based on microchip technology, and depending on the type of DNA chip used, it is used to detect mutations and DNA variations at the level of the entire genome or to study gene expression. The rapid development of biotechnology and bioinformatics has enabled the simultaneous analysis of a large number of genes through parallel (deep) sequencing, known as a new generation of DNA sequencing methods. This technology detects already known gene variants, new ones, as well as the presence of a predisposition. Today, in clinical practice, differently designed gene panels are used for postnatal diagnosis of monogenic and multifactorial diseases. Particularly noteworthy are the "clinical exome" panels with over 6,000 genes, the whole exome (about 22,000 genes) or the whole genome.*

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Conclusion: *Modern times have marked the development and improvement of molecular genetics methods for quick and more accurate diagnosis of hereditary diseases and developmental disorders, which gives a new perspective on the possibilities of prenatal, postnatal and preimplantation genetic testing.*

Keywords: *hereditary diseases, molecular methods, diagnosis*

INTRODUCTION

Genetic diseases imply changes in the hereditary basis. They can be at a level of chromosomes (numerical or structural), mutations of individual genes (nuclear or mitochondrial DNA), as well as changes in a genome that is between genetic and chromosomal in size, i.e., genomic mutations or copy number variations (CNVs). Furthermore, a large number of disorders present in the general population are multifactorial, and arise from the combination of a hereditary basis and numerous environmental factors. Due to such heterogeneous changes that can occur in the genome, the need to develop and improve techniques for more precise detection is constant. For example, because of limited resolutions, standard karyotype analysis cannot detect genomic microdeletions and microduplications smaller than 5Mb (CNVs). It is significant that these submicroscopic changes are associated with 6-15% of genetic diseases and are considered to play an important role in the occurrence of multiple malformations and mental retardation (Vissers et al., 2005, Vissers et al., 2010).

The rapid development of biotechnology and bioinformatics, especially in the last two decades, has enabled the development and improvement of new molecular genetic methods for quick and more accurate diagnosis of hereditary diseases and other disorders, thus enabling more comprehensive prenatal, postnatal and preimplantation diagnosis.

AIM

The goal of this work was to present modern methods of molecular genetics and their application in the diagnosis of hereditary diseases and developmental disorders.

METHODS

Having reviewed the relevant literature, insight was gained into the current development of molecular genetic methods and their practical application.

RESULTS AND DISCUSSION

Molecular karyotype

Molecular karyotype or Chromosomal "microarray" (Chromosomal Microarray Analysis, CMA) represents the analysis of all chromosomes in the genome, which, thanks to microchip (microarray) technology and high resolution, enables the detection of chromosomal microdeletions and microduplications (less than 1Mb), including the detection of copy number variation (CNV) along the entire genome in just one reaction. The analysis involves two methods of execution: 1. comparative genomic hybridization on a microchip (array Comparative Genome Hybridisation, aCGH), and 2. analysis of single nucleotide polymorphisms on a microchip (Single Nucleotide Polymorphism array, SNP array). The first analysis, aCGH, is based on the competitive binding of tested and control DNA (different fluorescent labelling), with probes consisting of short specific sequences of nucleotides imprinted on glass plates (several hundred thousand probes). Software analysis measures and compares the strength of the fluorescent signal of each sample, on the basis of which a conclusion is drawn in terms of an increase or decrease in the number of copies in the tested sample (Levy & Burnside, 2019). The second one, SNP array, is based on the hybridization of only the tested DNA with the samples on the microchip. These DNA probes come from regions of the genome that differ between individuals at the level of a single base pair. The analysis of the results involves comparing the fluorescent signal of the tested sample with the reference set (Levy & Burnside, 2019). These methods do not require cell culture, and the results are obtained in 3 to 4 days.

