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Original article

Incidence of cytogenetic abnormalities detected by FISH analysis in multiple myeloma: a seven-year study in King Chulalongkorn Memorial Hospital, Thailand (2018–2024)

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Abstract

Background: Multiple myeloma (MM) is a genetically heterogeneous plasma cell malignancy with cytogenetic abnormalities that influence the prognosis and treatment outcomes. Fluorescence *in situ* hybridization (FISH) is crucial for detecting clinically significant abnormalities, including immunoglobulin heavy chain locus (IGH) translocations and deletions, e.g., del(17p), particularly in non-dividing plasma cells. However, cost and accessibility challenges limit comprehensive testing in resource-constrained settings, such as in Thailand.

Objective: This study aimed to investigate the incidence of cytogenetic abnormalities detected by FISH in MM cases over seven years in a Thai population, thereby highlighting regional trends and barriers to comprehensive testing.

Methods: A retrospective analysis was performed on 360 bone marrow samples from patients with MM between 2018 and 2024. FISH analysis targeted key abnormalities using specific probes: t(4;14), t(11;14), t(14;16), del(17p), and 1q21 amplification. Furthermore, the demographic data and testing frequencies were analyzed, as well as the prevalence rates of abnormalities were reported.

Results: Among the 360 cases, 47.4% exhibited abnormalities. The most common were del(17p) (30.6%), del(13q) (16.9%), and t(4;14) (6.9%). Testing limitations led to selective probe usage, with del (17p) probes ordered in 96.7% of cases, while 1q21 amplification probes were only ordered in 3.3% of cases. Regional trends revealed lower frequencies of t(11;14) compared to Western cohorts, suggesting ethnic influences.

Conclusion: FISH analysis revealed critical cytogenetic abnormalities in Thai patients with MM. However, financial constraints limit comprehensive testing, thus potentially hindering optimal risk stratification and treatment. Expanding diagnostic accessibility and integrating advanced technologies such as next-generation sequencing could address these barriers and improve patient outcomes.

Keywords: Chromosomal abnormalities, FISH analysis, multiple myeloma, Thailand.

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation in the bone marrow, leading to organ damage, including hypercalcemia, renal dysfunction, anemia, and bone lesions (CRAB criteria). It is a genetically heterogeneous disease with various cytogenetic and molecular abnormalities that influence its clinical presentation, prognosis, and treatment response. [1, 2]

The key genetic alterations include chromosomal translocations involving the immunoglobulin heavy chain (IGH) locus on chromosome 14q32, such as t(4;14), t(11;14), and t(14;16), as well as chromosomal gains (e.g., trisomies) and deletions (e.g., del(17p), del(13q)). [3] These changes contribute to the

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pathogenesis of MM by deregulating oncogenes and tumor suppressor genes. MM is further classified into hyperdiploid (characterized by trisomies) and non-hyperdiploid (harboring translocations) subtypes. This genetic heterogeneity underpins the diverse clinical behavior of the disease, necessitating personalized treatment strategies based on cytogenetic and molecular profiling to improve patient outcomes. [3]

These cytogenetic abnormalities play a crucial role in the prognosis and treatment of MM. Furthermore, these abnormalities are often detected via techniques such as karyotyping and fluorescence *in situ* hybridization (FISH), which provide valuable insights into the disease progression, response to treatment, and overall patient outcomes. [4] Cytogenetic abnormalities in MM are categorized into standard- and high-risk groups based on their impact on prognosis. [5,6] High-risk abnormalities include t(4;14), t(14;16), t(14;20), del(17p13), and 1q21 amplification **(Figure 1)**. The t(4;14) is associated with the overexpression of *FGFR3* and MMSET genes, resulting in poor prognosis, although outcomes have improved with the use of proteasome inhibitors. Translocations such as t(14;16) and t(14;20) lead to deregulated oncogene expression and are also linked to adverse outcomes. Moreover, del(17p13) involves the loss of the *TP53* tumor suppressor gene, which contributes to treatment resistance and significantly reduces patient survival. Similarly, 1q21 amplification is correlated with aggressive disease biology and poor clinical outcomes.

