INTEGRATING OPTICAL GENOME MAPPING AND NEXT-GENERATION SEQUENCING IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS

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Introduction

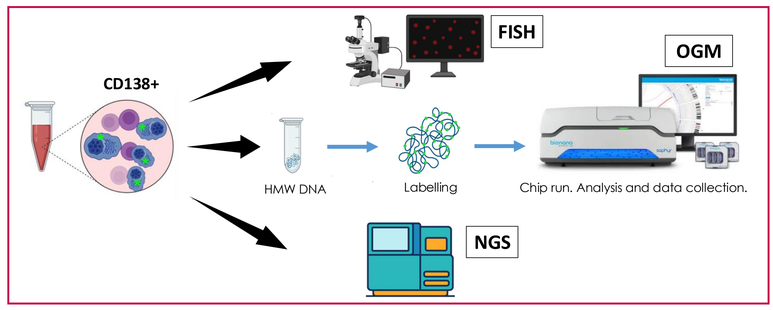
Genomic profiling is key to predicting outcomes in newly diagnosed multiple myeloma (NDMM). Although FISH remains the standard method for cytogenetic diagnostic, its targeted approach limits the detection of a broader and more diverse range of genomic abnormalities. Novel approaches such as **Optical Genome Mapping (OGM)** and **Next-Generation Sequencing (NGS)** provide a more comprehensive genomic landscape, uncovering additional alterations. Nonetheless, their prognostic value remains to be fully explored.

Aim

To evaluate **cytogenetic abnormalities** and the **molecular profiling** of CD138+ cells from **NDMM** patients using **OGM** and **NGS**.

Methods

Bone marrow pre-treatment samples from **53 patients with NDMM**, referred from our center and four additional institutions, were collected between 06/2023 and 02/2025. CD138+ cells were isolated with the RosetteSep™ MM Enrichment Cocktail. **FISH analysis** was routinely performed. High molecular weight DNA from CD138+ cells was extracted, labeled with DLE-1 enzyme and loaded on a Saphyr chip for subsequent analysis using a **Saphyr™ system (Bionano)**. Additionally, **NGS** was performed on CD138+ samples from a smaller cohort, using a lymphoid gene panel with analysis conducted via the **SOPHiA DDM™** platform.



Results

N = 53

Median age: 62 years (range 39–78)
Female patients: 26 (49%)

- **Monosomy 13** was the most frequent aneuploidy (43%).
- **Hyperdiploidy** was observed in 56% of pts (47–78 chromosomes).

- ***IGH* translocations** were identified in 20 cases:
  - *IGH*::*CCND1* (n=10, >50% associated with hypodiploidy).
  - *IGH*::*MAFB* (n=3); *IGH*::*FGFR3* (n=2); *MYC*::*IGH* (n=2), *IGH*::*CCND3* (n=1), *IGH*::*NFKB1* (n=1); *IGH*::*MAF* (n=1).

- ***MYC* translocations** were detected in 9 patients (**Figure 2**).
- **Chromoanagenesis** was identified in 9 cases:
  - Chromothripsis (n=8)
  - Chromoplexy (n=2)

- OGM was positive in all FISH-negative cases (n=9),
  - revealing *MYC*-r, *IGH*::*MAFB* and cryptic 1p deletions.

- NGS (available in 22 pts) revealed **at least one mutation in 9 cases (41%).**
- All ***KRAS*-mutated cases** (n=7) showed **hyperdiploidy.**
  - *MYC*-r were detected in two patients in this group.

