LETTER TO THE EDITOR

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Optical Genome Mapping as a New Approach to Detecting Cytogenetic Abnormalities: Why Is It Difficult in Multiple Myeloma?

Sitogenetik Anomalilerin Tespitinde Yeni Bir Yaklaşım Olarak Optik Genom Haritalama: Multipl Miyelomda Neden Zor?

Ayşe Gül Bayrak Tokaç[1], Mehmet Burak Mutlu[2], Simge Erdem[3], Aynur Aday[1]

[1]*İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Medical Genetics, İstanbul, Türkiye*
[2]*Detagen Genetic Diseases Evaluation Center, Kayseri, Türkiye*
[3]*İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye*

To the Editor,

Multiple myeloma (MM), the second most common type of hematological neoplasm worldwide, is a plasma cell (PC) neoplasm [1]. According to 2022 statistics, the age-standardized incidence rate is 1.8 with a total of 188,000 new MM cases worldwide. Taking into account population growth and aging criteria, the number of newly diagnosed MM cases is expected to increase by 71% and the mortality rate by 79% by 2045 [2]. Genetic abnormalities are important in determining the prognosis of the disease and fluorescence in situ hybridization (FISH) is the preferred method to detect these abnormalities [1]. Since the proportion of PCs in the bone marrow (BM) varies between 10% and 30%, FISH testing of enriched CD138-positive PCs is recommended [3]. Therefore, highly sensitive methods may be more useful in prognostication. Recently, the highly sensitive method of optical genome mapping (OGM) has been used as a new cytogenomic method integrating karyotyping, FISH, and microarrays to increase the detection rate of abnormalities in hematological neoplasms [4,5,6].

For our OGM study, heparinized BM samples of 3-6 mL were collected from MM patients. Mononuclear cells were isolated via the Ficoll-Paque protocol. PCs were separated by flow cytometry using CD56, CD38, CD138, CD45, and CD19 antibodies (BD Pharmingen, San Diego, CA, USA) labeled with different fluorophores. Cells were sorted using a FACSAria II device (BD Biosciences, Franklin Lakes, NJ, USA) and snap-frozen. The OGM procedure was performed in three steps that included the isolation, labeling, and staining of high-molecular-weight DNA as the first step, followed by the loading and running of samples on a Bionano Saphyr device (Bionano Genomics, San Diego, CA, USA) and then data analysis. First, frozen cells were thawed and counted. DNA isolation was applied for samples with ≥1.5 million cells. Genomic DNA was isolated using the Bionano Prep SP-G2 Frozen Cell Pellet DNA Isolation Kit. Only samples containing ≥40 ng/µL of good-quality DNA were loaded onto a chip and run on the Bionano Saphyr device. Data were analyzed using Bionano Access software.

OGM can identify almost all types of structural variation, including translocations, deletions, duplications, insertions, inversions, aneuploidies, and complex chromothripsis with 5% variant allele frequency [5]. The Bionano Rare Variant Pipeline was used with default settings to analyze the data obtained in this study. All variants were filtered to <1% according to the internal control database.

Obtaining the number of PCs required for OGM was challenging, especially in cases of patients with <20% PCs. CD138-negative cells were added to samples with ≤800,000 PCs to reach 1.5 million cells. Although the samples were shipped with adequate dry ice, long-distance transport was also problematic. PCs were frozen at -20 °C for 2 hours and then stored at -80 °C. Longer storage at -80 °C led to more cell loss and a maximum of one night at -80 °C gave the best results. This is probably due to the fragile nature of PCs, which are unsuitable for long-term transfer and storage. In addition, these cells should be processed slowly in wet laboratories. This is necessary to avoid cell destruction and DNA fragmentation. In our study, the PCs were separated by flow cytometry for 25 patients. For 14 patients, the number of PCs was <1 million (100,000 to 950,000). For 11 patients, 1-6 million PCs were obtained. Six of the 11 patients with ≥1 million cells had enough cells after transfer to be included in

the OGM study, while 5 had fewer than 800,000 PCs. Overall, all patients had cell loss of two-thirds after transfer. The PC counts obtained by morphological assessment and flow cytometry were discordant.

It has been predicted that OGM will contribute to the development of therapeutic targets by enabling the detection of new biomarkers that cannot be detected by conventional methods due to their low sensitivity [7]. In MM, the combination of OGM and high-throughput DNA sequencing will enable more comprehensive genomic analysis in the near future [8]. However, the heterogeneity of the number of PCs in MM, the necessity of obtaining more than 800,000 cells, difficulties in working with and transporting PCs, lack of equipment support, and high costs still hinder the widespread use of OGM in MM. If these difficulties are overcome, it seems that the detection of abnormalities in MM by OGM will contribute to improvements that will increase survival, allowing OGM to usurp the role of FISH in diagnosis and prognosis.

Keywords: Multiple myeloma, Genomic structural variation, Chromosome mapping

Anahtar Sözcükler: Multipl miyelom, Genomik yapısal varyasyon, Kromozom haritalama

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.E.; Concept: A.G.B.T., A.A.; Design: A.G.B.T., A.A.; Data Collection or Processing: A.G.B.T., A.A., S.E.; Analysis or Interpretation: A.G.B.T., A.A., M.B.M.; Literature Search: A.G.B.T., A.A.; Writing: A.G.B.T., A.A.

Conflict of Interest: Mehmet Burak Mutlu works for a genetic diseases evaluation company that is the distributor of OGM Technology in Türkiye. The other authors declare no conflicts of interest.

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Address for Correspondence/Yazışma Adresi: Ayşe Gül Bayrak Tokaç, Ph.D., İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Medical Genetics, İstanbul, Türkiye
E-mail: abayrak@istanbul.edu.tr **ORCID:** orcid.org/0000-0003-2228-0632

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