In contrast, standard-risk abnormalities are generally associated with more favorable prognoses. These include translocations such as t(11;14) [7] and t(6;14), which often respond well to treatment and may benefit from targeted therapies in selected cases. In addition, hyperdiploidy, characterized by the gain of odd-numbered chromosomes such as 3, 5, 7, 9, 11, and 15, is commonly associated with a more indolent disease progression and improved survival. Recurrent cytogenetic abnormalities detected at diagnosis or during relapse provide insights into the clonal evolution, aiding in treatment adjustments and predicting treatment resistance.

FISH is a crucial cytogenetic method for the detection of chromosomal abnormalities in MM, surpassing karyotyping in terms of practicality and reliability. It is exceptional in its capacity to analyze non-dividing plasma cells, its high specificity for identifying clinically significant abnormalities (e.g., IGH translocations and del(17p)), and its effectiveness with reduced sample sizes. FISH analysis is capable of

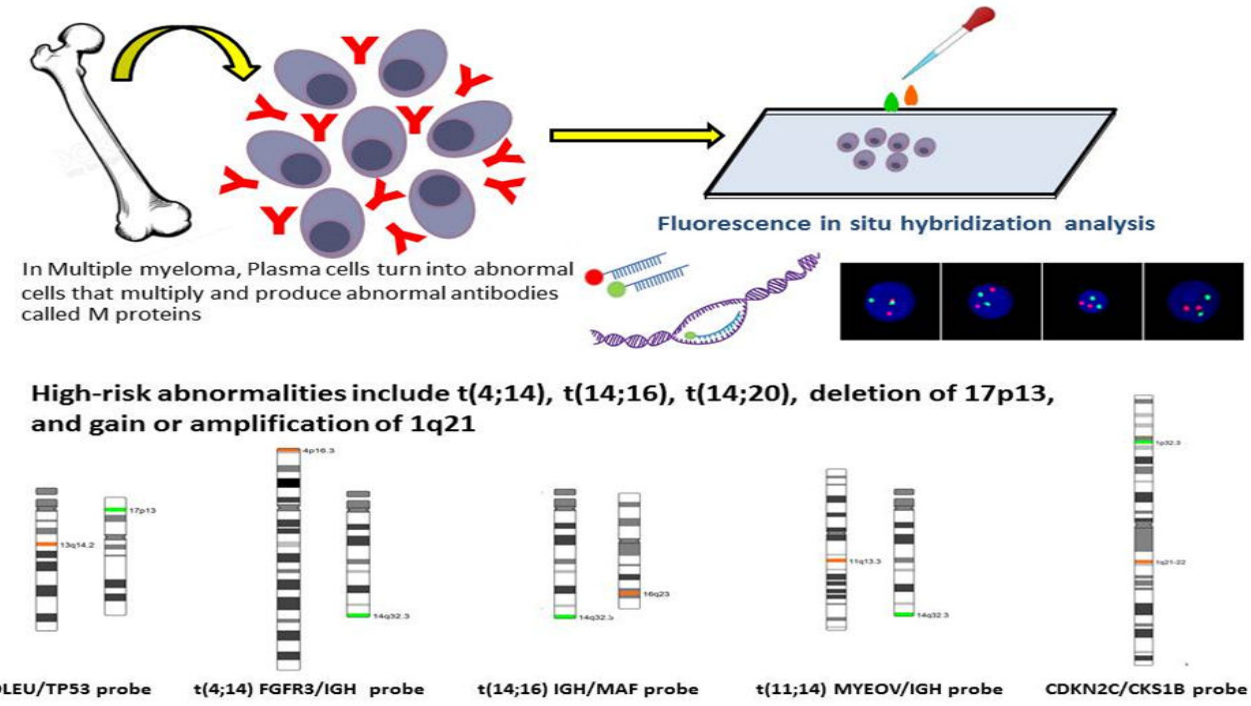

Figure 1. In multiple myeloma, Fluorescence *in situ* hybridization (FISH) is a genetic test that identifies chromosomal changes in myeloma cells. FISH results help hematologists classify the risk level of a patient's myeloma, which can inform treatment decisions. For example, specific abnormalities like t(4;14), t(14;16), or deletion 17p are considered high-risk according to multiple myeloma risk stratification systems.

detecting submicroscopic abnormalities, providing quicker results, and maintaining a high success rate, even in the event of karyotyping failure. Furthermore, FISH is essential for the diagnosis of MM, risk stratification, and timely implementation of treatment decisions, as it offers quantitative data to assess the disease burden. [8]