The advantage of the array method is the possibility of analyzing the entire genome at once, as well as the detection of microdeletions and microduplications, up to 50-100 kb in size (Levy & Wapner, 2018; Xiaouri et al., 2021). Clinical trial platforms generally contain trials targeting regions associated with well-defined microdeletion and microduplication syndromes (Levy & Wapner, 2018), and it is recommended that they allow the detection of CNVs of at least 400 Kb (Kearney, 2011). As the SNP array has a higher resolution, this technique can detect long regions of homozygosity (which may indicate uniparental disomy or consanguinity), triploidy, and contamination with twin or maternal cells (Kearney, 2011; Levy & Wapner, 2018; Xiaouri et al., 2021). Due to their advantages, CMA methods have been recommended since 2010 as the test of first line in the postnatal detection of CNVs associated with intellectual disabilities, autism spectrum disorders and/or multiple congenital anomalies (Kearney et al., 2011; Miller et al., 2010; Peters Peters & Pertile, 2014). The detection rate of pathogenic CNVs in patients tested for these disorders was 14–18% (Peters & Pertile, 2014; Stankiewicz & Beaudet, 2007). In prenatal diagnosis, CMA analysis is the first line for testing fetuses with ultrasound-identified anomalies (Liao et al., 2014; Shaffer et al., 2012), such as central nervous system anomalies and congenital heart defects where high rates of CNV are found, and clearly correlate with the clinical features (Charan et al., 2014; Liao et al., 2014; Shanshen et al., 2018; Syrmou et al., 2013; Xiaouri et al., 2021).

With the use of array technology, it was discovered that there are widespread variations in the number of copies in the human genome, from polymorphic variations in healthy individuals to new pathogenic variants (Kearney et al., 2011; Lovrečić et al., 2014). The question arose of how to define the nature of the detected CNVs and interpret the results obtained using genomic array. To ensure consistency, the American College of Medical Genetics and Genomics (ACMG) has created professional guidelines for evaluating copy number variations in postnatal testing (Kearney et al., 2011), and the last updated version was published in 2020 (Riggs et al., 2020). According to clinical importance, there are three basic categories of CNV - benign, pathogenic and a variant of uncertain significance (VOUS), which can be probably pathogenic, benign or without additional subclassification. Therefore, interpreting VOUS is a specific challenge when interpreting the results and giving genetic advice.

By testing the child (proband) and parents, and if necessary other family members, the result can show that the CNV in the proband is a *de novo* mutation, which supports the pathogenicity of the findings. In the event that a CNV is also found in the parents or one of the family members, the interpretation of this result can be very complex due to the absence of a clinical manifestations, incomplete penetrance of the gene, variable expression, the imprinted region, the mosaic CNV, the presence of another mutation, X - linked CNVs, or when the CNV found is not of the same size as in the proband (Kearney et al., 2011). Practice has shown that the interpretation of the CNVs found is often very difficult, and that there is no reliable way to separate a pathological CNV from a normal one. This is precisely why it is of great importance to report new cases of clinical significance and enter them into gene databases (OMIM, DECIPHER, GeneReviews, etc.).

The limitations of the array method is reflected in its inability to detect balanced translocations and inversions, in addition to a low percentage of mosaicism (Lovrečić et al., 2014).

Gene microarray

The gene microarray or gene chip is based on DNA chip technology and enables the analysis of a large number of genes in one reaction. Depending on the applied DNA-chip, the analysis is used to detect mutations and DNA variations at the level of an entire genome, or to study gene expression. There are two types of DNA-chips: microplates with imprinted complementary DNA (cDNA) and microplates with synthesized oligonucleotides, both equivalent to the DNA sequence of interest or gene of interest. One microplate can contain thousands of these points. The principle of the method is the binding of fluorescently labelled cDNA, obtained by reverse transcription of mRNA of the tested sample, to the corresponding nucleotide sequence (Lojo-Kadrić et al., 2018). The analysis of the results involves measuring the intensity of the fluorescent signal of each point, which provides an insight into the gene activity in the examined tissue.

