

Genomic proximity mapping: a promising next-generation cytogenomic assay for comprehensive assessment of acute myeloid leukemia

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Genetic abnormalities from cytogenetics and molecular profiling form the core of the 2022 European LeukemiaNet (ELN) risk stratification guidelines for adult acute myeloid leukemia (AML).¹ The current standard-of-care techniques for assessment of cytogenomic aberrations include chromosome banding analysis, fluorescence *in situ* hybridization (FISH) and chromosomal microarrays or array comparative genomic hybridization. As each technique differs with respect to resolution and limitation, they are typically considered complementary to each other and performed in combinations to maximize detection sensitivity and capacity of all clinically relevant abnormalities.

High-throughput genome-wide technologies have evolved rapidly in recent years. Optical genome mapping (OGM) represents an emerging cytogenomic technique that has been successfully applied for systematic evaluation of AML in clinical laboratories.²⁻⁴ In contrast, Genomic Proximity Mapping™ (GPM) is one of relatively newer transformative tools for cytogenomic diagnostics and is a short-read sequencing based platform that utilizes high-throughput chromosome conformation capture (Hi-C) technology by retaining three-dimensional chromosomal structure conformation within genomic loci and permitting analysis of genome-wide chromatin interactions in the cell nucleus.⁵ In this issue of *Haematologica*, Yeung and colleagues evaluate the clinical utility of GPM in identification of genomic aberrations using 48 archival cryopreserved specimens that had undergone conventional cytogenetic assessment at diagnosis.⁶ The aim of this study was to evaluate the extent to which GPM enhances cytogenetic analysis compared to standard-of-care cytogenetic methods in AML assessment.

Yeung and colleagues first evaluated GPM performance at the detection of cytogenetic risk variants specified by the ELN 2022 risk stratification scheme. In the categories classified as either favorable or adverse, GPM showed 100%

concordance with the standard-of-care cytogenetic methods, including translocations such as t(6;9)(p22.3;q34.1)/*DEK::NUP214*, inversions such as inv(3)(q21.3q26.1), and aneuploidies (monosomy 7). When considering variants in the intermediate risk category for cytogenetic and/or molecular abnormalities not classified as favorable or adverse, there was a lower concordance rate of 77.8% between GPM and conventional cytogenetics, with major discordant calls in aneuploidies, followed by copy number variants.

Besides the ELN-specified risk categories, GPM identified additional chromosomal rearrangements that were clinically significant variants but were not detected by conventional cytogenetics. Such examples included t(11;12)(p15.4;p13.33)/*NUP98::KDM5A*, inv(3)(p24.3q26.2) with associated *MECOM* rearrangement and *EV11* over-expression,⁷ and t(6;7)(p23;q36.3) resulting in deletion of the *JARID2* gene, a known tumor suppressor in myeloid neoplasms. Furthermore, a complex karyotype was detected in this study that showed six inter-chromosomal breakpoints, -7 and dup(21)(q22.12q22.12), features compatible with chromoanagenesis described in the OGM study of AML case series.⁴ In these cases, the identification of clinically important variants has a clinical impact on AML classification, risk stratification, and/or clinical trial eligibility.

In addition, GPM allows a more thorough description of small insertions and inversions with improved resolution compared to conventional cytogenetics. Novel inversions such as inv(12)(p13.32p13.2) and inv(9)(p13.3p13.1) have not been previously reported. Both variants are featured by paracentric inversion involving a submicroscopic interval of the genome. inv(9)(p13) has been previously detected only through a targeted re-sequencing effort of this pericentromeric region in adult cases of lymphoblastic leukemia.⁸ Of the other classes of structural variants, GPM was able to detect numerous aneuploidies and smaller deletions

and duplications of unknown significance that were not previously identified by routine cytogenetic analysis. Unsurprisingly, most additional variants called by GPM involve copy number alterations below the level of cytogenetic resolution (<5 Mb). Yeung and colleagues took extra effort by performing orthogonal testing with whole-genome sequencing to validate GPM or cytogenetic findings. Fourteen GPM calls were confirmed, whereas only four cytogenetic calls were confirmed over their respective counterparts. These observations corroborated increased detection capability of GPM, compared to traditional methods, for a variety of structural variants or copy number alterations. GPM offers several technological advantages. First, it overcomes the limitation of short-read sequencing by capturing ultra-long-range sequence information at a relatively low sequencing depth. Second, unlike FISH or targeted RNA sequencing, GPM is not restricted to specific targets, increasing the likelihood of identifying cryptic rearrangements and novel genomic aberrations that are often missed by conventional cytogenetics. Thirdly, GPM allows detection of copy number alterations below the level of cytogenetic resolution by overcoming the limitation of genomic location and/or size of the genomic interval in standard-of-care cytogenetics. Lastly, the Hi-C technology uses cross-linked chromatin and is applicable to a wide variety of sample types including formalin-fixed paraffin-embedded (FFPE) tissues and fixed cell pellets. The sample pass rate was robust (~97%) in this study, even under suboptimal sample conditions.

