

Impact of HLA Typing Resolution on Hardy-Weinberg Equilibrium: How 'Hidden Heterozygosity' Reveals Evolutionary Pressures?

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Abstract

Objective: The extreme polymorphism of the HLA system complicates Hardy-Weinberg Equilibrium (HWE) analyses. Low-resolution typing may create artificial homozygosity by grouping functionally distinct alleles. This study aims to determine how 2-, 4-, and 8-digit HLA typing resolutions systematically alter HWE results and to reveal mechanisms like "hidden heterozygosity".

Materials and Methods: High-resolution (8-digit) genotyping for HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 was performed using Next-Generation Sequencing (NGS) in 150 healthy, unrelated donors from Central Anatolia. The 8-digit data were reduced to 2- and 4-digit levels for comparison. HWE compliance was assessed using the Markov Chain Monte Carlo (MCMC) exact test via PyPop v1.2.1 software.

Results: Allele richness (**k**) increased systematically with resolution (e.g., HLA-B: 23 to 58 alleles), reducing observed homozygosity (e.g., HLA-C: 34 to 14 homozygotes). HWE compliance was highly resolution-sensitive. HLA-B consistently deviated from HWE at all resolutions ($p < 0.05$). Conversely, HLA-C showed deviation only at 2-digit resolution ($p < 0.0001$) but aligned with HWE at 4- and 8-digit levels, indicating a low-resolution artifact. Notably, HLA-DPB1 appeared compatible at lower resolutions but showed significant deviation only at the 8-digit level ($p < 0.0001$), revealing hidden evolutionary pressure.

Conclusion: Low-resolution typing causes a "dilution effect," masking allelic diversity and leading to erroneous HWE assessments. The emergence of significant deviations in loci like DPB1 only at high resolution proves that evolutionary forces are obscured by lower-resolution methods. Therefore, 8-digit typing should be the gold standard for accurate population genetics and disease association studies.

Keywords: HLA antigens, gene frequency, heterozygote, genetics, population, NGS

PP-10

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Published

July 13, 2026

DOI

10.36519/tji.2026.pp10



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