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Immunogenetic Echoes of Demographic Change: A Quarter-Century Temporal Analysis of HLA Evolution at a Single Turkish Centre

Demografik Değişimin İmmunogenetik Yankıları: Türkiye'de Tek Merkezli HLA Evriminin Çeyrek Yüzyıllık Zamansal Analizi

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Abstract

Objective: The distribution of human leukocyte antigen (HLA) allele frequencies is markedly heterogeneous among different populations, largely shaped by unique evolutionary pressures and demographic histories. This study aimed to analyse 25 years of HLA data from Central Western Anatolia to determine how low (2001–2011) and high (2011–2025) migration periods affected the regional HLA gene pool.

Material and Methods: In this retrospective study, HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 data from 6550 healthy donors were analysed. Allele frequency differences were evaluated by Fisher's exact test, and population genetics analyses, including Hardy–Weinberg equilibrium (HWE), were performed using the PyPop software.

Results: The frequencies of 18 alleles changed significantly ($p<0.05$). In the post-2011 period, the frequency of alleles with Middle Eastern/Asian origins (e.g., B*52, DRB1*03) increased, whereas the frequency of European-associated alleles (e.g., B*44, DQB1*05) decreased. The East Asian allele B*46 appeared for the first time, while two low-frequency alleles (DPB1*01, DPB1*19) were no longer detected. The cohort from the high-migration period showed a significant deviation from HWE, and the observed excess of homozygotes indicated a Wahlund effect resulting from population stratification.

Conclusion: The HLA gene pool has evolved, and this evolution is likely driven by the combined effects of not only gene flow from migration but also the resulting population substructure, ongoing natural selection, and genetic drift. Our findings underscore the

Öz

Amaç: İnsan lökosit antijen (HLA) frekansları küresel olarak farklılık gösterir. Türkiye'nin tarihi bir göç kavşağı olması ve 2011'den bu yana yaşadığı büyük demografik değişimler göz önüne alındığında, bu değişimlerin HLA üzerine olan etkileri incelenmemiştir. Bu çalışma, Orta Batı Anadolu'daki 25 yıllık HLA verilerini analiz ederek, düşük (2001–2011) ve yüksek (2011–2025) göç dönemlerinin bölgesel HLA gen havuzunu nasıl etkilediğini belirlemeyi amaçlamıştır.

Gereç ve Yöntemler: Bu geriye dönük çalışmada, 6550 sağlıklı donörden alınan HLA-A, -B, -C, -DRB1, -DQB1 ve -DPB1 verileri 2001–2011 ve 2011–2025 olmak üzere iki döneme ayrılarak incelenmiştir. Alel frekans farklılıkları Fisher'in Exact testi ile değerlendirilmiş ve Hardy–Weinberg dengesi (HWE) dahil olmak üzere popülasyon genetiği analizleri yapılmıştır.

Bulgular: On sekiz alelin frekansı anlamlı düzeyde değişmiştir ($p<0,05$). 2011 sonrası dönemde, Orta Doğu/Asya kökenli alellerin (örn. B*52, DRB1*03) frekansı artarken, Avrupa ile ilişkili aleller (örn. B*44, DQB1*05) azalmıştır. Doğu Asya aleli B*46 ilk kez ortaya çıkarken, düşük frekanslı iki alel (DPB1*01, DPB1*19) saptanamaz düzeye düşmüştür. Yüksek göç dönemindeki kohort, HWE'den anlamlı sapma göstermiş ve gözlenen homozigot fazlalığı, popülasyon katmanlaşmasından kaynaklanan bir Wahlund etkisine işaret etmiştir.

Sonuç: Orta Batı Anadolu'daki HLA gen havuzu, 2011'den sonra önemli ölçüde evrimleşmiştir. Bu durum sadece göçle gelen gen akışının değil, aynı zamanda bu durumun yarattığı popülasyon alt yapılanmasının, süregelen doğal seçilimin ve genetik sürük-

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need for transplant registries to be periodically updated to reflect current population immunogenetics and for public health initiatives to consider emerging HLA-associated disease risks.

Keywords Human leukocyte antigen (HLA) · immunogenetic · migration · evolution · Wahlund effect · Türkiye

lenmenin birleşik etkileriyle oluşmuş olabilir. Bulgularımız, transplantasyon kayıtlarının güncel popülasyon genetiğini yansıtacak şekilde periyodik olarak güncellenmesi ve halk sağlığı girişimlerinin ortaya çıkan HLA ile ilişkili hastalık risklerini dikkate alması gerektiğinin altını çizmektedir.