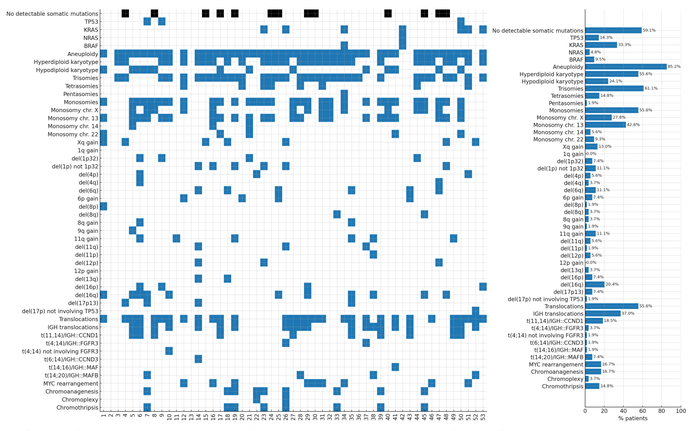


Figure 1. Landscape of Main Genomic Alterations in the Study Population.

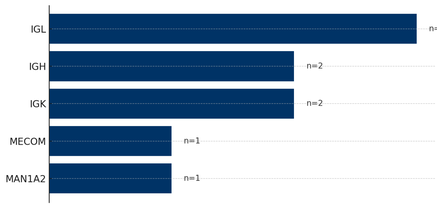


Figure 2. Partners of *MYC* translocations.

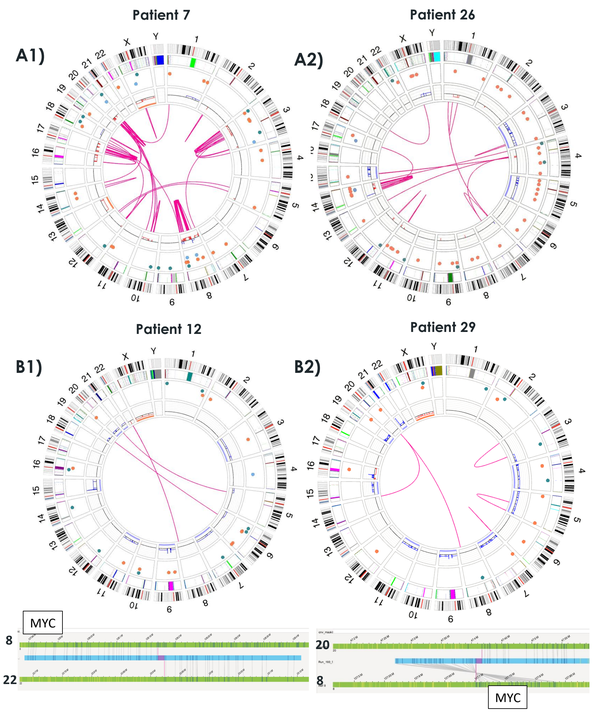


Figure 3. Examples of alterations detected with OGM. A) Chromoanagenesis events. A1) Chromothripsis involving chr. 3, 8, 17 y 20. A2) Chromoplexy involving chr. 1, 4, 7, 13 and 15; and chromothripsis of chr. 14. B) *MYC* rearrangements. B1) t(8;22)(q24.21;q11.22)/*IGL*::*MYC*. B2) t(14;20;8)(q32.33;q13.12;q24.21)/*IGH*::*MYC*.

Conclusions

- **OGM** and **NGS** reveal a **wider range of genomic changes** beyond standard methods.
- These findings support the added value of advanced genomic tools: **improving diagnostic resolution** and expanding our **understanding of genomic complexity**.
- **Ongoing analyses** at our center using Whole Exome Sequencing (WES) aim to correlate genomic alterations with clinical data in a larger cohort.

References

1. **Zou YS** *et al.* A comprehensive approach to evaluate genetic abnormalities in multiple myeloma using optical genome mapping. *Blood Cancer J.* 2024;14(1):1-5.
2. **Yoon J** *et al.* Characterization of MYC rearrangements in multiple myeloma: An optical genome mapping approach. *Blood Cancer J.* 2024;14(1):1-4.
3. **Guermouche H** *et al.* Deciphering Genomic Complexity of Multiple Myeloma Using Optimized Optical Genome Mapping. *J Mol Diagn.* 2025;27(4):306-22.