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AN APPROPRIATE APPROACH ON THE IMPLICATIONS OF MICROARRAY TECHNOLOGY FOR ANIMAL GENETIC RESEARCH

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Abstract

Microarray technology has emerged as a powerful tool in the field of animal genetic research, offering a comprehensive and high-throughput method for analysing the expression of thousands of genes simultaneously. This paper explores the implications of microarray technology in advancing understanding of animal genetics, focusing on its applications, challenges, and potential contributions to various aspects of genetic research. The paper begins by providing an overview of microarray technology, detailing its principles and the array of applications it offers for investigating gene expression, genetic variations, and regulatory mechanisms in animals. Furthermore, this paper addresses the challenges associated with microarray data analysis, emphasizing the importance of bioinformatics methods to extract meaningful insights from large-scale genomic datasets. This study aims to guide researchers in choosing appropriate methodologies, highlighting best practices, and fostering a deeper understanding of the implications and limitations of this technology in the context of animal genetic research. This exploration also contributes to the ongoing dialogue within the scientific community on optimizing the use of microarray technology to unlock the mysteries of animal genetics and advance the knowledge of biological systems.

Key words*: animal research, gene expression, genetic data analysis, microarray.*

INTRODUCTION

Microarray technology has enabled the identification of sets of genes over and under-expressed in various pathologies, including breast cancer, prostate cancer, lung cancer, as well as in the dysregulation of certain physiological processes such as apoptosis induction and response to therapy, not only in humans but also in animals. Integrated analyses of multiple studies have highlighted generalities and specificities of gene expression in certain pathologies (Spielbauer et al., 2005; Aizpurua et al., 2023).

The use of microarrays in biomedical research is not limited to determining gene expression profiles; they are also used to detect CNV (copy number variation) at the whole genome level, with high resolution, down to a level of 5-10 kilobases and even down to a resolution of 200 bp in the case of high-resolution array CGH variants (HR-CGH) (Madescu et al., 2019).

DNA microarray technology represents a multiplex technology used in molecular biology and veterinary medicine studies. It has evolved from the Southern Blotting analysis method - DNA fragments are attached to a substrate and hybridized with labelled probes representing gene fragments or entire genes. The spots can be short gene fragments - Probes - used for hybridization with cDNA - Target, under very well-defined conditions. The Probe-Target complexes can be visualized and quantified based on fluorescence detection of a fluorophore - fluorescent marker attached to the target for relative quantification of nucleic acid abundance in the target sample. DNA microarray technology can be used for both the detection of single nucleotide polymorphisms (SNPs) and for the detection of DNA (comparative genomic hybridization studies) or RNA (detected as cDNA after reverse transcription) which may or may not be

involved in protein translation (Bendixen et al., 2005; Gheyas et al., 2013).
Measuring gene expression levels based on cDNA is called "Gene Expression Analysis". Using traditional gene expression analysis methods, researchers can study a small number of genes per analysis. The development of new technologies allows tackling problems inaccessible through classical methods and discovering new targets for drug therapies (Singh et al., 2013).
"Microarrays", recently discovered DNA microarrays, allow researchers to analyse the expression of multiple genes rapidly and efficiently in a single experiment. They represent a major step in DNA analysis methodology and illustrate how new technologies provide "powerful tools" for research (Haley et al., 2006).
Overall, adopting an appropriate approach to the implications of microarray technology for animal genetic research involves leveraging its strengths while addressing its challenges, with a focus on advancing our understanding of animal genetics, improving breeding programs, and promoting animal welfare and sustainable agriculture (Stoughton et al., 2005; Kawecka et al., 2016; Szczerbal et al., 2021).
The aim of studying the implications of microarray technology for animal genetic research is multifaceted and encompasses several key objectives. This includes understanding genetic diversity within and between animal populations, mapping traits of interest, and discovering candidate genes associated with economically important traits such as growth, reproduction, disease resistance, and behaviour (Zhang et al., 2020). Additionally, the aim involves improving breeding programs through genomic selection and marker-assisted breeding, exploring functional genomics by elucidating gene expression patterns and molecular mechanisms underlying phenotypic variation, and conducting comparative genomic studies across different animal species to understand evolutionary relationships and species-specific adaptations. Furthermore, researchers aim to validate microarray-based findings using independent methods and integrate microarray data with other omics technologies for a more comprehensive understanding of complex biological systems. Ethical considerations, including the responsible use of animals in research and adherence to ethical guidelines and regulations, are also essential aspects of studying the implications of microarray technology for animal genetic research. Ultimately, the overarching goal is to advance our understanding of animal genetics, improve breeding programs, enhance animal health and welfare, and contribute to the sustainable management of animal populations for agricultural, conservation, and biomedical purposes (Khan et al., 2021).