The prevalence of these abnormalities can vary by population due to genetic, environmental, and healthcare-related factors. Studies in Asian populations, including Thailand, suggest slightly different incidences of certain abnormalities, which are likely due to ethnic and regional genetic predispositions. The prevalence of cytogenetic abnormalities in MM among Asian populations has been the subject of various studies, revealing similarities and unique patterns compared to Western cohorts. [9-15]

The high cost and limited financing within the state welfare system present substantial challenges when implementing FISH analysis in resource-constrained settings in Thailand. Many laboratories are unable to afford the cost of specialized probes, advanced apparatus, and skilled personnel. Moreover, financial strain is frequently imposed on patients, particularly those in low-income groups, as they are frequently required to pay a co-payment for the test. In rural areas, timely and accurate diagnosis is restricted by the limited access to FISH analysis, which impacts the treatment decisions and patient outcomes. The limitations of FISH testing in MM prevent clinicians from ordering all probes, which results in the majority of patients selecting only one or two tests. This is due to the patient co-payment requirements, which are financially unaffordable for those with limited financial resources. As a result, most clinicians prioritize one or two specific probes based on clinical utility and cost-effectiveness. The commonly ordered probes include t(4;14), t(14;16), and del(17p), given their well-established roles in risk stratification and treatment planning. [6] However, this selective approach could lead to an incomplete understanding of the genetic landscape, potentially overlooking other important cytogenetic abnormalities such as 1q21 amplification [13] or t(11;14). This may hinder comprehensive risk stratification and tailored treatment approaches, particularly in cases with complex or ambiguous clinical presentations. This study aimed to investigate the incidence of cytogenetic abnormalities detected by FISH in MM over seven years in a Thai population.

Materials and methods

This study was a retrospective analysis based on data retrieved from the cytogenetic laboratory database at King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand. Bone marrow samples were collected from patients with MM between January 2018 and December 2024. The study cohort consisted of 360 patients with MM who underwent FISH analysis for cytogenetic evaluation within one year of diagnosis. Of these, 49.7% were male and 50.3% were female, with a mean age of 64.8 years in males and 64.5 years in females. Standard laboratory protocols were followed for sample processing and analysis. Bone marrow aspirates were aseptically collected in sterile containers containing heparin as an anticoagulant to prevent clotting. The samples were processed immediately to preserve cellular integrity and ensure optimal conditions for cytogenetic analysis. Informed consent was obtained from all patients at the time of sample collection for cytogenetic analysis.

Direct harvesting protocol

The bone marrow aspirates were mixed gently. A hypotonic solution (0.068 M potassium chloride) was added to the specimen, and the mixture was incubated at 37°C for 20–30 min to swell the cells. The cells were fixed by gradually adding a fresh fixative solution (methanol:acetic acid in a 3:1 ratio), followed by repeated washes to remove debris and improve chromosomal clarity.

The clear cell pellets were diluted with a few drops of fixative, and 20 µL of cell suspension was dropped on a clean microscopic slide. The slides were kept at room temperature for a few hours to air dry. Thereafter, the slides were processed for FISH analysis following the manufacturer's protocol using locus-specific probes targeting clinically significant genetic abnormalities in MM (MetaSystems GmbH, Altlussheim, Germany). The slides were subjected to automated slide scanning, where the mononuclear cells are identified using a software classifier, Metacyte (MetaSystems GmbH). Probes used for the identification of the key abnormalities (MetaSystems GmbH) are as follows: XL t(4;14) FGFR3/IGH DF, XL t(11;14) CCND1/IGH DF, XL t(14;16) IGH/MAF DF, XL DLEU/TP53 Deletion probe, and XL CDKN2C/CKS1B Enumeration probe.

Statistical analysis

The prevalence rates of cytogenetic abnormalities were detected by each probe. The data are expressed as a percentage and a ratio.

Results

FISH analysis was requested for a total of 360 MM cases from 2018 to 2024. Among these, 16.7% requested one probe, 40.8% requested two probes, 33.1% requested three probes, 8.3% requested four probes, and 1.1% requested five probes. **Table 1** shows that the most often requested probe was DLEU/TP53, accounting for 96.7% of requests. The t(4;14) probe was the second most commonly requested, accounting for 83.1% of requests. The t(14;16) probe was the third most frequently requested, accounting for 44.2% of requests. The t(11;14) probe was the fourth most commonly requested, accounting for 9.2% of total requests. The probe that was least requested by clinicians was CDKN2C/CKS1B, which accounted for 3.3% of total orders.

