

# Hidden Hierarchy of HLA Haplotypes: Resolution-Independent Directional Relationships via Asymmetric Linkage Disequilibrium

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## Abstract

**Objective:** The Human Leukocyte Antigen (HLA) region is characterized by strong Linkage Disequilibrium (LD). However, traditional symmetric LD metrics fail to provide information on the direction of allelic relationships. This study aims to examine the effect of HLA typing resolution on directional relationships detected by Asymmetric Linkage Disequilibrium (ALD) and to investigate whether this hierarchy is a statistical artifact or a reflection of evolutionary architecture.

**Materials and Methods:** High-resolution (8-digit) HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 loci genotyping was performed using Next-Generation Sequencing (NGS) in 150 healthy and unrelated individuals of Central Anatolian origin. The 8-digit data were reduced to 2- and 4-digit levels to analyze three different resolution layers. Standard LD ( $D'$ ) and directional relationships (ALD) between locus pairs were calculated using PyPop v1.2.1 software.

**Results:** Standard LD ( $D'$ ) values increased significantly with higher resolution, showing the strongest signals in C: B ( $D'$ : ~0.94) and DRB1:DQB1 ( $D'$ : ~0.96) pairs. ALD analysis revealed that directional dominance was consistently preserved regardless of allele number or resolution. The predictive power of HLA-C for HLA-B was systematically higher than the reverse direction (C → B dominance) at all resolutions ( $p < 0.0001$ ). Similarly, HLA-DQB1 predicted HLA-DRB1 significantly better than the reverse (DQB1 → DRB1 dominance;  $p < 0.0001$ ). These hierarchies remained stable across 2-, 4-, and 8-digit levels.

**Conclusion:** ALD analysis is a powerful tool for revealing the hierarchical and directional structure of HLA haplotypes hidden by traditional symmetric metrics. The consistency of C → B and DQB1 → DRB1 directional relationships, unaffected by typing resolution, suggests this hierarchy reflects the evolutionary history and functional integrity of the HLA region rather than statistical coincidence. These findings offer new perspectives for mapping genetic architecture and donor selection algorithms.

**Keywords:** HLA antigens, linkage disequilibrium, haplotypes, immunogenetics, ALD

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