MATERIALS AND METHODS

In order to reach the objectives of this study, 35 bibliographic sources from specialized literature were consulted. The main issues addressed refer to the types of microchips (microchips for the detection of changes in the level of gene expression, comparative genomic hybridization-CGH microarrays, mutation/polymorphism analysis microchips); the structure of a microarray; the basic principle of the microarray technique, respectively the study of gene expression - DNA analysis by microarray and interpretation the results obtained and also are presented the advantages of microarray technique.
The research methods used in this study were observation, analysis, and graphical interpretation of data from specialized literature.

RESULTS AND DISCUSSIONS

A microarray is a laboratory tool used to detect the expression of thousands of genes at the same time. DNA microarrays are microscope slides that are printed with thousands of tiny spots in defined positions, with each spot containing a known DNA sequence or gene. These instruments play a crucial role in animal genetic analysis, facilitating accurate identification and in-depth examination of their genetic profiles, ultimately enhancing research and breeding programs.
These microchips will be presented in detail from the point of view of their structure and the analysis technique, bringing to the attention of researchers not only the advantages of their use

in genetic analysis (Ventimiglia et al., 2013; Wickramasinghe et al., 2014).

DNA Microarray - Genetic Testing of the Future

A microarray chip can be defined as a gene expression analysis test consisting of a micro membrane or glass slide, on which DNA samples from multiple genes are systematically arranged. Samples can be represented by DNA, cDNA, or oligonucleotides. The characteristics of these tools enable a systematic and comprehensive study of the genetic expression of an organism (Ashammakhi et al., 2020; Balakrishnan et al., 2022).

Three types of probes can be used to produce microchips: two are genomic and the third is "transcriptomic" (measuring mRNA levels). They differed in the type of DNA fixed in the spots (Table 1).

Microchips for detecting changes in gene expression levels

They are also known as gene expression analysis microchips (microarray expression analysis microchips or simply expression microchips). The spots on these microchips contained cDNA obtained by reverse transcription of mRNA from known normal or mutant genes. If the expression of a gene in the studied tissue is increased, more cDNA will hybridize at that point compared to the control, with fluorescence directed towards red (Chen et al., 2023).

Gene expression chips can be used for diagnosis of genetic diseases, identifying mutations in genes involved in multifactorial diseases (especially cell cycle control genes involved in the proliferation of neoplastic cells), drug development (for drug development, these microchips can be used to study whether a new drug reduces the overexpression of a gene involved, particularly in neoplastic development.

Comparative Genomic Hybridization (CGH) Microchips

Researchers have used this technique to identify gene amplifications and deletions in the genome, or to observe changes in the copy number of a gene involved in the genesis of a specific disease. These microchips target large portions of genomic DNA. The chromosomal location must be known for each target DNA spot on the chip. The hybridization mixture contained fluorescently labelled genomic DNA probes collected from both the normal and investigated tissues. Consequently, if the copy number of the studied gene increases, a larger amount of DNA extracted from the investigated tissue will hybridize with the target spots compared to a smaller amount of control DNA. As a result, the fluorescence of the spots turned red to a greater extent as the copy number increased (Figure 1).

