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EDITORIAL

# Challenges and Promises of Genetic Stratification of Risk in Multiple Myeloma

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Multiple myeloma resembles solid tumours at several levels: it develops and progresses through a well-delineated sequence of pre-malignant and asymptomatic stages, it represents a genetically highly complex and heterogeneous disease, and the laboratory diagnosis of its genetic abnormalities stringently mandates specific testing of the malignant cells, and not the other non-neoplastic marrow components [1]. Also, in contrast to acute leukemias, a focussed testing approach using a single technique i.e. fluorescent in situ hybridization (FISH)-based cytogenetic studies, is highly informative in myeloma. However, FISH is best performed on flow cytometrically sorted plasma cells, or in conjunction with cytoplasmic immunoglobulin staining to ensure specificity [2]. Conventional metaphase cytogenetics in contrast is easier, but has a diminishing role in this disease since it primarily indicates plasma cell proliferation and is insensitive to several of the genetic lesions [3]. Newer molecular level techniques holding out the promise of greater prognostic information also loom on the horizon.

Genetic abnormalities in myeloma can be grouped conceptually into two classes: the primary cytogenetic abnormalities include recurrent trisomies of odd-numbered chromosomes, 3, 5, 7, 9, 11, 15 and 17 and translocations involving the IgH locus. Mutually-exclusive across patients, they start appearing in MGUS and influence its initial pathogenesis. The few patients ($\sim$3%) who do not show these changes are believed to harbour either rarer untested abnormalities, or have laboratory technical restrictive issues like too few malignant cells or an inappropriate probe sequence. Secondary cytogenetic abnormalities, on the other hand, accumulate as the disease progresses, and more than one may occur in the same patient. They include del(13q), del(17p), del(1p), gain(1q21) and *MYC* translocations, with all except del(13q), indicating an adverse prognosis [1–3].

Cytogenetics predicts the risk of progression of disease at all stages from MGUS to overt symptomatic myeloma and increasingly impacts clinical decisions. For instance, finding high-risk abnormalities like t(4;14), del(17p) and gain(1q21) in smouldering multiple myeloma (SMM) should lead to a close follow-up and possibly, an offer of enrolment in an early intervention trial [4]. Interestingly, the prognostic connotation of cytogenetics is different at different stages and ages. Trisomies, for example, can indicate a greater risk of transformation of SMM to overt disease, but in a symptomatic myeloma patient may actually mean a *lower* risk of end-stage disease [3–5]. Similarly, data show that IgH translocations decrease with age and that p53 deletions in del(17p) are more ominous in patients aged over 60 years [6].

In addition to disease evolution, cytogenetics also correlates with clinical presentations. Greenberg et al. [7] have shown that patients with t(14;16) have a propensity for renal dysfunction and those with t(4;14) have very high free light chain levels, while patients showing t(11;14) or t(6;14) tend to present with bone disease. Genetic markers can also be both *prognostic* (i.e. indicate the likely outcome of the disease) as well as *predictive* (i.e. provide specific information about the likelihood of response or adverse events to a particular therapeutic agent or modality) [8]. Results can aid the selection of appropriate therapies. For instance, patients with t(4;14) respond better to regimens incorporating bortezomib and autologous transplantation

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while those with trisomies fare better with lenalidomide-containing regimens [3, 8].

Historically, molecular genetics has lagged behind cytogenetics in myeloma. Conventional reverse-transcriptase PCRs that are extremely useful in detecting recurring translocations in acute leukemias are challenging to design across the highly variable IgH locus and are also affected by variations in plasma cell numbers in samples. However, the increasing availability of magnetic and fluorescence-activated cell sorters has opened doors for direct application of high-end tools like gene-expression profiling (GEP) and SNP-array analysis on sorted malignant cells. GEP requires RNA extraction and bioinformatics. Several gene panels have been tested, with the number of interrogated/differentially-expressed genes varying from 6 to over 150, often different in different studies. A feasible 10-gene (chromosomal instability) signature and a comprehensive TC-classification (based on translocations and cyclin D expression) were developed early on, with the latter even finding mention in the 2008-version of the WHO classification [9, 10]. However, the lack of user-friendly, highly-reproducible platforms/chips means that GEP is yet to make a true switch from research to routine clinical practice [8]. PCR-based SNP-array analysis and array comparative genomic hybridization have been used to investigate the cytogenetic basis of myeloma. For instance, the SNP-arrays first demonstrated the poor prognosis of gain(1q) [11]. Although technically much more complex than FISH, they offer the advantages of diagnosing lesions at unsuspected loci as well. Next-generation sequencing, as everywhere else too, is being applied to myeloma. Studies describing its utility ranging from unravelling the genetic basis of gammopathy predisposition to practical applications in minimal residual disease detection are already available in literature [12, 13].

