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Optical genome mapping as a high-resolution tool for uncovering cytogenetic complex and cryptic alterations in a cohort of patients with MDS and AML

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Cytogenetic and molecular studies are the standard of care in the diagnosis of myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML), which are characterized by a highly heterogeneous genetic landscape. This complexity challenges accurate characterization, risk stratification, and treatment decision-making. Optical Genome Mapping (OGM) is emerging as a high-resolution technique capable of detecting cryptic structural variants (SVs) and copy number changes (CNVs). In this study, we analyzed 150 MDS and AML patients using standard diagnostic methods and complemented by OGM to assess its utility in resolving complex karyotypes and uncovering hidden genomic aberrations. The results revealed novel alterations and refined previous cytogenetic results (e.g., breakpoints, translocation partners) in 80% of cases, involving clinically relevant genes such as *MECOM*, *KMT2A*, and *NUP98*. Importantly, in complex karyotypes, undefined marker chromosomes and chromoanagenesis events were resolved by OGM, uncovering genomic aberrations with potential clinical relevance. Overall, our findings demonstrate that OGM enables a more comprehensive genomic characterization of patients, uncovering cryptic genomic alterations and resolving complex karyotypes in AML and MDS. The identified abnormalities have shown significant and potential clinical implications. Additionally, the discovery of novel alterations could offer insights into previously unknown pathogenic mechanisms, enhancing our understanding of AML and MDS pathogenesis.

Myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML) are hematologic malignancies characterized by impaired hematopoiesis and clonal expansion of hematopoietic stem and progenitor cells. While cytogenetic findings provide valuable diagnostic, prognostic, and therapeutic insights, complex karyotypes continue to be associated with poor prognosis and an increased risk of treatment failure despite recent advances in diagnosis and therapy[1–3]. Consequently, precise and individualized characterization is essential for accurate risk assessment and the development of tailored therapeutic strategies. These malignancies arise from the somatic acquisition of chromosomal abnormalities and gene mutations that disrupt

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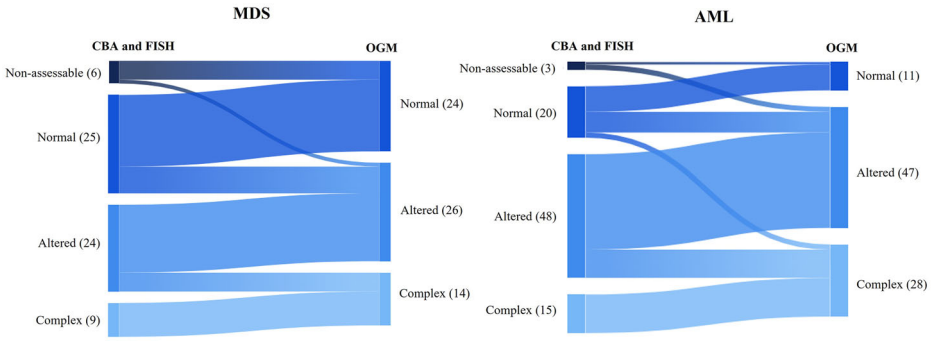


Fig. 1 | Alluvial diagram showing the reclassification of MDS and AML patients before and after the implementation of OGM analysis. Thirty-three patients were reclassified from normal to altered or complex cytogenetics, or from altered to complex cytogenetics. All non-assessable karyotypes were successfully assessable by OGM.

hematopoietic function. The wide heterogeneity of genomic alterations in AML and MDS makes diagnosis, prognosis, and treatment decisions particularly challenging.

Current diagnostic and prognostic guidelines stratify patients based on cytogenetic and molecular findings[3–6]. The most used guidelines include the World Health Organization (WHO)[7], the International Classification Consensus (ICC)[8], the International Prognostic Scoring System (IPSS)[9], and the European LeukemiaNet (ELN)[10]. As patient management increasingly relies on genomic insights, failure to detect cryptic changes or fully resolve complex karyotypes can hinder accurate classification and clinical decision-making, limiting the precision of patient management[11–14].

Standard-of-care (SOC) genetic testing techniques for the diagnosis of MDS and AML, including chromosome banding analysis (CBA), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS), present limitations in detecting cryptic or structurally complex events[4,7,15–17]. Recently, new high-resolution technologies are being implemented to enable a more comprehensive assessment of the genomic landscape, among which optical genome mapping (OGM) is a non-sequencing-based, high-resolution tool that comprehensively analyzes a broad spectrum of structural variants (SVs), including inversions, balanced or unbalanced translocations, copy number variations (CNVs), and also complex genomic events by aligning DNA molecules to a reference genome, identifying genomic alterations larger than 500 bp[18–22].

OGM technology complements karyotyping, FISH, chromosomal microarray and molecular techniques by resolving variations that remain undetected, including balanced translocations missed due to poor chromosome morphology. Unlike FISH, it provides a comprehensive whole-genome analysis, detecting even subtle gene-level changes. Considering the limitations of conventional methods, OGM serves as a single high-resolution platform capable of identifying SVs and CNVs at a resolution of up to 500 bp.

Previous studies have demonstrated the impact of OGM in uncovering cryptic abnormalities with clinical significance, refining the previous cytogenetic information in over 60% of patients[4,11]. OGM showed a high concordance (>90%) with SOC findings, but also described novel rare gene fusions, missed SVs and CNVs affecting clinically relevant regions and genes, novel abnormalities with unknown role, and elucidated genomic complexity. Novel alterations detected by OGM resulted in changes in prognostic stratification of 5–17% patients, identifying aberrations such as CNVs and characterizing clinically unclear rearrangements[11,23–25]. Moreover, OGM also showed valuable potential in the description of catastrophic chromosomal rearrangement events known as chromoanagenesis, including chromothripsis, chromoanasynthesis, and chromoplexy, typically arising in a single cellular crisis and present in complex karyotypes. Chromoanagenesis events are gaining attention due to their relevance in genome instability and adverse outcomes in diverse tumors[18,26,27].

