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Identification of Rare HLA Alleles with Non-Coding Region Variants by NGS and Their in Silico Evaluation at the Eplet Level

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Abstract

Objective: Genetic variation within the HLA region plays a pivotal role in transplantation compatibility and the shaping of immune responses. Next-generation sequencing (NGS) technology enables the detection of non-coding region variants that cannot be identified by conventional methods, thereby allowing a more comprehensive assessment of HLA allelic diversity. However, the structural differences of these rare variants at the eplet level and their potential immunogenic effects on KIR-ligand epitopes, namely Bw4/Bw6 and C1/C2 groups, have not yet been fully elucidated.

Materials and Methods: In this study, rare HLA alleles harboring non-coding region variants were identified among 15,350 HLA alleles characterized by NGS at the Tissue Typing Laboratory of Istanbul Faculty of Medicine. These alleles were validated and named through comparison with reference sequences in the IPD-IMGT/HLA database. The identified alleles were as follows: A02:01:01:164, A02:01:01:118, A02:06:01:15, A23:39, A24:02:01:02L, A24:314, A31:234, A02:01:01L, B44:02:01:35, B44:02:01:02S, B51:01:01:17 (in two individuals), B51:01:01:69, B51:11N, B58:01:01:10, C17:38, C02:02:02:47, C12:323, C15:171, DRB113:157, DRB114:23, DRB111:310, DRB401:03:01:02N, and DPB1*1321:01. Eplet characterization of these alleles was performed at the amino acid level by comparison with their respective reference alleles. In addition, Bw4/Bw6 epitopes of HLA-B alleles and C1/C2 epitope characteristics of HLA-C alleles were evaluated.

Results: For the majority of alleles, the observed differences were confined to non-coding regions and did not involve amino acid changes within the antigen-binding domain. Consequently, their eplet profiles and Bw4/Bw6–C1/C2 epitope characteristics were found to be similar to those of the corresponding reference alleles. However, certain alleles—namely C17:38, A23:39, A24:314*, A31:234*, C12:323*, C15:171*, and DRB1*13:157*—were predicted to harbor potential amino acid substitutions within the antigen-binding groove, which could theoretically give rise to novel eplet combinations. Alleles categorized as L, N, and S were also considered to be of potential clinical relevance due to their altered expression patterns.

Conclusion: Rare HLA alleles with non-coding region variants identified by NGS generally exhibit eplet and KIR-ligand (Bw4/Bw6, C1/C2) profiles similar to those of their reference alleles; however, certain variants may still possess immunogenic differences. These findings indicate that the combined evaluation of high-resolution HLA typing results at both the eplet and KIR-ligand levels may provide more precise predictive insights in transplantation immunology.

Keywords: Non-coding, NGS, HLA alleles, eplet analysis

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