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STRUCTURAL CHROMOSOMAL REARRANGEMENTS AND THEIR IMPLICATIONS IN DEVELOPMENTAL AND GENETIC DISORDERS

Eswari V[1], Ravindran K.R.R[2], Chamundeeswari D[3], Shanmuga Priyan[4], Saravana Kumar S[5]

[1]Professor & HOD, Pathology, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram, Tamil Nadu 631552. eswariv@maher.ac.in
[2]Assistant Professor, Pathology, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram, Tamil Nadu 631552. ravindrankrr@maher.ac.in
[3]Professor cum Principal, Pharmacognosy, Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research. chamundeeswarid@maher.ac.in
[4]Professor, Pharmacology, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram, Tamil Nadu 631552. priyan@maher.ac.in
[5]Associate Professor, Anatomy, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram, Tamil Nadu 631552. sskumar@maher.ac.in

ABSTRACT

Background: The structural rearrangements of chromosomes such as translocations, inversion, deletions, and duplications are major causes of developmental and genetic disorders. These changes may cause disruptions of the gene activity, chromosomal arrangement and control systems with a broad spectrum of clinical phenotypes.

Objective: This paper will compare the clinical and detection sensitivity of structural chromosomal rearrangements with both traditional cytogenetic and newer molecular technology.

Methodology: G-banding, fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH) and next-generation sequencing (NGS) were used to analyze 180 samples (clinical and research). Methodologies were compared in terms of the detection rates and rearrangement types.

Findings: G-banding was found to detect structural abnormalities in 46% of cases, giving way to better rates of 58 and 71 with FISH and aCGH respectively. NGS showed the best detection rate at 84% with detection of rearrangements (both balanced and complex) and microdeletions and cryptic translocations that could not be detected using conventional methods.

Conclusion: The new sophisticated genomic methods are very useful in identifying and characterizing structural chromosomal rearrangements. The combination of various methods enhances the accuracy of the diagnosis and offers more explanations on the molecular mechanisms of developmental and genetic disease.

KEYWORDS: Structural chromosomal rearrangements, Translocations, Inversions, Deletions, Duplications, NGS, aCGH, Cytogenetics, Genetic disorders

1 INTRODUCTION

Genomic changes, which include a change in chromosome architecture without necessarily an increase or decrease in the total DNA content, are known as structural chromosomal rearrangements. These rearrangements are translocations, inversions, deletions, and duplications which are critical in the pathogenesis of developmental disorders, anomalies at birth and infertility as well as other genetic syndromes. These changes may disturb the genes activity, can modify regulatory factors or may form new gene fusions thus causing abnormal phenotypic phenomena [1,2]. Structural rearrangements have become more and more important in terms of clinical significance especially in cancer genomics and neurodevelopmental disorders.

Cytogenetic methods like G-banding karyotyping have traditionally been used to identify chromosomal rearrangements. Although these techniques offer a genome-wide view, they have a limitation of low resolution, which is generally used to identify abnormalities larger than 5-10 Mb. Therefore, smaller/cryptic rearrangements tend to be unnoticed thus resulting in underdiagnosis of a clinically significant genomic alteration [3]. Fluorescence in situ hybridization (FISH) led to better detection because it allowed some specific locations of the chromosomes to be analyzed, but this is limited to pre-defined loci and does not permit a comprehensive screening of the entire genome [4].

Detection and characterization of structural variations have been greatly improved with the introduction of molecular cytogenetic technologies. Single nucleotide polymorphism (SNP) arrays like array comparative genomic hybridization (aCGH) allow to study copy number variations in high-resolution once throughout the genome, which are often linked to developmental and genetic diseases [5,6]. Nonetheless, with these methods, it is difficult to identify balanced rearrangements, like inversions and reciprocal translocations, which entail no gain or loss of genetic material.