OGM has been used to enhance cytogenetic profiling in hematological malignancies such as acute lymphoblastic leukemia (ALL)[28], AML[11], chronic lymphocytic leukemia (CLL)[29], MDS[22,24], and myelofibrosis (MF)[30]. Moreover, OGM is also being implemented in other neoplasms[31–33], identifying clinically relevant rearrangements useful for diagnosis, showing its potential as a diagnostic tool. As an example, in solid tumors, OGM clarified complex events, supporting the characterization of the underlying genomic complexity of these neoplasms[34], including lymphoma, soft tissue and bone tumors[32,35], prostate[36] or breast cancer[37].

In the present work, we analyzed the genetic landscape of a cohort of 150 MDS and AML patients using conventional techniques, including CBA, FISH, and NGS, and compared the results to OGM analysis, as detailed in Supplementary Data 1. The primary aim of this work was to evaluate whether cryptic alterations to CBA and FISH could be identified by OGM. We also focused on its potential to resolve complex karyotypes and unclear genomic events, thereby refining the cytogenetic description and classification of patients with myeloid neoplasms.

Results

Patient samples and cytogenetic profiling

Study participants included 64 MDS and 86 AML adult patients ranging from 20 to 85 years old (median age 62), with a male predominance (60%). Cytogenetic classification based on CBA, FISH, and NGS reported SVs and CNVs resulted in 45 patients with normal karyotypes, 72 with abnormal karyotypes, and 24 with complex karyotypes. Additionally, 9 patients had uninterpretable karyotypes by CBA, and FISH analysis was only not assessable in 1 patient due to lack of metaphases. NGS was successfully performed in all patients, however, complete data are unavailable because certain samples were processed and analyzed at an external hospital.

OGM analysis yielded conclusive results in all samples. Overall, OGM showed 97% concordance (137/141) with karyotype findings. Four cases presented discordant results, involving balanced whole-arm translocations or centromeric/telomeric rearrangements, or low VAF events that were identified by CBA but not by OGM. This can be attributed to the limitations of OGM in mapping and aligning molecules within telomeric and centromeric regions, which exhibit low coverage due to their highly repetitive sequences, or events with <5% VAF[20,38]. Moreover, additional findings were reported in 114 patients with assessable CBA (80%), describing cryptic events and resolving the origin of marker chromosomes. In particular, 16 patients previously described with normal karyotypes changed to altered ($n = 14$) and complex ($n = 2$) with the application of OGM, identifying novel SVs, CNVs and rearrangements. Likewise, 17 patients initially reported with altered karyotypes were reclassified as complex, identifying CNVs affecting relevant regions, translocations affecting genes such as *TP53*, and chromoanagenesis events. Finally, in the nine cases non-assessable by SOC techniques, OGM enabled their classification as normal ($n = 6$) and altered ($n = 3$), describing CNVs losses and gains affecting different regions, complex translocations, and other complex genomic events. Figure 1 shows the classification of patients before and after the application of OGM in each cytogenetic category. Additionally, novel findings described by OGM changed the risk category of 2 MDS patients, increasing their risk category from Moderate High to High and from Moderate Low to High, and 1 AML patient, changing from Intermediate to Adverse. Supplementary Data 1 summarizes the cytogenetic characteristics observed across the cohort.