Abnormalities were identified in 47.4% of the patients analyzed using the DLEU/TP53 probe, with 25.9% of these instances demonstrating *TP53* del(17p) (25.0% of all MM cases). The *DLEU* del(13q) was identified in 11.8% of FISH results, which corresponds to 11.4% of all tested patients with MM. The deletion rates for the *DLEU* and *TP53* loci were both 5.7%. Typical and atypical fusions were detected in 8.4% (6.9% of MM cases) using the t(4;14) probe. Other 14q rearrangements were identified in 23.1% (11.4% of MM cases), and hyperdiploidy (+4) occurred in 9.4%. Only 1.3% (0.6% of MM cases) of the cases examined using the t(14;16) probe had typical and atypical fusions. Whereas other 14q rearrangements were identified in 32.7% of patients (8.6% of MM cases), and 13.2% of cases exhibited hyperdiploidy. In 3.0% (0.3% of MM cases), the t(11;14) probe test identified typical and atypical fusions. Moreover, the other 14q rearrangements were identified in 36.4% (1.4% of MM patients), while hyperdiploidy (+11) was noted in 21.2% of MM cases. This is illustrated in **Table 1.**

Discussion

The findings from this seven-year study highlight the importance of cytogenetic abnormalities in MM management. In this study, the DLEU/TP53 probe was the most frequently requested, followed by t(4;14), t(14;16), t(11;14), and CDKN2C/CKS1B. Therefore, the higher frequency of detected abnormalities in DLEU/TP53 likely reflects probe utilization patterns rather than the true incidence of these abnormalities **(Figure 1)**. Due to the selective testing approach driven by financial constraints, the true comparative prevalence of all cytogenetic abnormalities cannot be determined in this study. Globally, the incidence of abnormalities such as t(4;14), t(14;16), del(17p), and gain of 1q varies but aligns with the literature on the adverse prognostic implications of these markers. [9, 12, 14] Comparatively, the incidence rates observed in this Thai population highlight some unique regional trends. For example, while t(11;14) is a relatively common translocation worldwide, its frequency in this study was lower [7], which is consistent with reports from other Asian populations. This suggests possible ethnic or genetic influences on the pathogenesis of MM and warrants further exploration. Regional studies have revealed that Asian populations might exhibit distinct cytogenetic patterns compared to those of Western cohorts, such as a higher prevalence of hyperdiploidy or certain chromosomal gains. [9, 11, 12, 14-16] Recent studies from Asia have provided additional insights into the incidence of cytogenetic abnormalities in MM detected by FISH analysis. **Table 2** summarizes the findings from selected Asian countries. These variations could arise from genetic predispositions, environmental exposures, or differences in healthcare practices. This study contributes to a more comprehensive understanding of MM in Southeast Asia, offering a crucial foundation for tailored risk stratification and treatment approaches. [12]

The observed cytogenetic patterns have important implications for MM management in Thailand. High-risk abnormalities such as del(17p) and gain of 1q, which were prevalent in this cohort, emphasize the necessity for their routine assessment during diagnosis. However, the limited use of certain probes, as seen in the low testing rates for 1q21 amplification, reflects a critical gap in comprehensive risk stratification.

The selective testing approach, dictated by financial constraints, might lead to suboptimal treatment decisions, particularly for patients who present with complex clinical features. To improve patient outcomes, healthcare policies should prioritize the inclusion of comprehensive FISH panels in their standard diagnostic protocols and subsidize their costs to ensure equitable access.

Table 1. Illustrated the incidence of recurrent cytogenetic abnormalities detected by each specific probe

Dual fusion probes	**Percent of tests requested**	**Typical/atypical fusions (%)**		**Other 14q rearrangement (%)**		**Hyperdiploidy (%)**		
		Total tests	**Total cases**	**Total tests**	**Total cases**	**Ch**	**Total tests**	**Total cases**
t(4;14) FGFR3/IGH	83.1	8.4	6.9	23.1	11.4	+4	9.4	7.8
t(11;14) CCND1/IGH	9.2	3.0	0.3	36.4	1.4	+11	21.2	1.9
t(14;16) IGH/MAF	44.2	1.3	0.6	32.7	8.6	+16	13.2	5.8
Enumeration probes	**Percent of tests requested**	**Deletion or duplication total tests/total cases (%)**						
DLEU/TP53	96.7	del(13q) = 17.5/16.9 del(17p) = 31.6/30.6						
CDKN2C/CKS1B	3.3	Gain/amplification of 1q = 16.7/0.6						