Anahtar Kelimeler İnsan lökosit antijeni (HLA) · immünogenetik · Wahlund etkisi · Türkiye · göç · evrim

INTRODUCTION

The human leukocyte antigen (HLA) system comprises highly polymorphic genes that regulate immune responses and tissue compatibility. HLA allele frequencies vary markedly among populations due to geographic, ethnic, and historical demographic factors, influencing transplant outcomes, disease susceptibility, and drug reactions (1-4). Monitoring the regional HLA distribution over time is therefore important for both medical and sociogenetic insights.

Türkiye's unique geographic position has led to diverse migration waves throughout history, shaping a genetic landscape that blends different cultures and populations. Previous surveys have indicated that the Turkish HLA allele and haplotype frequencies resemble those of European and Middle Eastern populations while retaining unique characteristics (5). Changes in HLA profiles can result from evolutionary forces such as natural selection and genetic drift, as well as sudden demographic upheavals such as war-driven mass migration (6, 7). While since 2011, civil unrest in neighbouring countries (Syria, Afghanistan, etc.) has triggered a massive refugee influx that made Türkiye host to the world's largest refugee population, the country's demographic profile is also continually being reshaped by significant internal migration from east to west. The potential impact of these combined migratory dynamics on the national HLA landscape has not been systematically studied (8).

This study addresses this gap by analysing 25 years of HLA data from a Central Western Anatolia donor pool to determine how two distinct periods—2001–2011 (low migration) and 2011–2025 (high migration)—affected the regional HLA gene pool. The HLA-DPB1 locus, now routinely considered in donor-recipient matching due to its influence on transplant outcomes (9, 10), was included alongside HLA-A, -B, -C, -DRB1, and -DQB1. To the best of our knowledge, this study represents the first comprehensive temporal analysis documenting changes in HLA allele distributions in Türkiye in response to major demographic shifts. The findings underscore the need for periodic updates to HLA surveys and highlight how intensified demographic mobility can reshape the genetic architecture relevant to transplantation and public health planning.

MATERIAL AND METHODS

Population

This retrospective cross-sectional study evaluated all healthy volunteer donors who underwent HLA typing at the Eskisehir Osmangazi University Hospital Tissue Typing Laboratory from January 2001 to April 2025. Most donors were from Eskişehir and nearby provinces (Central Western Anatolia), although they do not represent the entire region. A total of 6550 donors were analysed and divided into two cohorts: Group 1 (January 2001–March 2011, n=2089) and Group 2 (April 2011-April 2025, n=4461). The two groups had similar gender distributions (~47% female, ~53% male) and mean ages (around 40 years), with no significant differences (p>0.05). Data from six different HLA loci (A, B, C, DRB1, DQB1, and DPB1) were analysed based on the maximum number of donors available for each locus during the relevant period. Donors with molecularly typed HLA data from at least three loci (A, B, DRB1) were included in the study, whereas those with incomplete or serologically typed data were excluded. Not all loci were typed in every donor, especially in the early period, so the sample size per locus varied (particularly fewer data for HLA-C, -DQB1, and -DPB1 before 2011). However, all available molecular typing data were used to provide a comprehensive and comparable HLA frequency set for each period.

HLA typing method

HLA genotyping was performed using standard molecular methods. Genomic DNA was extracted from EDTA-anticoagulated peripheral blood and typed by PCR amplification with sequence-specific oligonucleotide probes (PCR-SSO), as described previously (11). Two-digit resolution allele data were used for all loci to maintain consistency between time periods. Allele assignments were based on the IMGT/HLA database (version 3.43.0). All HLA typings from before 2010 were converted to the current allele nomenclature to ensure comparability.

Statistical analysis

Prior to analysis, the HLA data were validated using the GENE[RATE] online tool (12). Population genetics analyses were then conducted with PyPop software (versions 0.7.0

and 1.2.0) (13, 14). Allele and haplotype frequencies were estimated by the Expectation-Maximisation algorithm, and the Hardy–Weinberg equilibrium (HWE) was tested using both the standard chi-square and the Guo–Thompson Markov chain Monte Carlo (MCMC) methods. We assessed linkage disequilibrium (LD) between all pairs of loci (calculating D and D′ coefficients with permutation tests) and examined asymmetric LD (ALD) to evaluate directional associations between loci. Ewens–Watterson homozygosity tests were performed to assess neutrality, and chi-square tests were applied to compare observed versus expected common genotype counts. Fisher's exact test was used to evaluate the differences in allele and haplotype frequencies between the two periods, with $p<0.05$ considered statistically significant. An LD threshold of D′≥0.5 was used to denote a strong linkage. Donor demographic comparisons (age and sex) were carried out using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical approval

This study was approved by the Ethics Committee of Eskisehir Osmangazi University (Date: 26.06.2025, Protocol No. 28) and was conducted in accordance with the principles of the Declaration of Helsinki.