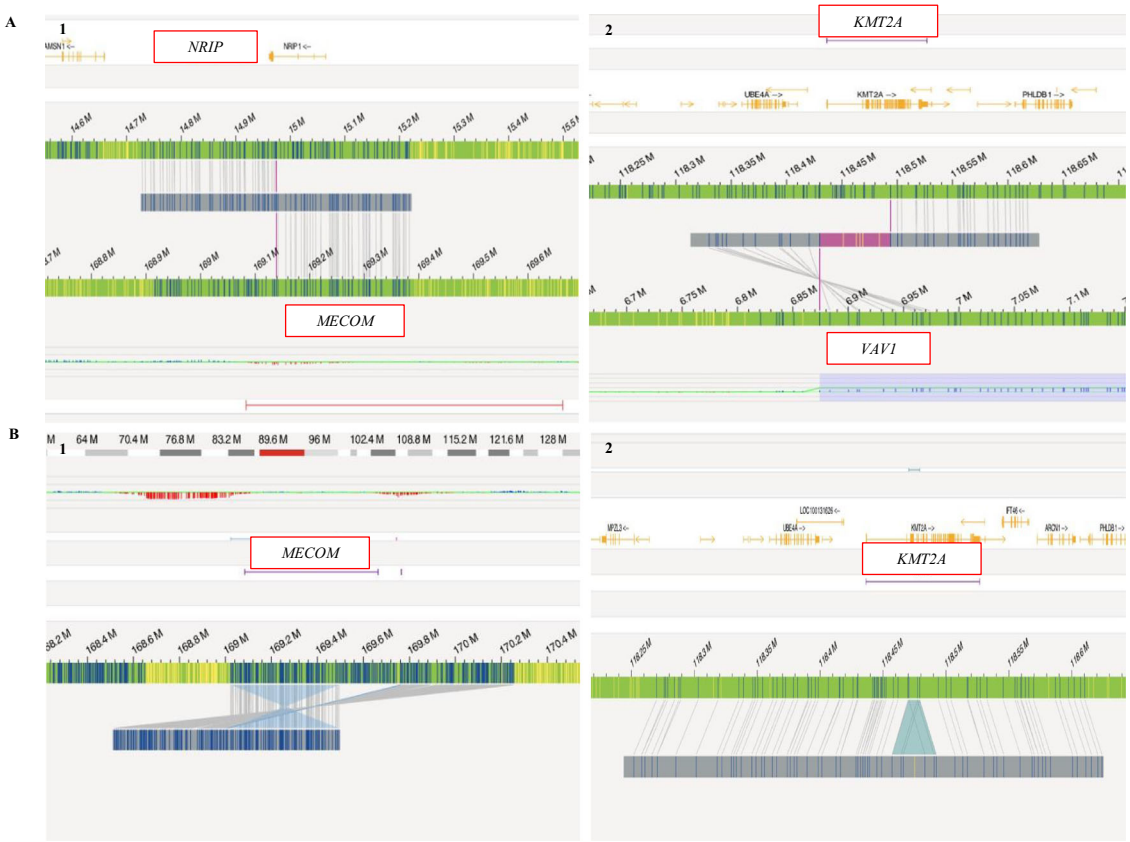


Fig. 2 | Alterations of clinically relevant genes identified by OGM. A Partner identified in rearrangements involving 1) *MECOM* [t(3;21)(q26;q11)(*MECOM*::*NRIP1*)]; and 2) *KMT2A* t(11;19)(q23.3;p13.11)(*KMT2A*::*VAV1*). **B** SVs affecting 1) *MECOM*, affected by an inversion [inv(3)(q26.2q26.2)] and described as overexpression by NGS; 2) *KMT2A*, affected by insertion, shown in blue, by OGM [ins(11;?)(q23.3;?)], and confirmed as *KMT2A*-PTD by NGS.

Identification of clinically relevant cryptic SVs and CNVs using OGM

Using the recommended filtering criteria (Bionano Genomics), we identified 4321 SVs and 1850 CNVs. From these, 960 SVs and 818 CNVs were finally reported (Supplementary Data 2), filtering the alterations using two Browser Extensible Data (BED) files, a GRCh38/hg38 file including all human genes and a leukemia-specific file (Supplementary Table 1), followed by an intensive manual revision of the identified genes. Although the majority of these variants had uncertain clinical implications, OGM revealed numerous cryptic gains, losses, and translocations involving genes with potential pathogenic relevance[12,13,18,39]. These genes have been previously reported as altered in cancer patients, affecting molecular pathways involved in pathogenesis, and potentially holding clinical significance.

Additional CNVs identified included losses affecting genes such as *KMT2A* ($n = 2$), *TET2* ($n = 2$), and *NUP98* ($n = 1$), as well as gains involving *DNMT3A* ($n = 2$), *RUNX1* ($n = 2$), *KMT2A* ($n = 1$), *MECOM* ($n = 2$) and *ASXL1* ($n = 3$). SVs not detected by CBA or FISH techniques included deletions in *TET2* ($n = 1$), *RUNX1* ($n = 4$), *CUX1* ($n = 2$), *EZH2* ($n = 1$), *ETV6* ($n = 6$), and *TP53* ($n = 1$), insertions in *NRAS* ($n = 1$), *MECOM* ($n = 1$) and *KMT2A* ($n = 2$), duplications in *KMT2A* ($n = 3$) and *NUP98* ($n = 1$), and inversions in *MECOM* ($n = 2$). In the 3 patients with SVs and CNVs affecting *MECOM* described by OGM, *MECOM* overexpression was also identified by NGS (Supplementary Data 1). The overexpression and oncogenic role of *MECOM* are frequently attributed to rearrangements that juxtapose *MECOM* with potent enhancer elements, such as those from *GATA2*, resulting in its up-regulation[40,41]. Nonetheless, non-canonical abnormalities affecting *MECOM* expression are still under study to define their biological significance. Moreover, the insertions and duplications within the *KMT2A* gene were classified as *KMT2A-PTD* and validated by NGS (Supplementary Data 1).

Regarding chromosome rearrangements, both intrachromosomal and interchromosomal translocations were identified. Clinically relevant rearrangements included t(10;13)(q21.3;q34)/*TET1*::*GRK1* and t(3;9)(q21.2;p24.3)/*ZNF148*::*SMARCA2*, described in literature in one MDS patient[42], and t(9;11)(q34.11;p15.4)/*NUP98*::*PRRX2*, confirmed by NGS. In 12 patients, OGM refined previously reported translocations by identifying their missing partner, involving *MECOM* ($n = 6$), *KMT2A* ($n = 1$), *RUNX1* ($n = 4$), *NUP98* ($n = 1$), and *TP53* ($n = 1$) (Fig. 2).

Further SVs were identified affecting genes not included in the clinical guidelines but that have been previously implicated with cancer. These included deletions of *CSF1R* ($n = 1$), *CUX1* ($n = 1$), *NF1* ($n = 4$), in *CDKN2A/B* ($n = 4$), insertions of *TCF4* ($n = 2$), and inversions of *HMGA2* ($n = 1$). Novel translocations of uncertain clinical significance were also described, such as t(7;12)(q31.1;q24.11)/*CUX2*::*NRCAM*, t(8;8)(p21.2;q22.1)/*PTK2B*::*MTERF3*, and (7;7)(q32.1;q34)/*UBN2*::*SND1*.

Resolution and characterization of complex and masked karyotypes by OGM

Interpreting karyotypes can be challenging due to their genomic complexity, particularly in the context of CBA. In our cohort, 17 patients showed unresolved composite karyotype, where CBA had reported marker chromosomes and complex chromosomal aberrations. In these patients, OGM refined the karyotype by mapping breakpoints of known alterations, determining their translocation partners, and uncovering new abnormalities.