Compared to OGM, GPM showed comparable performance in the identification of every major class of genomic aberrations in a single cost-effective assay for AML (Table 1), other hematologic malignancies and constitutional disorders.^{6,9,10} In contrast, GPM differs from OGM by capturing preserved chromatin interactions, offering three-dimensional genomic architecture, and allowing linkage of structural variants with functional outcomes, whereas OGM is a bulk DNA assay and cannot assess epigenetics or chromatin structure. In addition, OGM demands intact ultra-high molecular weight DNA, and requires fresh samples or live cells, restricting its clinical applicability in FFPE tissues and hypocellular specimens.

GPM has its own analytic limitations. The limit of detection is 5-10% leukemic blasts for confident variant calls.^{6,9} lower than FISH and chromosomal microarrays, making it challenging to detect aberrations in specimens with low-level disease. GPM might struggle with detection of mosaic changes, polyploidy variants and copy-neutral loss of heterozygosity. Its resolution is dependent on sequencing depth, limiting sensitivity for small-scale variants, such as single-nucleotide variants, small inversions, or small insertions/deletions.

In summary, the study presented by Yeung and colleagues has clearly demonstrated that GPM is a promising next-generation cytogenomic platform for comprehensive

assessment of AML. GPM excels conventional cytogenetics at the detection of cryptic alterations and additional variants of known or unknown significance not specified in the ELN risk guidelines. The utility of GPM in detecting some other structural variants, such as small duplications

Table 1. Comparison of optical genome mapping and genomic proximity mapping for cytogenomic assessment of acute myeloid leukemia.

Features	OGM	GPM
Technology		
Principle	Linear mapping of ultra-long DNA molecules with sequence-specific labels	Detects physical proximity of genomic regions inside the nucleus
Labeling strategy	Fluorescent labeling at specific motifs	Ligation of spatially proximal fragments
DNA preparation	UHMW DNA	Crosslinked chromatin
Sequencing	No (imaging based)	NGS-based
Output	Lineage genome maps/Linear structural arrangement	Interaction heatmaps/3D spatial co-localization
Platform examples	Saphyr (Bionano Genomics)	CytoTerra (Phase Genomics)
Resolution	≥500 bp ~ 5 kb	>10-100 kb
Sensitivity	5-10%	5-10%
Sample		
Cell number	1-2 million	0.2-0.5 million
DNA amount	~750 ng	≥10 ng
Sample type	Viable/frozen cells	Viable/frozen/fixed cells/tissue
FFPE compatibility	No	Yes
Structural variants*		
Translocations		
Intrachromosomal	Excellent	Excellent
Interchromosomal	Excellent	Excellent
Inversions	Excellent	Excellent
CNA (indels/dups)	Excellent	Excellent
Aneuploidy		
Hypoploidy	Moderate	Moderate
Polyploidy	Poor	Poor
cnLOH	Moderate	Moderate
Chromoanagenesis	Yes	Possible
Regulatory interactions	No	Yes

*The performance of optical genome mapping and genomic proximity mapping was compared with standard-of-care cytogenetic methods, and is indicated as “excellent”, “moderate”, or “poor”, if performance excels, equals, or is inferior to the routine cytogenetic methods, respectively. OGM: optical genome mapping; GPM: genomic proximity mapping; UHMW: ultra-high molecular weight; NGS: next-generation sequencing; 3D: three-dimensional; FFPE: formalin-fixed paraffin-embedded; CNA: copy number alterations; cnLOH: copy-neutral loss of heterozygosity; indel: insertions and/or deletions; dups: duplications.

(e.g., *KMT2A* partial tandem duplications), has not yet been fully evaluated, and awaits further exploration in more case scenarios and other myeloid neoplasms.

Disclosures

No conflicts of interest to disclose.

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