Limitations

Certain limitations should be considered. The donor pool consisted of self-selected volunteers rather than a random population sample, so some bias is possible even though it broadly represents the region's immunogenetics (e.g., frequencies of key alleles such as HLA-A*02 are consistent with national data). Detailed donor demographics (e.g., ethnicity) were unavailable, limiting the attribution of HLA changes to specific migrant groups and necessitating interpretation in general terms. Additionally, all data were at two-digit resolution, and the number of typed donors was smaller for some loci in the early period, which may have masked or exaggerated certain rare allele frequency changes (i.e., some differences could stem partly from increased sample size and typing coverage after 2011). Finally, because comprehensive HLA data from migrant source populations (e.g., Syria, Afghanistan) are limited, we inferred the origins of observed allele shifts based on broad regional patterns rather than direct population comparisons.

RESULTS

Changes in the allele distribution

During the 25-year period, 131 distinct HLA alleles were detected across the HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 loci. While the most frequent alleles (e.g., A*02, B*35, C*07, DRB1*11, DQB1*03, DPB1*04) remained stable (11, 15), 18 alleles showed significant frequency changes between the two periods ($p<0.05$; Table 1–Table 2, Figure 1). Eight alleles—including those common in Middle Eastern or Asian populations (e.g., B*52, DQB1*06, DRB1*03)—increased in frequency after 2011, while 10 alleles, such as B*44 and DQB1*05 (more common in Europeans), decreased. Notably, the rare East Asian allele B*46 appeared only after 2011, and two low-frequency alleles (DPB1*01, DPB1*19) were not detected in our donor records in the later period. Most of these shifts were statistically robust (10/18, $p<0.01$), reflecting real changes in the HLA pool rather than random fluctuations.

Table 1. HLA Alleles with Statistically Significant Frequency Changes Between the Pre- (2001–2011) and Post-Migration (2011–2025) Periods

HLA Allele	Group 1 (2001–2011)			Group 2 (2011–2025)			p-value
	n/Total	AF	AF (%)	n/Total	AF	AF (%)	
B*37	80/4178	0.0191	1.91	107/8922	0.0120	1.20	0.002**
B*44	354/4178	0.0847	8.47	614/8922	0.0688	6.88	0.001**
B*46	1/4178	0.0002	0.02	14/8922	0.0016	0.16	0.048*
B*50	119/4178	0.0285	2.85	326/8922	0.0365	3.65	0.017*
B*52	88/4178	0.0211	2.11	305/8922	0.0342	3.42	<0.001***
B*57	60/4178	0.0144	1.44	187/8922	0.0210	2.10	0.009**
B*59	5/4178	0.0012	0.12	1/8922	0.0001	0.01	0.015*
C*03	11/374	0.0294	2.94	193/3296	0.0586	5.86	0.017*
C*05	16/374	0.0428	4.28	78/3296	0.0237	2.37	0.036*
C*16	25/374	0.0668	6.68	119/3296	0.0361	3.61	0.007**
DRB1*01	328/4178	0.0785	7.85	594/8922	0.0666	6.66	0.014*
DRB1*03	273/4178	0.0653	6.53	790/8922	0.0885	8.85	<0.001***
DRB1*09	35/4178	0.0084	0.84	134/8922	0.0150	1.50	0.002**
DQB1*05	123/466	0.2639	26.39	133/754	0.1764	17.64	<0.001***
DQB1*06	73/466	0.1567	15.67	161/754	0.2135	21.35	0.017*
DPB1*01	8/464	0.0172	1.72	0/620	0.0000	0.00	0.001**
DPB1*05	15/464	0.0323	3.23	5/620	0.0081	0.81	0.005**
DPB1*19	4/464	0.0086	0.86	0/620	0.0000	0.00	0.033*

Abv: AF=Allele Frequency; AF (%)=Allele Frequency percentage; p-value=Statistical significance of frequency change (Fisher's exact test). $p<0.05$, ** $p<0.01$, *** $p<0.001$. Only statistically significant changes are shown. For $p<0.001$, values are presented as "<0.001".