CBA described a total of 16 patients with marker chromosomes that were successfully resolved and characterized using OGM analysis. Thus, OGM enabled the redefinition of aneuploidies that were previously unclear. Most of the marker chromosomes had large CNV losses and/or complex rearrangements, which made their identification challenging by CBA.

Furthermore, OGM reclassified previous aneuploidies described by CBA and described them as chromosomal CNV losses and chromoanagenesis events. These alterations mainly affected chromosomes 4 ($n = 2$), 5 ($n = 1$), 8 ($n = 2$), 9 ($n = 2$), 17 ($n = 4$), and 21 ($n = 2$). In some cases, OGM reclassified the altered chromosome described with CBA. For example, distinguishing monosomy 18 from monosomy 16 (case #33), and monosomy 16 from monosomy 13 (case #54, Fig. 3A), as well as resolving an isochromosome i(7q) that had been previously misidentified as i(8q) (case #83).

OGM reveals chromoanagenesis events associated with TP53 alterations

Chromoanagenesis events were described in 17 patients (9 MDS, 8 AML). In 5 patients, single isolated chromothripsis events were identified. One of them involved chromosome 1q; two affected chromosome 3, involving *GATA2* and *MECOM;* and the rest involved chromosome 6p and chromosome 11, with chromosome 11 exhibiting amplification up to 8–9 copies of *KMT2A* (Fig. 3A). In 3 patients, double chromothripsis events were found affecting two independent chromosomes in each patient. These resulted in gains and losses of material in chromosomes 4, 5, 12p, 13, 20, and 21, involving genes such as *TET2*, *PDGFRB*, *NRAS*, *ETV6*, *FOXO1*, *RUNX1*, and *U2AF1*. Additionally, apart from chromothripsis translocations, putative gene fusions affecting cancer-related genes were identified, such as t(12;20)(p12.1;q13.33)/*ETFRF1*::*KRAS* and t(1;1)(p34.3;p35.1)/*CSMD2*::*PPIEL*.

Further, complex chromoanagenesis events were identified in 9 patients. One of these patients presented complex rearrangements involving chromosomes 5, 6, 7, 11, 16, 17, 19, and 20, describing a chromoanagenesis event (case #54, Fig. 3B) resulting in the loss of leukemia-relevant genes that included *TP53*, *NF1*, *CSF1R*, *DDX41*, and *NPM1*. OGM revealed the rearrangements and chromosomes involved, and redefined alterations previously reported by CBA, including CNV and monosomies, and identified the two marker chromosomes. Another patient presented complex rearrangements affecting chromosomes 1, 3, 4, 5, 7, 8, 9, 10, 17, 18, 20, 21, reported as chromoanagenesis event (case #113, Fig. 3C), describing a highly complex genome. Monosomies reported by CBA were redefined by OGM and the marker chromosomes were identified. Some events resulted in gene fusions, affecting relevant genes such as t(5;5;21)(q12.3;q12.3;q22.12)/*ADAMTS6*::*MTREX*::*RUNX1*, or genes with potential role including t(12;12)(q14.3;q24.23)/*HMGA2*::*PXN*, t(6;11)(q22.31;q13.5)/*MAN1A1*::*PAK1*, and t(5;5;17)(q13.3;q34;q12)/*SV2C*::*TENM2*::*LINC01992*.

Importantly, since there is no clear relationship between the presence of *TP53* alterations with complex chromoanagenesis events, we investigated the association of these events with *TP53* mutational state in MDS and AML (Supplementary Data 3). Our results showed a significant association between *TP53* mutations and the occurrence of genomic catastrophic events ($p < 0.0001$) (Fig. 4). Among the 150 patients, *TP53* monoallelic mutations were described in 15 patients (10%), and biallelic mutations in 20 patients (13%). Of note, all 17 patients presenting catastrophic events had alterations in *TP53*, whereas no chromoanagenesis events were described in patients with wild-type *TP53*. Statistical analysis showed a significant increase of chromoanagenesis occurrence in patients with monoallelic ($p = 0.0002$) and biallelic ($p < 0.0001$) *TP53* mutations. Interestingly, these differences were also significant when comparing monoallelic (4/15, 27%) and biallelic (13/20, 65%) *TP53* cases ($p = 0.0409$), suggesting that biallelic mutations induce a higher genome instability than those with monoallelic *TP53* (Fig. 4).

Discussion

This study demonstrates that OGM matches the diagnostic scope of current SOC methods in 97% of cases, while providing a more comprehensive cytogenetic description in 80% of patients. Overall, OGM redefined the cytogenetic classification in 33 patients: 16 previously diagnosed with normal karyotypes, and 17 with altered karyotypes. In complex karyotypes, OGM also unveiled cryptic alterations and refined chromoanagenesis events, including abnormalities involving clinically relevant genes. In this study, we also demonstrate OGM's utility in resolving non-assessable cases by CBA. Herein, we show the potential of OGM in hematological cytogenetics, offering deeper insight into the cytogenetic heterogeneity of AML and MDS. Our findings align with previous studies showing that OGM significantly improves patients' cytogenetic characterization and diagnosis[11–13,18,22,24].

Using OGM, we performed a comprehensive cytogenetic analysis of the cohort, describing abnormalities with clinical significance, refining previous alterations, and clarifying unclear events. This included the detection of unusual rearrangement partners of *MECOM*[22,43], *KMT2A*[44–46]; *RUNX1*[47], or *NUP98*[39,48], as well as SVs affecting key genes such as *MECOM*, *RUNX1*, *TET2*, *ASXL1*, *EZH2*, and *STAG2*, either alone or co-occurring with point mutations (Supplementary Data 1), emphasizing the complementary value of OGM and NGS[4,49–51].

