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Common Origins and Somatic Mutation Patterns of Composite Lymphomas - Two Models of Lymphomagenesis

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In rare instances, two histopathologically distinct lymphoid malignancies occur concurrently in a patient, which is termed a composite lymphoma. It is a major question whether the two lymphomas derive from the same lymphocyte or occurred independently. Even if the lymphomas do not derive from the same mature B or T cell, they may originate from a common pre-malignant cell, considering that some mutations in lymphomagenesis may already occur in hematopoietic stem or precursor cells. Here, we studied four cases of combined classical Hodgkin lymphoma (HL) and B cell non-Hodgkin lymphoma (B-NHL) as well as two instances of combined B-NHL and T cell lymphoma by analyzing whole exome sequencing (WES) data for shared and distinct somatic mutations.

For the composite HL and B-NHL cases, their relationships were also studied by determining their rearranged IgV genes. The analysis revealed that in three of the composite lymphomas, the HL and the B-NHL were derived from the same germinal center (GC)-experienced B cell, while in the fourth HL/B-NHL case, the malignancies originated from separate B cells. The three cases with clonally related lymphomas also share somatic mutations according to WES analysis, whereas the other three cases do not. We analyzed the somatic mutations that were only found in one of the lymphoma partners, as these may represent later events that lead to morphological and clinical differences between the two types of lymphoid malignancy. In addition, we identified somatic variants in lymphoma-related genes that were already present in the non-tumor control cells in two of the composite lymphoma cases that were not clonally related, indicating that early germline/hematopoietic variants may also contribute to lymphomagenesis in combined lymphomas/leukemias.