(%) Total tests, positive finding/number of tests requested of each probe

(%) Total cases, positive finding/total MM cases requested for FISH analysis

Table 2. The incidence of recurrent cytogenetic abnormalities in MM, as detected by FISH analysis, varies across different populations. This is a summary table highlighting the frequencies of key cytogenetic abnormalities in MM patients from selected countries.

Cytogenetic abnormality	**Taiwan (%)**	**India (%)**	**Morocco (%)**	**Western countries (%)**	**China (%)**	**Asian myeloma network study (%)**	**Thailand (%)**
t(4;14)(p16;q32)	8.7	8.6	14	10 - 15	14	10.5	6.9
t(11;14)(q13;q32)	8.7	6	N/A	15 - 20	11.8	17.4	0.3
t(14;16)(q32;q23)	1.3	1.8	N/A	2 - 5	N/A	4.4	0.6
1q21 Gain	38.1	35.5	13	35 - 40	46.1	N/A	0.6
17p Deletion	10.4	8.6	12	10	9.9	13.3	30.6
Hyperdiploidy	29.2	41	9	50 - 60	N/A	N/A	N/A
13q Deletion	N/A	4.7	N/A	N/A	N/A	12.7	16.9

N/A, not available

FISH testing remains the cornerstone of MM cytogenetic analysis, but its implementation in resource-constrained settings, such as Thailand, faces substantial barriers. The high cost of probes and equipment, coupled with limited funding within the state welfare system, restricts access to this essential diagnostic tool. [6] Patients from low-income groups often bear the financial burden of co-payments, which leads to selective probe ordering based on affordability rather than clinical necessity.

This financial limitation hinders complete genetic profiling and disproportionately affects rural and underserved populations, where access to advanced diagnostics is already limited. Strategic interventions are required to address these barriers, such as cost-reduction initiatives, government subsidies, and public-private partnerships to expand diagnostic capabilities.

This study has several limitations. First, the use of FISH probes was selective, largely driven by financial constraints within the state welfare system. Clinicians frequently prioritized one or two probes based on their perceived clinical utility and cost-effectiveness, which may have led to the omission of other clinically significant abnormalities, such as 1q21 amplification, thereby resulting in incomplete risk stratification. Second, the sample size for certain abnormalities was small. The limited testing of specific probes, such as t(11;14) and 1q21 amplification, restricted the ability to accurately determine their true incidence and clinical relevance in the Thai population. Third, as the study was performed at a single cytogenetic laboratory, the findings may not be representative of the broader Thai population or reflect variations in healthcare access and diagnostic capabilities across the different regions of the country. Lastly, the study relied exclusively on FISH analysis due to its practicality in resource-limited settings. Although FISH is effective for detecting key chromosomal abnormalities, it does not identify gene-level mutations or submicroscopic changes, which could provide further insights into the disease pathogenesis and prognosis. Addressing these limitations in future research may improve the understanding of MM cytogenetics in Thailand and contribute to more comprehensive and equitable diagnostic strategies. To overcome the limitations of current practices, integrating next-generation sequencing (NGS) with FISH could provide a more comprehensive genetic analysis, capturing chromosomal abnormalities and gene-level mutations. While NGS may currently be cost-prohibitive, advancements in technology and potential cost reductions could make it an available option in the future. [17]

Conclusion

This study highlights the crucial role of FISH analysis in identifying key cytogenetic abnormalities in MM, with substantial implications for risk stratification and treatment decisions in Thailand. Despite the challenges posed by financial constraints, the findings emphasize the need for equitable access to comprehensive diagnostics to improve patient outcomes. Collaborative efforts to address these limitations, in addition to advancements in genomic technologies, could revolutionize MM management in resource-limited settings. In summary, while there are overarching similarities in the cytogenetic landscape of MM between Asian and Western populations, distinct differences exist that warrant further investigation to optimize management strategies for Asian patients.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Data sharing statement

All data generated or analyzed in the present study are included in the published article. Further details are available for non-commercial purposes from the corresponding author upon reasonable request.

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