Additionally, we identified novel alterations affecting genes whose relevance in AML and MDS biology is not yet clarified, but have been described in other hematological, including *TCF4*[52], *NF1*[53], *HMGA2*[54], *UBN2*[55]. Given their relevance in other malignancies, their alteration may play a role on MDS and AML pathogenesis or therapy response[11,38,56,57]. Therefore, discovery of novel affected genes holds significant potential in the description of novel biomarkers in leukemia, crucial for guiding the development of novel therapeutic strategies[1,13,14,38]. Accumulating many more such cases will help substantiate the relevance of these findings.

To date, there is no consensus regarding the number or type of chromosomal alterations that should be considered when analyzing MDS and AML patient genomes using OGM[20,58]. This is particularly relevant for ELN and IPSS-M risk scores[9,59], which incorporate nonspecific aberrations to classify patients within the cytogenetic risk groups. Clear criteria for reporting the number and type of alterations in comprehensive patient analyses are still needed. In our cohort, due to the identification of new alterations, 22% of patients changed their cytogenetic classification, and their cytogenetic risk increased in 16% of patients. Nonetheless, due to the high relevance of SNVs detected by NGS in the prognostic scores, the detection of novel alterations only reclassified 3 patients. Most patients classified as adverse or high-risk showed mutations affecting adverse prognostic genes, including *TP53*, *ASXL1*, *RUNX1*, *SF3B1*, or rearrangements affecting *MECOM* or *KMT2A*, among others[9,10]. Remarkably, risk assessment in patients with non-assessable karyotype was performed using the OGM described karyotype.

This highlights that integrating novel findings detected by OGM, including insertions, deletions, inversions, or duplications affecting clinically relevant genes, or the presence of chromoanagenesis events, may be of great value for future clinical guidelines, given the significance of these alterations in oncogenesis[24,58]. Importantly, after the application of OGM, the prognostic risk assessment was more concordant with the cytogenetic risk assessment regarding NGS mutations in AML patients ($n = 14$) and increased the risk score in MDS patients ($n = 10$) whose cytogenetic category was modified. In our cohort, we identified novel abnormalities affecting key genes such as *RUNX1*, *NRAS*, *MECOM*, and *DNMT3A*, which are currently included as SNVs in clinical guidelines, but SVs may also hold biological and prognostic significance in leukemia. Nonetheless, further studies are needed to elucidate their biological role and clinical impact on patient outcomes before their incorporation into diagnostic and prognostic frameworks.

Furthermore, in this study, OGM was particularly effective in refining cytogenetic abnormalities in complex karyotypes, identifying masked SVs and CNVs, and clarifying ambiguous events. In line with previous works describing complex karyotypes on AML[12], CLL[29], and multiple myeloma (MM)[60], among others[4,13,18,61], we demonstrate the utility of OGM in characterizing complex karyotype events in AML and MDS. Regarding chromoanagenesis events, we were also able to identify subtle translocations resulting in gains and losses, or putative gene fusions, affecting clinically relevant genes and leukemia-associated genes. Notably, in patient #148, OGM described a chromoanagenesis event between chromosomes 5 and 17, and the CBA described a loss in 5q [del(5)(q13q31)]. This patient evolved to