Next-generation sequencing (NGS) technologies have transformed genomic analysis, particularly to the base-pair level, in more recent times. The NGS based methods enable detection of a broad range of structural variants including balanced and complex rearrangements which are typically overlooked by traditional methods [7,8]. Also, new technologies like the long-read sequencing and optical genome mapping have further enhanced the skills to solve cohesive genomic areas and advertisement sequences and present fresh information about chromosomal association [9].

The above optimistic developments notwithstanding, the modern genomic technologies have some obstacles to clinical application. The cost, computational needs, and the challenge of explaining variants of uncertain significance (VUS) remain barriers to widespread use. Moreover, ethical aspects involved in incidental findings and the privacy of genomic data should be taken into careful consideration [10].

Overall, structural chromosomal rearrangements play a major role in a diverse spectrum of genetic and developmental disorders. Even though conventional cytogenetic techniques are still useful, kinematic technologies currently give the best resolution and diagnostic potential. This paper will discuss the identification, characterization, and clinical consequences of structural chromosomal rearrangements by combining an integrated cytogenetic and molecular method.

2 LITERATURE REVIEW

New research shows that there has been massive improvement in the detection and interpretation of structural chromosome rearrangements majorly because of the improve on genomic technologies. The most recent advancements in the field remain next-generation sequencing (NGS), and with enhanced algorithms, more balanced and complex structural variants are identified, such as cryptic translocations and inversions that could not be identified at all previously [11]. Also, long-read sequencing technologies have been brought to the forefront because of their proficiency of covering repetitive genomic areas and recombining complicated rearrangements with superior accuracy over short-read systems [12].

OGM has come in as a supplementary method with high throughput of detecting large structural variations at better sensitivity and accuracy. According to the recent studies, OGM has been shown to detect clinically informative rearrangements, previously unnoticed by both conventional cytogenetics and sequencing, especially in cancer genomics, and in the diagnostics of rare diseases [13]. Moreover, array-based technology like aCGH and SNP array is still useful in identifying a copy number change, but there are still limits when identifying a balanced rearrangement with the technology [14].

The artificial intelligence (AI) and machine learning integration has been an important boost in the interpretation of genomic information. Tools based on AI are becoming more popular to identify structural variants in type, predict pathogenicity, and eliminate the workload of variants of unclear value (VUS) in clinical diagnostics [15]. In addition, improving analytical capability of the functional implications of structural rearrangements Multi-omics analyses integrating genomic, transcriptomic, and epigenomic are increasingly offering more information [16].

Regardless of these developments, standardizing of analytical pipelines and clinical applicability across a wide population are still challenges. The recent literature indicates that there is a requirement to have integrated diagnostic frameworks, which involve bringing together various technologies in order to enhance accuracy and clinical outcomes [17].

3 MATERIALS & METHODS

3.1 Sample Collection

In this study 180 samples were analyzed, 140 of clinical and 40 of research samples. The samples were provided both as clinical samples and as table 1, without any indication of the clinical presentations of patients that came with developmental disorders, congenital anomalies, and suspected genetic syndromes. These were peripheral blood, amniotic fluid, as well as tissue biopsy. Samples were based on known cell lines and curated genomics datasets to test the accuracy of detection and reproducibility. Each and every procedure was done in line with ethical standards and approved institutional guidelines, informed consent was obtained by all the participants [18].

Table 1: Distribution of Samples

Sample Type	Number of Samples	Source
Developmental disorders	60	Peripheral blood
Congenital anomalies	50	Amniotic fluid/tissue
Genetic syndromes	30	Blood/biopsy
Research samples	40	Cell lines/datasets
Total	180	—

3.2 Experimental Workflow

There was a standardized multi-step pipeline of workflow in the experiment. First, samples were prepared and cell culture in some cases was prepared to do cytogenetic analysis as depicted in figure 1. Validated commercial kits were used to perform DNA extraction to guarantee quality-genomic material. The different techniques adopted varied in cytogenetic and molecular processing, which included metaphase chromosome preparation in G-banding, probe hybridization in FISH, DNA labeling in aCGH, and library preparation in NGS.