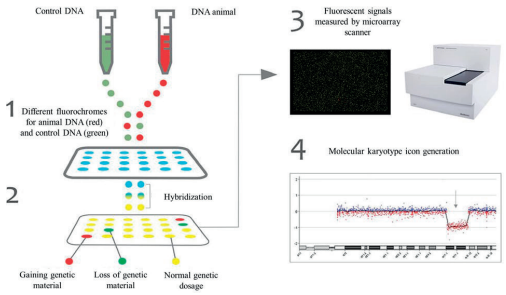

Figure 1. The basic principle of the microarray methodology (www.euroimmun.com)

The microarray CGH technique allows for the identification of Copy Number Variants (CNVs). They are classified into five categories: benign, Variants of Unknown Significance (VOUS) possibly benign, VOUS with uncertain significance, possibly pathogenic VOUS, and clearly pathogenic.

These submicroscopic genomic rearrangements are widespread throughout the genome and represent important factors in evolution, phenotypic differentiation, and susceptibility to certain conditions (Liu et al., 2015).

The advantages of the array CGH method are defined by increased clinical utility and an average detection resolution of approximately 60kb, providing a perspective on the entire genome at a high resolution, which is 10 times higher than that of classical karyotyping. It detects submicroscopic duplications and deletions, unbalanced chromosomal rearrangements, and does not require cell culture such as classical karyotyping (Naidu et al., 2012).

Mutation/Polymorphism Analysis Chips

Researchers have used these microchips to detect mutations in a single gene or single nucleotide polymorphism (SNPs).

Table 1. Types of microchips

Types of microarray	***Applications***
Microchips CGH *(comparative genomic hybridization arrays)*	tumor classification risk evaluation predicting prognosis
Expression microarrays gene *(microchips for the detection of changes in the level of gene expression)*	the development of new drugs assessment of response to medication the development of drug therapy
Analysis microchips a mutations/SNPs *(microchips for analysis of mutations or polymorphisms)*	the development of new drugs assessment of response to medication the development of drug therapy following the evolution of diseases

(data processed after Heller et al., 2002; Jenkins et al., 2002; Huang et al., 2015)

The structure of a microarray

A microarray chip consists of a small solid support onto which probes containing DNA sequences of hundreds or thousands of different genes are fixed at well-defined positions. The support usually consists of microscope slides (glass) of a standard size or can be made of silicon or polymeric membranes (nylon). DNA probes are printed in the form of spots or synthesized directly onto the support. It is crucial that the DNA probes are fixed to the support in a well-defined order, because gene identification is based on their localization in the microarray (Figure 2).

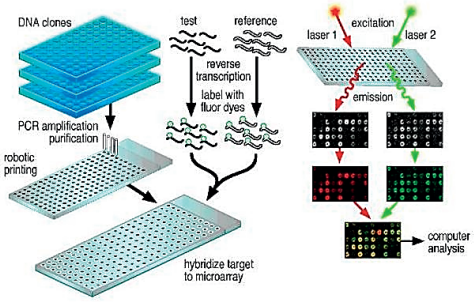

Figure 2. Structure of microarray
(www.euroimmun.com)

Microarrays are miniature tests of gene fragments that are attached to glass slides. Presenting thousands of gene fragments in a single test allows the detection of gene expression changes in a significant fraction of the total genome. Linear arrays of molecules are immobilized at discrete locations on an inert surface, which allows simultaneous analysis. Microarray technology is commonly used because it is easy to implement and well controlled. A microarray is a stamp-sized glass slide that contains thousands or hundreds of thousands of spots. Each spot contains a synthetic DNA strand with a known sequence. A microarray consists of a portion (partial) of specific genes, created by placing a known DNA sequence (Nies et al., 2024).

The basic principle of the microarray technique

The basic principle of microarray technology is similar to the Southern blot (DNA-DNA hybridization) and Northern blot (RNA-DNA hybridization) techniques. It relies on the complementarity of gene sequences to recognize each other and detect the presence or absence of the DNA or RNA of interest using a series of radiological, fluorogenic, or chemiluminescent detectors (Figure 3).