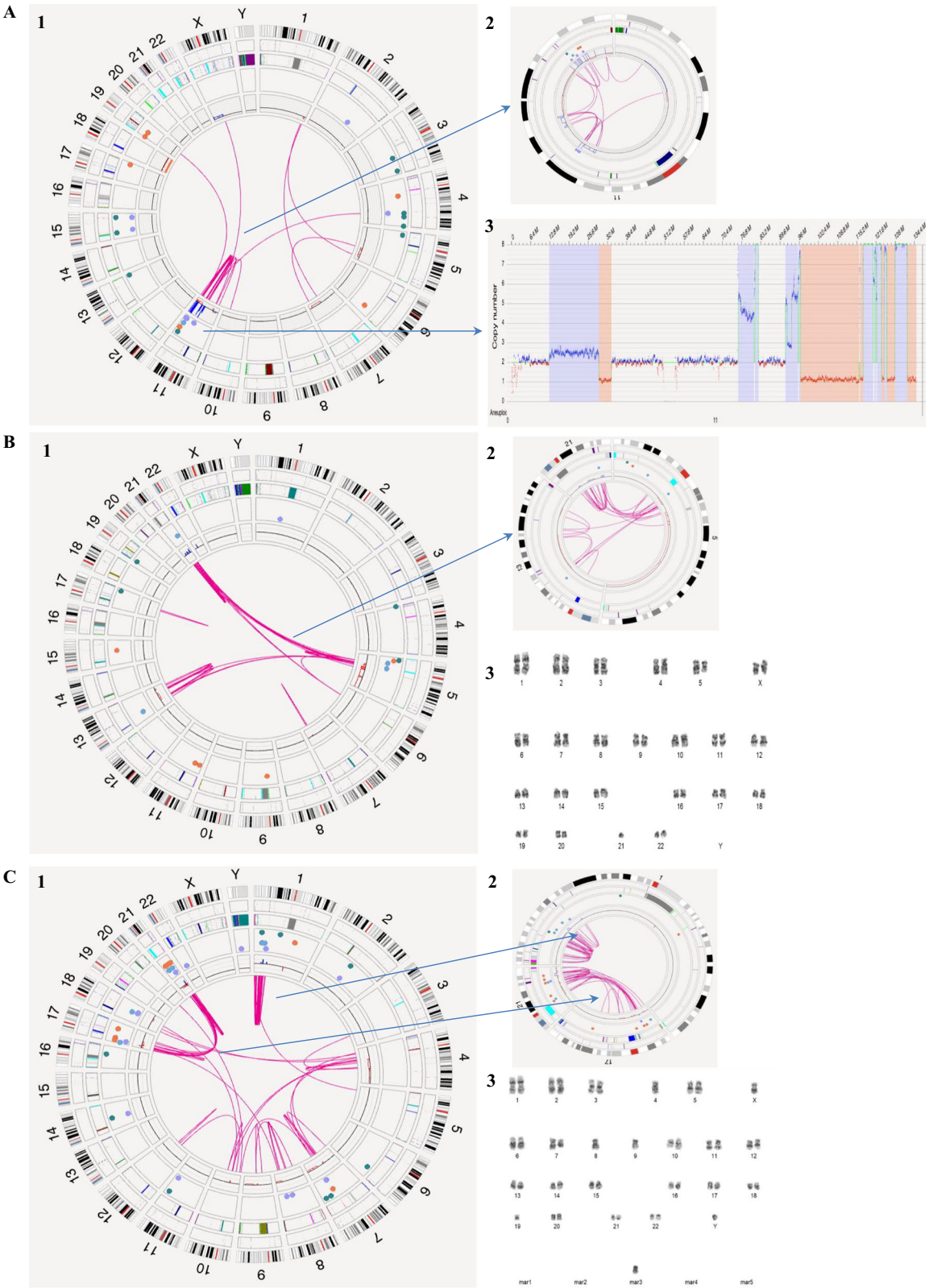


Fig. 3 | Selection of AML and MDS patients showing genome complexity. A AML patient (case #64) with complex karyotype. 1) Circos plot. OGM analysis showed translocations affecting chromosomes 1, 5, and 7 resulting in CNV losses, and a chromothripsis affecting chromosome 11 and resulting in more than 9 copies of *KMT2A*. 2) Circos plot. Graphical representation of chromosome 11 and rearrangements. 3) CNV. Representation of CNVs occurring in chromosome 11 as a result of the chromothripsis event. **B** AML patient (case #54) with chromoanagenesis. 1) Circos plot. OGM analysis described complex rearrangements affecting multiple chromosomes, describing a chromoanagenesis event; 2) Circos plot. Graphical representation of chromosomes 5 and 17, showing multiple translocations between them; 3) CBA. Karyotype described by CBA, including monosomies in chromosomes 5, 13, 14, 15, 20, also losses in 7p and 12p, and gains in 11p. **C** MDS patient (case #113) with complex chromoanagenesis. 1) Circos plot. Multiple translocations resulting in a chromoanagenesis event; 2) Circos plot. Graphical representation of chromosomes 1, 17, and 21, showing multiple translocations affecting them; 3) CBA. Karyotype described by CBA, including monosomies in chromosomes 4, 8, 9, and 17, also losses in 7q and 10q.

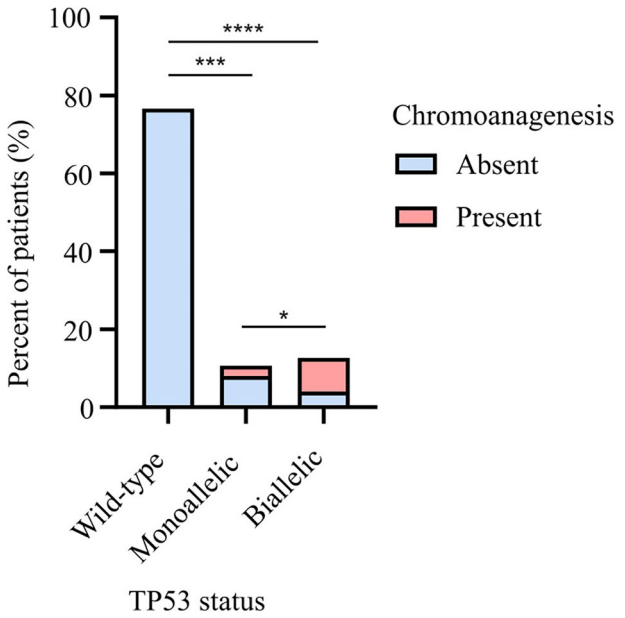


Fig. 4 | *TP53* mutational status impacts chromoanagenesis occurrence in AML and MDS patients. 150 AML and MDS patients were studied, describing three groups of patients regarding *TP53* status: 115 wild-type (76%), 15 monoallelic (10%), and 20 biallelic (13%). Chromoanagenesis events were only identified in patients with altered *TP53*: in 4 patients with monoallelic *TP53* (25%) and in 13 patients with biallelic *TP53* (68%). χ^2 test was used to assess global differences in the presence of chromoanagenesis events in all patients, and Fisher's exact test with pairwise comparisons to explore the presence of chromoanagenesis between each group. Significant differences were found between the three groups (χ^2 test $p < 0.0001$), showing a higher prevalence when *TP53* was altered ($p < 0.001$). Notably, in patients with *TP53* altered, chromoanagenesis events were more present in patients with biallelic state ($p = 0.0409$). *$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$.

a karyotype with loss in 5q and 17p, regions affected by the chromoanagenesis. This suggests that studying complex cases using OGM can help to detect abnormalities that will evolve into complex events and adverse patient outcomes.

Another key topic in genetic characterization is the exact definition of chromoanagenesis and its potential effect on disease biology and aggressiveness. Particularly, determining which clinically uncertain alterations should be reported remains challenging, especially when they are part of highly complex chromosomal rearrangements. Therefore, the clinical implications of chromoanagenesis events, aside from the complexity of the genome and genomic instability, remain to be defined in the prognostic guidelines[26,58,62]. Moreover, chromoanagenesis events are known to play a significant role in the prognosis of other malignancies[26], including sarcoma[32], lung[63], prostate[64], among others[65–67]. Therefore, techniques enabling comprehensive genome-wide characterization are of paramount importance for accurate patient stratification and clinical management[62,68–70].