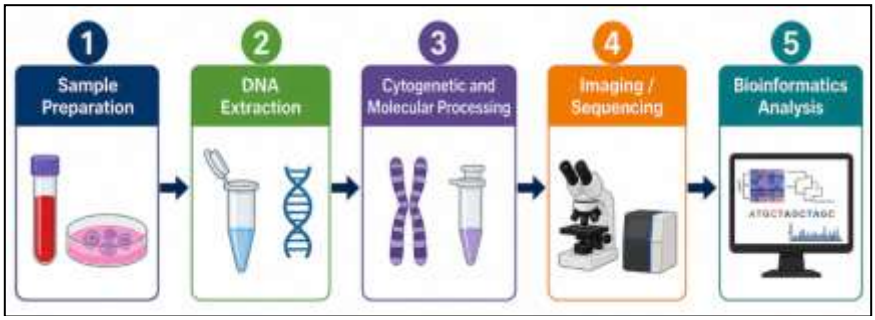

Fig.1.Experimental workflow

The imaging (G-banding and FISH) was then done with a fluorescent microscope and sequencing (NGS) involved high-throughput systems. The Bioinformatics analysis involved the use of specific software to Align, Call variants and structurally annotate variants. At every point, quality control was carried out in order to see data accuracy and reproducibility [19].

3.3 Techniques Use

The structural chromosomal rearrangements were identified with the help of four complementary techniques:

a. G-Banding: Large rearrangements of the chromosomes including translocations and inversions could be visualized and the resolution was about 5-10 Mb.

b. Fluorescence in Situ Hybridization (FISH): Fluorescent references to reveal certain regions of the genome, enabling specific identification of reorganization.

c. Array Comparative Genomic Hybridization (aCGH): Offered genome-wide calls on copy number changes i.e. deletions and duplications.

d. Next-Generation Sequencing (NGS): It provides high quality determination of structural changes, such as balanced and complex rearrangements.

Table 2: Summary of Techniques

Technique	Resolution	Detectable Variants	Key Advantage
G-Banding	Low (5–10 Mb)	Large rearrangements	Whole chromosome overview
FISH	Moderate (~100 kb)	Targeted rearrangements	High specificity
aCGH	High (~50 kb)	CNVs (deletions/duplications)	Genome-wide screening
NGS	Very high (<10 kb)	All structural variants	Comprehensive detection

All in all, cytogenetic and molecular techniques allowed detecting and validating all structural chromosomal rearrangements depicted in table 2. A hybrid nature of several methods enhanced the capability in diagnosing and reduced the outcomes of false-negative, especially in complex genomic changes [20,21].

4 RESULTS

The findings reveal a relative comparison of cytogenetic and molecular methods in the identification of structural rearrangement of the chromosomes. Comparison of 180 samples showed a great fluctuation in the empirical detectabilities of the techniques. High-tech genomic methods were found to be sensitive and resolutory than traditional methods. The results of the study show that the combination of several diagnostic instruments is essential to both locate balanced and unbalanced rearrangements. On the whole, it can be stated that the findings highlight the high quality of next-generation sequencing (NGS) when it comes to the detection of intricate and submicroscopic chromosomal defects [22].

4.1 Detection Rates of Structural Rearrangements

Table 3: Detection Efficiency

Method	Samples Tested	Rearrangements Detected	Detection Rate (%)
G-Banding	180	82	46%
FISH	180	104	58%
aCGH	180	128	71%
NGS	180	152	84%

There was steadily growing efficiency in detection between the old-fashioned and modern systems. The lowest detection was with G-banding (46%) as it failed to detect submicroscopic rearrangements. FISH enhanced detection (58%), by targeting

individual genomic scenes whereas aCGH supported sensitivity (71됨) using a genome-wide analysis of CNVs as in table 3. The highest detection rate (84%) was observed with NGS, which was able to identify both balanced and unbalanced rearrangements, with cryptic structural variants. These results are consistent with recent literature pointing towards improved diagnostic output of sequencing-based methods [11].

