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COMMENT

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Cytogenetics in the genomics era: why karyotyping still matters

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Abstract
Despite advances in next-generation sequencing and optical genome mapping, conventional cytogenetics, particularly karyotyping, remain indispensable in modern medical genomics. It continues to provide critical diagnostic value in constitutional and hematological disorders, offering cost-effective detection of chromosomal abnormalities and complementing molecular tools, especially in complex cases and resource-limited settings.

Keywords Karyotype, Cytogenetics, Chromosomes, Genomics, Cytogenomics, OGM, NGS

Introduction

The advent of next-generation sequencing (NGS) and optical genome mapping (OGM) has undoubtedly revolutionized medical genomics, prompting debate over whether conventional cytogenetics (standard chromosome analysis), especially karyotyping, still has a place in modern genomics. However, karyotyping continues to hold critical value in the setting of both constitutional and hematological genetics. Indeed, rather than being replaced, karyotyping continues to serve as an essential complement to modern genomic technologies, particularly in certain clinical situations and in resource-limited settings.

Why karyotyping still matters

Karyotyping remains the gold standard for detecting large-scale numerical and structural chromosome abnormalities, such as aneuploidies, balanced translocations, Robertsonian translocations and low-level mosaicism [1]. For example, Robertsonian translocations or centromeric fusions may not be reliably detected using short-read sequencing or even chromosomal microarrays (CMA). Moreover, karyotyping directly visualizes metaphase chromosomes and provides an intuitive assessment of ploidy and structural architecture. Therefore, karyotyping remains a basic and routinely used tool in medical genetics, but it can only reveal large-scale chromosomal changes (> 5–10 Mb) and lacks the finer resolution of molecular or genomic methods [2].

In constitutional genetics, a 20-year review by the American College of Medical Genetics (ACMG) found that karyotyping remained routinely employed and cost-effective for constitutional abnormalities. The authors stated that conventional karyotyping is frequently used in the diagnostic investigation of a wide range of constitutional genetic disorders, including testing patients referred for intellectual disability, congenital anomalies, pregnancy loss or concern for aneuploidy [2]. Despite the use of OGM, karyotyping remains an essential tool in medical genetics laboratories.

In hematological malignancies, OGM is increasingly being evaluated and optimized for clinical use; however, several limitations currently prevent it from fully replacing conventional karyotyping [3]. For example, in a cohort of acute myeloid leukemia (AML) patients, OGM

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captured cryptic, and additional, anomalies missed by conventional karyotyping. The authors stated that OGM has the potential to be the standard-of-care methodology for cytogenomic evaluation of patients with AML, however they emphasized that karyotyping retains utility especially where OGM fails. Among the limitations of OGM that has been documented [4] :

- **Requirement for high-molecular-weight DNA:** OGM requires intact, ultra-high-molecular-weight DNA obtained using special extraction kits, limiting its applicability to fresh or frozen samples and precluding analysis of archival DNA or formalin-fixed paraffin-embedded (FFPE) (the latter is also a limitation of karyotyping).
- **Restricted detection in repetitive regions:** Structural variants located exclusively within centromeric or telomeric regions may not be reliably detected by OGM.
- **Limited sensitivity for low-frequency variants:** At standard coverage levels (~ 300x), OGM may miss variants present at ≤ 5% allele fraction; higher routine coverage (> 1000×) is expected to mitigate this limitation.
- **Low throughput**: The current instrument throughput remains limited, posing challenges for adoption in high-volume clinical laboratories.
- It is worth noting that OGM is a **non-sequencing assay**, so it cannot identify point mutations or small indels (which also applies to karyotyping).
- In addition to all the above, **cost-effectiveness** is an important factor. High cost of instrumentation and consumables currently limit the widespread adoption of OGM, particularly in low- and middle-income countries.

Collectively, these findings highlight the continued importance of conventional karyotyping within the broader cytogenomic diagnostic framework. Despite recent advances in high-resolution molecular techniques, karyotyping remains a fundamental tool for comprehensive genome assessment.