Population structure and HWE deviation

Our analyses showed that the heterozygote counts were generally consistent with Hardy-Weinberg expectations across both periods, except for DQB1 in the second period (Figure 2a, Supplement File 1 Appendix 1). In contrast, significant deviations from HWE were observed in homozygote frequencies, particularly in the second period, with marked excesses at the A, B, C, DRB1, and DQB1 loci (Figure 2b, Supplement File 1 Appendix 2). This effect was most pronounced at loci B, C, and A after 2011, while DPB1 remained in equilibrium throughout the study.

Table 2. Clinical and Geographic Implications of HLA Alleles with Significant Frequency Changes after Migration

Allele	**Frequency Change in the Study Fold Change/Direction (AF %)**	**Geographic Distribution/Ethnic Association (Common to rare)**	**Clinical Significance/Disease Associations**
B*46	8.00 ↑ Increased (0.02% → 0.16%)	**East Asia:** Taiwan (15%) ‡, Thailand (13%) ‡, China (11%) ‡, Japan (5%) ‡, Korea (5%) ‡, Other: Russia (3%) ‡, Iraq/Iran (1.3-2.2%) ‡ Rarely seen in Turkish (28).	Nasopharyngeal carcinoma, EBV-LPD, TB resistance, HIV progression, Graves, COVID-19 susceptibility (39)
C*03	1.99 ↑ Increased (2.94% → 5.86%)	**Asia:** Mongolia (30%) ‡, China (20%) ‡, Japan (22%) ‡, Pakistan (10%) ‡, Russia (9%) ‡, Iraq (6%) ‡. **European**: Norway (21%) ‡, Sweden (18%) ‡, UK (15%) ‡.	HIV, HCV clearance, T1D, AS (39)
DRB1*09	1.79 ↑ Increased (0.84% → 1.5%)	**East Asia:** China (18.3%) ‡, Japan (17%) ‡, Taiwan (16%) ‡, Korea (10%) ‡. Rare in Anatolia and Europe (28).	T1D, T2D, Graves, Hep B, COVID-19, SJS, Alzheimer's drug HSR (e.g., carbamazepine, phenytoin, allopurinol) (39)
B*52	1.62 ↑ Increased (2.11% → 3.42%)	**East Asia:** Japan (11%) ‡, India (9.8%)‡ **Central Asia/Middle East:** Pakistan (8.4%) ‡, Syria (7.1%) (20), Iran (7.3%) ‡. Iraq (7%) ‡, Jordan (4.6%) ‡. Low in Western European populations (25).	Takayasu arteritis, RA, Behçet's, Hep B, HIV, COVID-19 (39)
B*57	1.46 ↑ Increased (1.44% → 2.1%)	**Central Asia and Latin America**: Mongolia (9.8%) ‡, Sri Lanka (9.4%) ‡, Brazil (6%) ‡, India (6%) ‡, Ireland (6.3%) ‡, the United Kingdom (5.8%) ‡, Germany and Russia (4.5%) ‡. Decreasing from east to west	Abacavir hypersensitivity, HIV elite control, HCV, psoriasis, Behçet's (39)
DRB1*03	1.36 ↑ Increased (6.53% → 8.85%)	**Middle East:** Pakistan (39%) ‡, UAE (19%) ‡, India (17%) ‡, Syria (15%) ‡, Saudi Arabia (15%) ‡. **Europe**: UK (15%) ‡, Ireland (12%)(5, 25).	T1D, SLE, autoimmune hepatitis, HIV, TB, Sjögren, myasthenia gravis; pharmacogenetic risks (e.g., chlorpromazine-induced agranulocytosis, hydralazine) (39)
B*50	1.28 ↑ Increased (2.85% → 3.65%)	**Middle East, South Asia, and Mediterranean**: Saudi Arabia (18%) ‡, Iran (18%) ‡, UAE (9.4%) ‡, Jordan (7%) ‡.	HIV, HCV, Behçet's, AS, autoimmune disorders, carbamazepine hypersensitivity (39)
DQB1*06	1.36 ↑ Increased (15.67% → 21.35%)	**Middle East and Asia:** South Africa (43%) ‡, Tanzania (42%) ‡, Russia (34%) ‡, Sudan (31%)‡,China (31%)‡, Pakistan (32%)‡, Saudi Arabia (26%)‡, Iraq (26%)‡.	Narcolepsy, MS, SLE, HIV, EBV (39, 40)
B*37	1.59 ↓ Decreased (1.91% → 1.2%)	**European:** Australia (3%)‡, Ireland (2%)‡. Lower in Asia/Middle East: China (1.9%)‡, Syria (0.5%)(20).	Spondyloarthropathies, HIV, allopurinol hypersensitivity (39)
B*44	1.23 ↓ Decreased (8.47% → 6.88%)	**European:** Spain (23%)‡, Ireland (18%)‡, UK (17.5%)‡, England (17.5%)‡, France (16%)‡, Germany (14%)‡, Italy (12%)‡, Syria (7.6%)‡, Iran (4%)‡.	HCV, HIV, Behçet's, allopurinol reaction, T1D, AS (39)
B*59	12.0 ↓ Decreased (0.12% → 0.01%)	**Rare worldwide**: Except for Japan and Thailand (2%)‡. Not been reported in Syria (20).	Arthritis (weak), allopurinol hypersensitivity; rare allele may complicate donor matching (39)
C*05	1.80 ↓ Decreased (4.28% → 2.37%)	**European:** England (11%)‡, France (10%)‡, Spain (9%)‡, Italy 6.9%)‡. **Eastern:** Iran (1%)‡, Japan (0.2%)**(28)**.	HIV, COVID-19, GVHD, psoriasis (39)
C*16	1.85 ↓ Decreased (6.68% → 3.61%)	**European, Middle East, and North Africa:** Spain (8%)‡, France (7%)‡, Iran (5%)‡, Syria (3.6%)(20).	HIV-1 elite control, Hep B, Behçet's, RA (39)
DRB1*01	1.18 ↓ Decreased (7.85% → 6.66%)	**European:** Portugal (14%)‡, Russia (13%)‡, UK (12%)‡ , Norway (12%)‡, Sweden (11.5%)‡, Germany (10.2%)‡. **Middle East/East:** Iran (5%)‡, Jordan (5%)‡. China (4%)‡.	RA, MS, HIV, pemphigus, Hep B (39)