Comparing the gene expression in healthy and diseased tissue will indicate a change in the level of gene expression in genetically altered or diseased organisms, and therefore the analysis is suitable for the diagnosis of rare diseases, the determination of gene variations, as well as disease predisposition (Tomašić Paić et al., 2010).

DNA sequencing

The discovery of gene variants as the cause of diseases or disorders has been made possible by the Next Generation Sequencing method (NGS). This technique provides the simultaneous analysis of a large number of genes through parallel (deep) sequencing by "reading" each nucleotide several times, and then comparing the results obtained by bioinformatic analysis with the reference genome. In this way, known gene variants, new ones, as well as the presence of a predisposition are detected. During NGS analysis, pathogenic variants that were not the reason for testing (incidental finding) can be detected, which is important in the pre-symptomatic period, so it is recommended to report findings for a list of 73 genes (Miller et al., 2021).

NGS analysis involves several lines of testing. Gene panels enable the analysis of a limited number of clearly defined genes that are associated with a given phenotype. These targeted gene panels contain specific sets of genes and are designed according to the clinical characteristics and possible differential diagnosis (Novaković & Maksić, 2014). They are most often used in the diagnosis of genetically heterogeneous disorders such as developmental delay and intellectual disabilities (Bean et al., 2020; Redin et al., 2014). The "clinical exome" or "mendelioma" panel contains over 6,000 genes mostly associated with monogenic diseases. A new approach in selecting genes for analysis is according to the observed phenotype, i.e., as per the Human Phenotype Ontology (HPO) database in which different phenotypes are associated with the responsible group of genes, which increases the success of diagnosis (Maver et al., 2016). The clinical exome test is recommended for an atypical phenotype, or a phenotype where a specific gene panel cannot be applied. These include neurodevelopmental disorders, intellectual disabilities, epilepsy, cardiovascular diseases and neuromuscular diseases (Gieldon et al., 2018; Pajusalu et al., 2018). Whole-exome sequencing (about 22,000 genes) covers more than 95% of exons that include 85% of mendelian disease mutations, as well as genomic changes in the form of SNPs associated with pathological phenotypes (Rabbani et al., 2014). This has been shown to be significant in patients with neurodevelopmental diseases, including moderate and severe forms of intellectual disability, especially in the detection of *de novo* mutations (Bowling et al., 2017; Hamdan et al., 2014; Hiraide et al., 2021; Kuperberg et al., 2016; Rauch et al., 2012, all according to Ruml Stojanović, 2020). There is an increasing number of identified genes (more than 150) associated with various disorders, of which about 25 new genes are responsible for the occurrence of syndromic or non-syndromic mental retardation (Rabbani et al., 2014). Whole genome sequencing can provide more genetic information, and its effectiveness is the subject of recent research.

The DNA sequencing method is also used in Non-invasive Prenatal Diagnosis (NIPT) in the detection of the most common chromosomal aberrations in the fetus, microdeletions, and monogenic diseases, by analyzing fetal DNA present in the mother's blood (Novaković & Maksić, 2014). Furthermore, an important field of application of NGS methods is in pharmacogenetics and represents the future of personalized medicine.

Preimplantation genetic testing

Preimplantation Genetic Testing (PGT) is the earliest form of prenatal diagnosis that enables the selection of embryos with a normal karyotype for in vitro fertilization. PGT is used in couples who are at risk of having offspring with a hereditary disease or chromosomal aberrations. The techniques used in preimplantation testing are the array method and NGS, especially in the diagnosis of monogenic diseases, trinucleotide repeat diseases and chromosomal aberrations (Jeremić et al., 2021).

CONCLUSION

Thanks to the development and improvement of molecular genetic methods, quick and more accurate diagnoses of hereditary diseases and developmental disorders are available today. This has led to a real revolution in the field of medicine and sheds new light on the possibilities of prenatal, postnatal and preimplantation genetic testing.

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