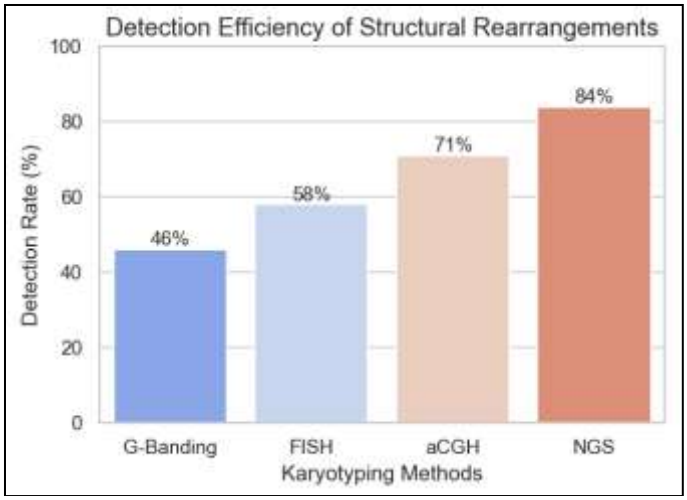

Fig.2. Detection efficiency of structural rearrangements

The efficiency of various methods to detect structural chromosomal rearrangements is represented in the figure 2. G-banding has the lowest detection rate of 46% as it can only detect large abnormalities. By analyzing the target, FISH increases the detection to 58%. aCGH also can maximize sensitivity to 71% through detecting genome-wide copy number changes. NGS shows a high efficiency of 84 percent, and its high resolution and capability to identify both complex and subtle structural changes across the genome highlight this advantage.

4.2 Types of Structural Rearrangements

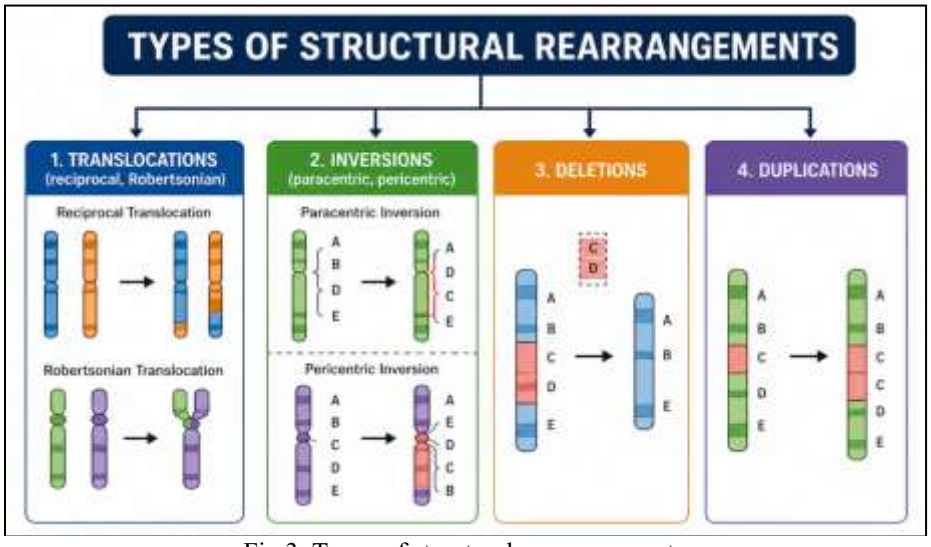

Fig.3. Types of structural rearrangements

The paper has found that there are several forms of structural rearrangements such as translocations, inversions, deletions and duplications as depicted in figure 3. Both clinical and research samples exhibited a large amount of translocations (reciprocal and Robertsonian). Inversions (paracentric and pericentric) were linked to changes in the gene expression, deletions and duplications were linked to the loss of genes, or an imbalanced dose of genes. Balanced rearrangements were typically characterised by minor phenotypic consequences yet being reproductively dangerous and unbalanced rearrangements closely related to developing and genetic diseases.

