New assay helps determine lymphoma subtypes simply, quickly, and inexpensively

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With the advent of targeted lymphoma therapies on the horizon, it becomes increasingly important to differentiate the two major subtypes of diffuse large B-cell lymphoma (DLBCL), which is the most common non-Hodgkin lymphoma. These are germinal center B-cell-like (GCB) and activated B-cell-like (ABC), which differ in management and outcomes. A report in The *Journal of Molecular Diagnostics* describes use of the reverse transcriptase?multiplex ligation-dependent probe amplification (RT-MLPA) assay for differentiating DLBCL subtypes. RT-MLPA is as accurate as the current gold standard technology and offers advantages such as simplicity, flexibility, short turnaround time, low cost, and efficiency.

"Differences in the progression of the disease and clinical outcomes can, at least in part, be explained by the heterogeneity of lymphoma, which can be classified into two major subtypes with different outcomes. Unfortunately, these lymphomas are morphologically undistinguishable in routine diagnosis, which is a major problem for the development of targeted therapies. Furthermore, array-based gene expression profiling (GEP), which is considered the gold standard for discriminating these tumors, remains poorly transposable to routine diagnosis, and the surrogate immunohistochemical (IHC) algorithms that have been proposed are often considered poorly reliable," explained lead investigator Philippe Ruminy, PhD, of the Centre Henri Becquerel, Institute for Research and Innovation in Biomedicine, University of Rouen (France).

Investigators evaluated a simple and rapid RT-MLPA assay. They analyzed lymph node biopsies from 259 patients with de novo DLBCL, including 195 patients from the Centre Henri Becquerel and 64 from an external group (the Lymphoma Study Association).

The RT-MLPA assay was compared to the gold standard method of distinguishing the two lymphoma subtypes. In a training series of 50 randomly selected DLBCL cases, the new method classified 90% of the cases into the expected subtypes (20 GCB and 25 ABC), whereas 10% were considered unclassifiable. In a second independent validation series, 93% of 65 samples were classified correctly with RT-MLPA.

The investigators also showed that RT-MLPA is sensitive for analyzing archived formalin-fixed, paraffin-embedded (FFPE) tissue samples. Comparison of samples from paired frozen and FFPE biopsies showed that the RT-MLPA assay correctly classified 89.3% of 28 cases. "Because RT-MLPA requires only short cDNA fragments for the correct binding and ligation of the gene-specific oligonucleotide probes, it is less affected by the use of low RNA concentrations and RNA degradation. It could thus be used for the retrospective analysis of archival collections and for the inclusion of patients in prospective clinical trials, because only a few institutions routinely collect frozen biopsy material," noted Dr. Ruminy.

To evaluate the prognostic value of the assay, the researchers looked at survival in 135 treated lymphoma patients diagnosed between 2001 and 2011. They found that patients determined to have the ABC subtype by the RT-MLPA assay had significantly worse progression-free survival and overall survival than those with the GCB subtype. They also found that expression of several individual genes within the MLPA signature was significantly associated with prognosis (ie, high LMO2, high BCL6, and low TNFRSF13B expression).

"The robust and cost-effective RT-MLPA assay can yield results within one day and requires reagents costing less than $5 per sample. Since RT-MLPA utilizes materials and equipment that are standard in many laboratories, the process can easily be implemented for routine use," stated Dr. Ruminy.

More information: "Accurate Classification of Germinal Center B-Cell-Like/Activated B-Cell-Like Diffuse Large B-Cell Lymphoma Using a Simple and Rapid Reverse Transcriptase Multiplex Ligation-Dependent ProbeAmplification Assay: A CALYM Study," DOI: 10.1016/j.jmoldx.2015.01.007. Published online ahead of *The Journal of Molecular Diagnostics*, Volume 17, Issue 3 (May 2015) published by Elsevier.

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