Additionally, this study demonstrates that the presence of *TP53* alterations, particularly in patients with monoallelic or biallelic alterations, is significantly associated with the occurrence of chromoanagenesis events in MDS and AML patients. Our findings, together with previous works[13,27,71], may aid in defining this emerging category of leukemic patients with chromoanagenesis events associated with *TP53* alterations. This is consistent with the emerging understanding of *TP53* mutations as key drivers of genomic instability and disease progression in hematological malignancies[18,27,62,65]. Notably, patients harboring biallelic *TP53* mutations exhibited a significantly higher frequency of catastrophic events compared with those carrying monoallelic mutations[27,72], supporting previous reports that biallelic *TP53* inactivation confers a worse prognosis and drives greater genomic instability[71,73–75]. These findings suggest that the interplay between *TP53* alterations and chromoanagenesis may drive genomic instability and contribute to poor clinical outcomes in myeloid malignancies. Therefore, further investigation into the cooperative pathological mechanisms between chromothripsis and *TP53* alterations may contribute to a better understanding of their role in genomic instability.

Although OGM shows promising results, it also presents certain limitations, such as the use of ultra-high molecular weight (UHMW) DNA, the inability to detect low-frequency clones (<5% VAF for SVs and 10–15% for CNVs), the inability to detect alterations smaller than 500 bp, description of ploidy, identification of LOH regions, and the challenge of resolving specific genomic regions, including centromeres and telomeres, or small chromosomes with highly repetitive sequences such as chromosome Y. These limitations can, however, be mitigated through complementary high-resolution bioinformatic approaches currently implemented by the manufacturer, such as the de novo and *guided assembly* pipelines, as well as the VIA™ Analysis Software, which enhance resolution for SVs, CNVs, and even CN-LOH detection[19–22,58]. Moreover, OGM in combination with other techniques, such as Whole Exome Sequencing or Target Sequencing, would allow for a better description of the patient's genomics, complementing their analysis[76].

In summary, our findings strongly support the integration of OGM into the diagnostic routine workflow for AML and MDS, particularly in cases with non-assessable or complex karyotypes and ambiguous genomic alterations. OGM provides a comprehensive genome-wide view in a single assay, shows high concordance with conventional techniques, and enables the detection of cryptic alterations and clarification of complex cytogenetics. Its incorporation into clinical practice has the potential to refine genetic profiling, identify clinically relevant biomarkers, improve risk stratification, and guide the development of tailored therapeutic strategies for the precise management of myeloid neoplasms.

Methods

Sample selection and conventional testing

This study included 150 patients diagnosed with MDS ($n = 64$) or AML ($n = 86$) at La Fe University and Polytechnic Hospital (HUPLAFE). Samples consisted of bone marrow aspirates (BMA; $n = 127$) and peripheral blood (PB; $n = 23$) at diagnosis ($n = 118$), follow-up ($n = 19$) or relapse ($n = 13$). Samples were collected and preserved at −80 °C at the Biobanco La Fe until analysis.

All patients' samples were analyzed by CBA, NGS, and OGM as part of the diagnostic workflow for hematologic malignancies, with all findings verified and approved by the supervising specialist. All methods in the cytogenetics and molecular biology laboratories are standardized and comply with high standards for diagnosis according to national and international audits. All procedures were performed in accordance with ISO 15189–accredited quality standards at the Molecular Diagnostics Laboratory and with ISO 9001:2015 standards at the Hematological Diagnostics Unit of La Fe University and Polytechnic Hospital. The diagnostic classification was made according to WHO 2022[7] and ICC 2022[8] guidelines, and the prognostic stratification was made following the IPSS-M[9] guidelines for MDS patients and ELN[10] guidelines for AML patients. All data were obtained from the same sample, to compare results at the same time point. FISH analysis was performed in 116 patients according to standard procedures to identify specific alterations, and the probes were selected according to patients' clinics and suspected diagnosis. FISH was not performed when the diagnostic abnormalities were described by CBA (Supplementary Data 1). Cytogenetic reports followed the International System for Human Cytogenetic Nomenclature 2024 (ISCN 2024)[77]. Following ISCN guidelines, we analyzed 10 metaphases when abnormalities were found, and 20 when a normal karyotype was described, indicating the number of abnormal and normal clones. Non-assessable karyotypes were described when no metaphases were obtained.

For NGS analysis, Myeloid Solution by Sophia CE-IVD panel was used for MDS patients and Oncomine Myeloid Assay GX v2 panel for AML patients (SOPHiA Genetics™) (Supplementary Table 2). These panels are

targeted DNA/RNA assays that include clinically relevant genes in MDS and AML and allow the identification of abnormalities such as *KMT2A*-PTD, *FLT3*-ITD, gene fusions affecting genes such as *ABL1*, *ETV6*, *JAK2*, *KMT2A*, *NUP98*, *PICALM*, or *RUNX1*, and detect the expression of genes including *MECOM*. For MDS patients, DNA extraction, quantification, library preparation (Myeloid Solution by Sophia CE-IVD), sequencing, variant calling, and reporting were automatically performed using the Sophia DDM v4 software. NGS reports were further studied and confirmed by the specialist. For AML patients, genomic DNA was extracted using the QIAsymphony DNA Midi Kit (Qiagen, Hilden, Germany) and RNA the QIAsymphony RNA Mini Kit (Qiagen) on the QIAsymphony SP Automated Extraction Instrument (Cat 9001297, Qiagen) following the manufacturer's recommendations. DNA and RNA quantification were assessed with Nanodrop (Thermo Fisher Scientific, Waltham, USA) and Qubit fluorometer (Thermo Fisher Scientific). Quality parameter criteria for both panels: uniformity (> 85%) and mean read depth of 1000x. Consensus criteria for variant report: DNA all pathogenic or probably damaging variants with VAF ≥ 2%; RNA > 20 reads targeted fusions and >100 reads non-targeted fusions.

