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Genetic mechanism for the loss of *PRAME* in B cell lymphomas

Marek Mraz

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Letter to the Editor | Immunology

To the Editor: Takata et al. (1) reported that patients with diffuse large B cell lymphoma (DLBCL) relatively frequently (13% of patients) harbor a deletion at the 22q11.22 locus that involves the PRAME gene, and that PRAME loss is associated with poor outcomes and leads to cytotoxic T cell immune escape. The authors comment that “deletions...were located close to the Igλ gene.” I would like to bring to the attention of the authors and readers that the PRAME gene and neighboring ZNF280A, ZNF280B, and GGTLC2 genes are located between variable (V) subgenes for the immunoglobulin lambda (Igλ) light chain (Figure 1). The PRAME deletion is inevitable when a B lymphocyte (normal or malignant) rearranges the Igλ locus and utilizes one of the many V subgenes located more distantly from the J-C region. It is known that approximately 30% to 40% of B lymphocytes express Igλ (~60%–70% express Igκ, since this locus for the Ig light chain is rearranged before Igλ). Therefore, it is not surprising that the loss of PRAME has been previously noted in multiple B cell malignancies, especially chronic lymphocytic leukemia (2–4). Takata et al. (1) observed that patients with PRAME deletions more often have an Igλ rearrangement, but they also report cases of DLBCL with a PRAME deletion and rearranged Igκ. However, it is not clear if […]

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To the Editor: Takata et al. (1) reported that patients with diffuse large B cell lymphoma (DLBCL) relatively frequently (13% of patients) harbor a deletion at the 22q11.22 locus that involves the *PRAME* gene, and that *PRAME* loss is associated with poor outcomes and leads to cytotoxic T cell immune escape. The authors comment that "deletions...were located close to the Igλ gene." I would like to bring to the attention of the authors and readers that the *PRAME* gene and neighboring *ZNF280A, ZNF280B*, and *GGTLC2* genes are located between variable (V) subgenes for the immunoglobulin lambda (Igλ) light chain (Figure 1). The *PRAME* deletion is inevitable when a B lymphocyte (normal or malignant) rearranges the Igλ locus and utilizes one of the many V subgenes located more distantly from the J-C region. It is known that approximately 30% to 40% of B lymphocytes express Igλ (~60%–70% express Igκ, since this locus for the Ig light chain is rearranged before Igλ). Therefore, it is not surprising that the loss of *PRAME* has been previously noted in multiple B cell malignancies, especially chronic lymphocytic leukemia (2–4). Takata et al. (1) observed that patients with *PRAME* deletions more often have an Igλ rearrangement, but they also report cases of DLBCL with a *PRAME* deletion and rearranged Igκ. However, it is not clear if in such cases the Igκ rearrangement was productive and what the status of the Igλ locus was. A defective allelic exclusion process might lead to Igκ and Igλ expression in one B cell. *PRAME* deletion associates with prognosis in DLBCL (1), but it should be considered that such a deletion could also be viewed as a surrogate marker for the use of one of the distal Igλ V subgenes (Figure 1), and it is known that Igλ usage associates with prognosis and B cell receptor (BCR) pathway deregulation in B cell malignancies (5).

In summary, loss of *PRAME* is an expected phenomena in a portion of normal or malignant B cells with Igλ rearrangement. It remains puzzling why in evolution *PRAME* has been placed between Igλ subgenes and why its expression is activated in DLBCL.

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Conflict of interest: The author has declared that no conflict of interest exists.

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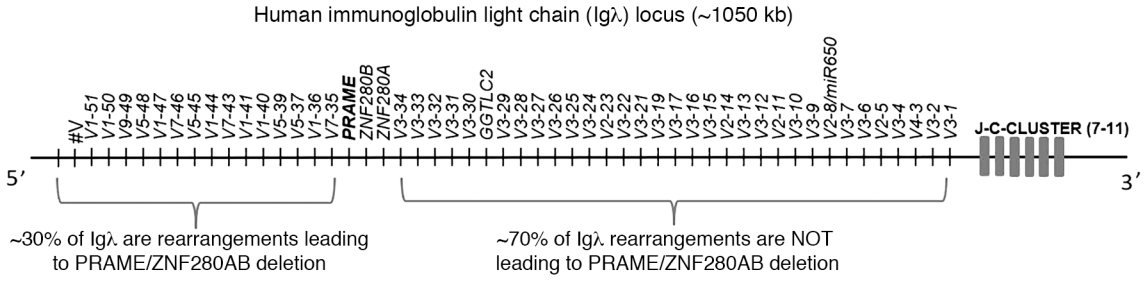

Figure 1. Schematic of the human Igλ locus organization and the location of the *PRAME* gene.

See related response: https://doi.org/10.1172/JCI161979.