Contexts where karyotyping remains indispensable

1. **Balanced rearrangements and Robertsonian translocations:** Karyotyping can identify centromeric fusions which probably will be missed by CMA, OGM or NGS.
2. **Low-level mosaicism** (< 5% clone): Cultured metaphases allow detection of mosaic clones that may fall below the detection threshold of certain molecular assays.
3. **Centromeric/pericentromeric rearrangements or marker chromosomes:** Regions poorly covered by microarray or short-read NGS benefit from metaphase visualization. Indeed, karyotyping allows the detection of centromeric fusions/anomalies, some telomeric fusions/anomalies, and the presence of marker chromosomes.
4. **Low-resource settings and cost-effectiveness:** In many settings, especially in low- and middle-income countries, karyotyping remains affordable, rapid and feasible even when NGS/OGM are unavailable. Its continued availability can ensure diagnostic equity.

It is also important to note that several experts emphasize the need for complementary verification of OGM or CMA findings, particularly in complex genomic rearrangements. This limitation is illustrated in some published cases reporting mosaicism, supernumerary marker chromosomes, or segmental gains, where the pure molecular approach and the absence of cytogenetic evaluation has led to misinterpretation of results.

The evolving cytogenetic frontier and the role of cytogeneticists

While karyotyping remains valuable, it should be integrated thoughtfully within modern genomic workflows rather than being entirely abandoned. New methods, including OGM and NGS, offer higher resolution and broader structural variant detection in a single assay; but remain limited by cost, sample requirements and infrastructure. In many labs, a tiered approach has emerged: starting with karyotype (and/or FISH/CMA) in relevant cases, followed by NGS/OGM if negative or for complex rearrangements.

Importantly, training in cytogenetics remains critical. Although some have claimed that "cytogenetics is dying" [5, 6], many laboratories continue to rely on it as a foundational and complementary tool alongside molecular techniques. In this context, it has been observed that enthusiasm for innovative technologies may lead to the premature assumption that they can substitute several already-established and less-costly tools. However, practical experience often reveals that these new methods may not fully meet initial expectations and sometimes require greater resources and expertise, contributing over time to a decline in the maintenance of essential skills in conventional cytogenetics.

Despite the acknowledged importance of karyotyping, an emerging global problem is arising. Across many countries, it has been reported that there is a need for cytogeneticists; and at the same time some universities have stopped educating cytogeneticists [7]. Recent studies showed that artificial intelligence (AI) tools like ChatGPT, a Large Language Model (LLM), still make frequent

errors in reporting and analyzing complex cytogenetic cases, emphasizing the need for expert interpretation [8]. Also, it was reported that while AI and automation can ameliorate the outcomes of cancer cytogenetics, karyotyping and skilled cytogeneticist are still needed in the era of genomics [9]. Together, these findings highlight that karyotyping remains a cornerstone of genomic diagnostics, especially in the context of complex cases or limited resources. The expertise of trained cytogeneticists remains essential for accurate interpretation and clinical correlation.

Conclusion and call to action

In conclusion, karyotyping is not obsolete; it continues to hold an important place in genetic diagnostics, offering cost-effective and complementary information in both constitutional and hematological settings. Rather than relying on a single molecular approach (one-size-fits-all), laboratories and clinicians are encouraged to adopt a cytogenomic strategy that integrates karyotyping, FISH/array, NGS, and OGM in a complementary and context-specific manner. In low-resource settings, investment in cytogenetics infrastructure still provides a sustainable and cost-effective diagnostic solution. Finally, ongoing training is essential to maintain cytogenetic expertise, and diagnostic guidelines should explicitly define the context where karyotyping is still critical.

Abbreviations

CMA	Chromosomal microarray
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescent in situ hybridization
NGS	Next Generation Sequencing
OGM	Optical genome mapping

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