The study was approved by the Ethics Committee of the La Fe University and Polytechnic Hospital (Drug Research Ethical Committee, CEIm, No.2022-178-1), and all participants provided informed consent following the Declaration of Helsinki.

Optical genome mapping

For OGM, UHMW DNA was extracted from PB or BMA and fluorescently labeled using the DLE-1 enzyme following the manufacturer's protocols (Bionano Genomics, USA). The samples were then loaded onto a chip and analyzed using the Bionano Saphyr system. SVs analysis was performed using Bionano Access software (v1.8.2), and alignments were based on the GRCh38/hg38 human reference genome[20,24].

The median effective genome coverage achieved was 414.02x (>300x), theoretically enabling the detection of alterations over 5% variant allele frequency (VAF), a median label density of 15.25, and a median map rate of 87.9%. Detailed information on quality metrics can be found in Supplementary Table 3 and Supplementary Data 4.

For the bioinformatics analysis and description of the variants detected through OGM, the rare variant analysis (RVA) pipeline was used as the primary analysis workflow. Only SVs > 2 Kb and CNVs > 500 Kb were considered. For the initial filtering, we used the manufacturer's recommended settings, based on size and confidence scores >0.9 (Supplementary Table 4). Variants that fulfilled the quality thresholds were further filtered and manually revised using a custom BED file that includes the coding regions of clinically relevant genes associated with leukemia and MDS (Supplementary Table 1), based on clinical guidelines. Additionally, a second revision to detect potentially relevant genes not yet described in leukemia was performed using a GRCh38/hg38 known canonical BED customized by Bionano Genomics[78], selecting genes not included in our custom BED file, but relevant in other cancers. These genes were reported if they were found to be affected in more than 2 patients, or if they were described as relevant in tumorigenesis in the literature. Using these two BED files allowed for a more uniform genomic coverage across all chromosomes, and SVs and CNVs affecting leukemia or cancer-related genes were reported.

OGM results were compared with CBA, FISH, and NGS. Concordance was defined when the same cytogenetic abnormalities were detected by all techniques. Refined results were considered when OGM identified additional SVs or CNVs, even when the alterations were not completely concordant. Discordance was noted when abnormalities differed between CBA, FISH, and OGM. Regarding NGS, only SVs and CNVs were compared; single-nucleotide variants (SNVs) were excluded due to limitations in the resolution of CBA, FISH, and OGM. Only *TP53* mutations were included in the comparison given their relevance in complex karyotypes and genome instability. Regarding validation of clinically relevant rearrangements described by OGM, the affected genes included in the NGS panels mentioned above were validated by NGS to determine the number of reads and the partner (Supplementary Data 1 and Supplementary Table 2).

Karyotype complexity was divided into three categories: (i) complex karyotypes, when 3 or more cytogenetic abnormalities were detected by CBA, FISH, and NGS, or when 5 or more chromosomal alterations were detected by OGM; (ii) altered karyotypes, when fewer alterations were identified; (iii) normal karyotypes, when no cytogenetic alterations were found. The threshold of 5 or more alterations detected by OGM for defining a karyotype as a complex is based on the higher sensitivity of the technique in identifying genomic abnormalities[13].

Within the category of complex karyotypes, some cases exhibited mechanisms of chromoanagenesis, including chromothripsis, chromoplexy, and chromoanasynthesis. Chromoanagenesis was described when more than 7 rearrangements were detected. Because the clinical definitions of these terms are not yet fully established, we describe three groups of chromoanagenesis: (i) cases with isolated chromothripsis events; (ii) cases with multiple chromothripsis events, each affecting one chromosome; and (iii) cases with complex rearrangements events affecting multiple chromosomes, with or without accompanying chromothripsis events, which we refer to as complex chromoanagenesis[20,26,58,64].

Statistical analysis

Statistical differences in the presence or absence of chromoanagenesis events across three categorical variables (*TP53* status: wild-type, monoallelic, and biallelic) were assessed using χ^2 and Fisher's exact test with pairwise comparisons. *TP53* monoallelic status was defined by a single mutation or deletion, while biallelic status was defined by two or more mutations, or one mutation with VAF > 50% or co-occurring with a *TP53* deletion[8,74]. Statistical significance was defined as $p < 0.05$. All analyses were performed using GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA).

Data availability

For inquiries about original data, please contact such_esp@gva.es. All data generated or analyzed during this study are included in this published article as supplementary files: Supplementary Data 1: Full cytogenetic and molecular description of the patients selected; Supplementary Data 2: SVs and CNVs identified in the studied cohort by OGM; Supplementary Data 3: Recompilation of all patients and their status regarding *TP53* mutations and the presence of catastrophic events; Supplementary Data 4: Quality parameters of the samples analyzed using the OGM RVA pipeline; Supplementary Table 1: Genes associated with leukemia were included in the BED file; Supplementary Table 2: NGS panels information; Supplementary Table 3: Quality parameters and recommended values for genome mapping analysis in hematologic neoplasm samples; Supplementary Table 4: Quality filters applied for OGM analysis.

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Competing interests
The authors declare no competing interests.

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