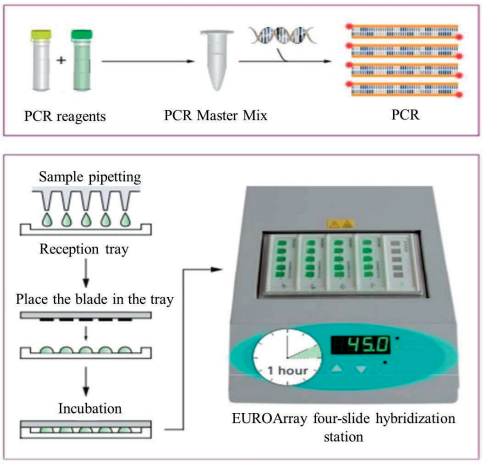

Figure 3. Microarray analyzer - EUROArrayScanner
(https://microbenotes.com)

The operating principle is based on the ability of mRNA molecules to hybridize with the corresponding DNA matrix molecules. Using a microchip containing multiple DNA probes, the expression levels of hundreds or even thousands of genes in a cell can be determined in a single experiment by measuring the amount of mRNA bound to each probe on the microchip. The resulting data on the quantity of DNA bound at each spot and the gene expression profile of the cell are displayed on a computer (Figure 4).

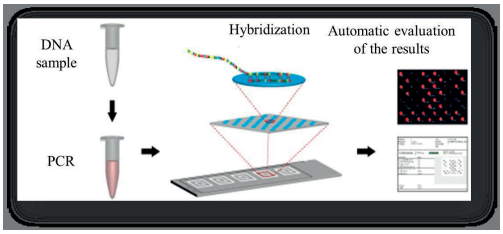

Figure 4. The operating principle of the microarray technique (https://microbenotes.com)

The first step involves isolating DNA from the blood. The DNA sequences of interest were amplified millions of times by PCR. Primers define the region to be copied, and if the DNA contains the respective sequence, the primers bind to it and amplification occurs. The samples obtained by PCR were fluorescently labelled and incubated (Pena et al., 2014).

Gene expression study - DNA analysis through the microarray technique

After hybridization, the microarray was placed in a special scanner composed of several lasers, specialized microscope, and camera. The fluorescent spots were excited by laser beams, and the microscope and camera created a digital image of the microarray. The data were stored and analysed using a computer equipped with specialized software to calculate the red/green fluorescence ratio and to analyse the intensity of each spot on the digital image of the microchip (Bao et al., 2012).

Microarray experimental setup

The hybridization step was performed with two cDNA probes for comparison (samples from diseased tissue/healthy tissue; treated cells/untreated cells) labelled with two different fluorophores (Slonim et al., 2009).

Fluorescent markers: Cy3 with an emission wavelength of 570 nm (corresponding to the green light spectrum) and Cy5 with an emission wavelength of 670 nm (corresponding to the red light spectrum) (Rajagopal et al., 2020).

The two types of probes, Cy-labeled cDNA, were mixed and hybridized on the same microarray chip, which was scanned to analyse the fluorescence signal intensity of the two fluorophores.

The relative intensities of the fluorescent signals of the two markers were analyzed as a ratio to identify genes with upregulated or downregulated expression (Figure 5).

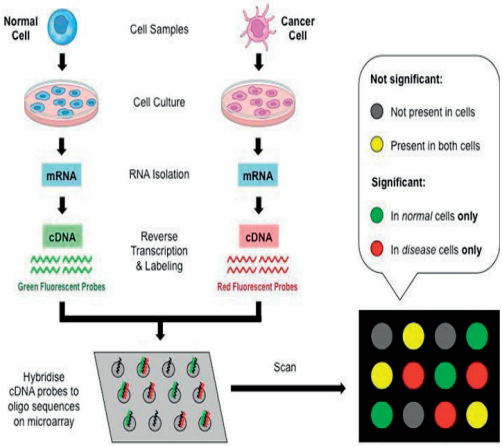

Figure 5. Experimental protocol for DNA analysis by the technique microarray (https://microbenotes.com)

Affymetrix is one of the first companies to produce microarrays, developing technology and synthesis based on combinatorial chemistry. These methods have been applied to construct high-density matrices of oligonucleotides on glass or silicon substrates (microchips) (Dufva et al., 2009).

Interpretation of the results obtained through the microarray technique

Each spot on the microchip represents a specific gene; each color represents the DNA extracted from healthy tissue (control) or the DNA sample extracted from the tissue under investigation (sample). Depending on the type of chip used, the location and intensity of each color specify the expression level (presence/absence) of a gene (or its mutation) in the DNA samples (Figure 6).