4.3 Clinical Impact of Rearrangements

Table 4: Clinical Associations

Rearrangement Type	Common Disorders	Clinical Impact
Translocations	Leukemia, infertility	Gene disruption
Inversions	Developmental delay	Altered gene expression
Deletions	DiGeorge syndrome	Loss of gene function
Duplications	Autism spectrum disorders	Gene dosage imbalance

Rearanging of the structures recorded significant correlations of certain clinical conditions highlighted in table 4. Translocations were most often related to cancers and infertility because of broken genes. The gene regulation was impacted by inversions which led to developmental delays. Removals lead to the loss of important genomic contigs and duplication lead to gene dose effects. The results obtained indicate the clinical significance of proper identification of structural abnormalities to make a diagnosis and plan treatment [23].

4.4 Case Study Analysis

Case studies also demonstrate how various techniques can be used to complement each other. Case 1 had a large deletion detected by G-banding, but with NGS, they found other smaller deletions, which is more sensitive. In Case 2 the rearranged sequence was found to be balanced as demonstrated by FISH, whereas aCGH did not. These illustrations underscore the importance of integrating both the use of cytogenetic as well as the use of molecular procedures in order to get complete and proper diagnosis.

4.5 DISCUSSION

This study results support the work of other researchers that structural chromosomal rearrangements can play a significant role in the existence of a broad range of developmental and genetic diseases. The traditional methods of cytogenetics, including G-banding, are useful in detecting gross chromosomal abnormalities, but have a low resolution and cannot detect submicroscopic and complex rearrangements. Contrary to this, new genomic technologies, especially next-generation sequencing (NGS), prove to be much more sensitive and resolute. NGS allows any form of detection, both balanced and unbalanced structural variants, in elaborate detail including cryptic rearrangements that are usually overlooked by both traditional and array-based technologies. These findings underscore the need to combine use of a range of diagnostic technologies to have precise and comprehensive coverage of genomes.

5. Clinical Applications

The structural chromosomal rearrangement analysis is also used in a wide clinical usage, such as:

a. Diagnosis developmental disorders: Essential production of genomic malformations that call on intellectual disability and congenital anomaly.
b. Cancer cytogenetics: The identification of chromosomal rearrangements of tumorigenesis and therapeutic targets.
c. Prenatal genetic screening: Earlier detection of abnormalities in the chromosomes to educate clinical decision-making.
d. Infertility testing: Identification of balanced rearrangements, which could be involved in infertility.

6. Future Perspectives

Further progress in this area is likely to achieve higher levels of diagnostics:

a. An appendix of artificial intelligence (AI) to enhance structural variant detection and interpretation.
b. Development of long-read sequencing studies to solve genomic regions of complexity.
c. Application of real-time clinical genomic diagnosis into clinical processes.
d. Better availability and affordability of genomic technologies.

7. CONCLUSION

The rearrangement of chromosomes on a structural level is a critical determinant of the pathogenesis of developmental and genetic disorders since it affects the functions of genes along with their regulatory and genomic stability. The research paper has brought out the drawbacks of traditional cytogenetic methods and highlighted the benefits of the more advanced methods involving molecules and sequencing. The new technologies like NGS offer better resolutions and the ability to detect simple

and complex structural changes which identify lesions at a high diagnostic accuracy. A combination of several complementary technologies will provide a complete system of detecting chromosomal abnormalities. With the ongoing advancements in genomic technologies, they will become more accessible and powerful in analysis, which will promote better clinical diagnostics, early disease detection, and the development of precision medicine and genetic research.

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