MYC break-apart FISH probe set reveals frequent unbalanced patterns of uncertain significance when evaluating aggressive B-cell lymphoma

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Few reports have assessed the breadth of MYC FISH rearrangement patterns in DLBCL and HGBL. In a cohort including 51 cases of MYC-R DLBCL detected by FISH BAP, Copie-Bergman et al., identified a MYC/IGH fusion in 23 cases, a MYC/IGL fusion in 1 case and no IG partner was observed in 26 cases [5]. In a larger patient cohort by Rosenwald et al., encompassing 264 MYC-translocated DLBCL patients, rearrangements involved an IG partner in 107 cases while 88 cases did not display an IG partner [3]. In a previous study by our group including 87 MYC-R cases, the rearrangement partner was IGH in 39, IGL in 7, IGK in 6 and no IG partner was observed in 35 cases [6]. However, there is an overall dearth of literature pertaining to atypical MYC rearrangements by FISH BAP. Our work calls attention to this phenomenon of uncertain significance and its unexpectedly high frequency. While our observations suggest that some of these unbalanced cases appear to represent true MYC rearrangements, as identified by fusion signals with the IG heavy or light chain loci on DF FISH assays, the significance of cases for which no IG partner is identifiable remains unclear (accounting for 7.5% of total cases and 63.0% of unbalanced cases), as these could arise from different genomic alterations such as rearrangements with non-IG partners but also deletions or others. Our study underscores the importance of delineating the genomic mechanisms underlying these atypical FISH findings to allow accurate interpretation of results, especially considering that in multiple myeloma, these have been shown to represent true MYC rearrangements [12].

Importantly, the clinical and prognostic significance of atypical MYC signals by break-apart FISH assays also remain unresolved. As a large reference clinical genomics laboratory with the inability to obtain comprehensive clinical data for patients treated at other institutions, our study is limited by the absence of outcome data to elucidate potential differential prognostic implications of distinct FISH patterns. Additional work to correlate atypical MYC findings with clinical information should be sought. It should also be noted that we solely focused on MYC rearrangements as identified by BAP FISH strategy. However, our group and others have previously highlighted false negative findings with MYC BAP assays, which may occur at a rate of at least 4% [9, 10, 13–15]. Finally, our study may include cases for which the final diagnosis was not restricted to DLBCL or HGBL, a limitation which is inherent to investigation algorithms of suspected aggressive B-cell lymphoma.

In summary, our study provides the largest portrayal of MYC FISH patterns in aggressive B-cell lymphomas evaluated in paraffin tissue. Importantly, our findings enable appreciation for the existence of frequent unbalanced MYC FISH results with the most used FISH strategy, a MYC BAP probe, resulting in 11.9% of total MYC rearrangement cases with an unbalanced BAP MYC result. In addition, the concurrent application of all 3 DF probes (MYC/IGH, MYC/IGL and MYC/IGK), which are not available/applied in most genomics laboratories, still resulted in 7.5% of total MYC-R cases with an unbalanced BAP MYC result of unclear significance. The genomic alterations leading to these unbalanced FISH patterns should be further explored to guide appropriate interpretation in the clinical laboratory. As a diagnosis of HGBL with MYC and BCL2 and/or BCL6 rearrangements relies, amongst others, on the identification of a MYC rearrangement in a lymphoma with otherwise variable morphology, it is imperative to understand the significance of these atypical FISH findings.
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AUTHOR CONTRIBUTIONS

MG wrote the manuscript; KEP, RPK analyzed the raw data; MG, KEP, RPK, PTG, XX, NLH, EDM, RLK, LBB, JFP reviewed and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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