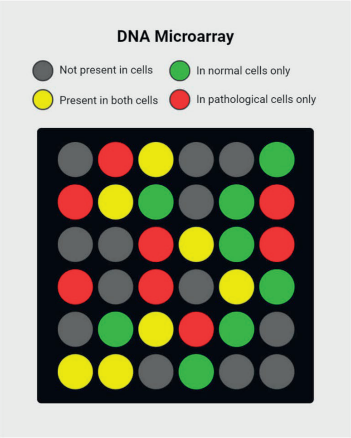

Figure 6. DNA microarray interpretation (https://microbenotes.com)

Although still in its infancy, microchip technology represents a significant first step in the field of genetics. This new technology enables scanning of the entire genome for relevant polymorphisms using gene microchips. Multiple thousands of polymorphisms can be determined simultaneously for a single subject. Currently, SNPs are selected as markers distributed throughout the genome, with the hope that functionally important polymorphisms can be associated with specific markers due to their proximity on the chromosome (Fan et al., 2010).

Such whole-genome association studies are already being used to detect susceptibility genes in a disease. Whole-genome scanning can be used similarly to determine genes involved in drug response, even when the mechanism of action of that drug is not known.

There are several advantages of microarray technology: microarrays allow for the simultaneous analysis of mRNA expression from several thousand genes; microchips can also be used to determine the gene expression pattern in a target tissue, contributing to demonstrating the mechanisms of action of a pharmacological agent in a genomic context; they can track interindividual differences in drug response in different tissues; up to 30,000 genes can be analysed at the same time; they can indicate quantitative changes in mRNA related to gene expression: during the cell cycle, during organism development from embryo to adult, after exposure to various stimuli, in pathological conditions versus normal conditions; they provide information about the functioning of a system as a whole, etc (Shinde et al., 2023; Shukla et al., 2020a; Shukla et al., 2020b).

CONCLUSIONS

Currently, microarrays are considered powerful tools in the field of genetics. This new technology allows for disease diagnosis and a better understanding of how gene expression is altered under different conditions. Furthermore, it enables the comparison of control tissue with tissue treated with a particular drug to study the effects of a potential medical treatment. To do this, the normal state and the diseased state are compared before and after administration of the medication.

The microarray technique holds significant importance in the field of animal genetics for several reasons:

Genetic Variation Analysis: Microarrays allow researchers to analyse genetic variations within animal populations. By studying thousands of genetic markers simultaneously, microarrays facilitate the identification of genetic variants associated with desirable traits, such as disease resistance, productivity, or adaptation to specific environments.

Gene Expression Profiling: Microarrays enable the comprehensive study of gene expression patterns in animals. By examining the expression levels of thousands of genes simultaneously, researchers can gain insights into the molecular mechanisms underlying various biological processes, such as development, immune response, metabolism, and behavior.

Disease Diagnosis and Biomarker Discovery: Microarrays are valuable tools for diagnosing genetic diseases in animals and identifying potential biomarkers for disease detection and monitoring. By comparing gene expression profiles between healthy and diseased animals, researchers can identify molecular signatures associated with specific diseases, leading to the development of diagnostic tests and targeted therapies.

Breeding and Selection Programs: Microarrays can aid in animal breeding and selection programs by facilitating the identification of

genetic markers linked to economically important traits, such as milk production in dairy cattle, meat quality in livestock, or disease resistance in poultry. This information can be used to inform breeding decisions and accelerate genetic improvement efforts.

Pharmacogenomics and Toxicogenomics: Microarrays play a crucial role in pharmacogenomic and toxicogenomic studies in animals. By analysing gene expression changes in response to drugs or environmental toxins, researchers can elucidate drug mechanisms of action, predict drug responses, and assess the safety of pharmaceuticals and chemicals in animals (Davidescu et al., 2020; Davidescu et al., 2021; Davidescu et al., 2022).

Overall, the microarray technique is a powerful tool for advancing our understanding of animal genetics, improving animal health and welfare, and enhancing breeding and selection programs in livestock, poultry, aquaculture, and companion animals.

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