In the midst of these developments, it is instructive to remember that among the most robust risk stratification models applicable to over 90% myeloma patients even today is combining the ISS (International Staging System using albumin and β2-microglobulin) with a limited FISH panel for t(4;14), del 17p13 and gain(1q21) [3, 8]. Thus, the future goal should be to develop a practical approach to defining clinically relevant genetic heterogeneity in this enigmatic and challenging disorder.

## References


1. Hervé AL, Florence M, Philippe M, Michel A, Thierry F, Kenneth A, Jean-Luc H, Nikhil M, Stéphane M (2011) Molecular heterogeneity of multiple myeloma: pathogenesis, prognosis, and therapeutic implications. J Clin Oncol 29:1893–1897
2. Moore S, Suttle JM, Nicola M (2017) Cytoplasmic immunoglobulin light chain revelation and interphase fluorescence in situ hybridization in Myeloma. Methods Mol Biol 1541:127–142
3. Rajan AM, Rajkumar SV (2015) Interpretation of cytogenetic results in multiple myeloma for clinical practice. Blood Cancer J 5:e365
4. Dispenzieri A, Stewart AK, Chanan-Khan A, Rajkumar SV, Kyle RA, Fonseca R, Kapoor P, Bergsagel PL, McCurdy A, Gertz MA, Lacy MQ, Lust JA, Russell SJ, Zeldenrust SR, Reeder C, Roy V, Buadi F, Dingli D, Hayman SR, Leung N, Lin Y, Mikhael J, Kumar SK (2013) Smoldering multiple myeloma requiring treatment: time for a new definition? Blood 122:4172–4181
5. Rajkumar SV, Gupta V, Fonseca R, Dispenzieri A, Gonsalves WI, Larson D, Ketterling RP, Lust JA, Kyle RA, Kumar SK (2013) Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. Leukemia 27:1738–1744
6. Ross FM, Ibrahim AH, Vilain-Holmes A, Winfield MO, Chiecchio L, Protheroe RK, Strike P, Gunasekera JL, Jones A, Harrison CJ, Morgan GJ, Cross NC, UK Myeloma Forum (2005) Age has a profound effect on the incidence and significance of chromosome abnormalities in myeloma. Leukemia 19:1634–1642
7. Greenberg AJ, Rajkumar SV, Therneau TM, Singh PP, Dispenzieri A, Kumar SK (2014) Relationship between initial clinical presentation and the molecular cytogenetic classification of myeloma. Leukemia 28:398–403
8. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, Munshi N, Palumbo A, Miguel JS, Sonneveld P, Cavo M, Usmani S, Durie BG, Avet-Loiseau H, International Myeloma Working Group (2014) IMWG consensus on risk stratification in multiple myeloma. Leukemia 28:269–277
9. Zhan F, Huang Y, Colla S, Stewart JP, Hanamura I, Gupta S, Epstein J, Yaccoby S, Sawyer J, Burington B, Anaissie E, Hollmig K, Pineda-Roman M, Tricot G, van Rhee F, Walker R, Zangari M, Crowley J, Barlogie B, Shaughnessy JD Jr (2006) The molecular classification of multiple myeloma. Blood 108:2020–2028
10. Bergsagel PL, Kuehl WM (2005) Molecular pathogenesis and a consequent classification of multiple myeloma. J Clin Oncol 23:6333–6338
11. Kamada Y, Sakata-Yanagimoto M, Sanada M, Sato-Otsubo A, Enami T, Suzukawa K, Kurita N, Nishikii H, Yokoyama Y, Okoshi Y, Hasegawa Y, Ogawa S, Chiba S (2012) Identification of unbalanced genome copy number abnormalities in patients with multiple myeloma by single-nucleotide polymorphism genotyping microarray analysis. Int J Hematol 96:492–500
12. Amend SR, Wilson WC, Chu L, Lu L, Liu P, Serie D, Su X, Xu Y, Wang D, Gramolini A, Wen XY, O'Neal J, Hurchla M, Vachon CM, Colditz G, Vij R, Weilbaecher KN, Tomasson MH (2015) Whole genome sequence of multiple myeloma-prone C57BL/KaLwRij mouse strain suggests the origin of disease involves multiple cell types. PLoS ONE 10:e0127828
13. Bolli N, Li Y, Sathiaseelan V, Raine K, Jones D, Ganly P, Cocito F, Bignell G, Chapman MA, Sperling AS, Anderson KC, Avet-Loiseau H, Minvielle S, Campbell PJ, Munshi NC (2016) A DNA target-enrichment approach to detect mutations, copy number changes and immunoglobulin translocations in multiple myeloma. Blood Cancer J 6:e467