Allele	**Frequency Change in the Study Fold Change/Direction (AF %)**	**Geographic Distribution/Ethnic Association (Common to rare)**	**Clinical Significance/Disease Associations**
DQB1*05	1.50 ↓ Decreased (26.39% → 17.64%)	**Western:** America (25-48%) ‡, Serbia (33%) ‡, Romania (30%) ‡. **Middle East:** Iraq (17%) ‡, Saudi Arabia (12%) ‡, Jordan (9%) ‡.	RA, coeliac disease, HCV, HIV, chronic rejection, autoimmune hepatitis, renal transplant outcomes (39)
DPB1*05	3.99 ↓ Decreased (3.23% → 0.81%)	**Limited:** Myanmar Bamar (7.6%)‡, Myanmar Kayin(%4.5) ‡, Norway (2.6) ‡, England (1.7%)‡.	CMV/EBV risk, GVHD, transplant relapse risk, donor matching difficulty (9, 39)
DPB1*01	— ↓ Undetected (1.72% → 0.0%)	**Europe (West Eurasian):** Norway (6.7%) ‡, England (6.3%) ‡, Argentina (6.1%) ‡, France 5.5%) ‡. Lower frequencies in Eastern: Myanmar Bamar (2.1%) ‡, Colombia (0%) ‡.	GVHD, SLE, DM, CMV/EBV reactivation, transplant failure, acute GVHD, donor match limitation (9, 36, 39)
DPB1*19	— ↓ Undetected (0.86% → 0.0%)	**Rare, Limited**: England (0.5%) ‡, Norway (1%)‡	Adenovirus/fungal infection risk, acute GVHD, engraftment failure, rare allele surveillance (9, 36, 39)

Abv: AF (%)=Allele Frequency percentage; ↑=Statistically significant increase; ↓=Statistically significant decrease; GVHD=Graft-versus-host disease; EBV=Epstein-Barr Virus; CMV=Cytomegalovirus; TB=Tuberculosis; HCV=Hepatitis C Virus; T1D=Type 1 Diabetes; T2D=Type 2 Diabetes; MS=Multiple Sclerosis; SLE=Systemic Lupus Erythematosus; AS=Ankylosing Spondylitis; RA=Rheumatoid Arthritis; HSR=Hypersensitivity Reaction; DM=Diabetes Mellitus; LD=Linkage Disequilibrium; MHC=Major Histocompatibility Complex; p-value=Statistical significance of observed frequency change (see Methods for threshold). Common → Rare=Indicates whether the allele is common or rare in the specified region or ethnic group. — Undetected=Allele not detected in the second period. ‡=Data supported by reference databases (AFND); see main text for details. Fold decrease/increase=Calculated as the ratio between periods (see Methods). Parentheses ( ) indicate the frequency range or country-specific frequency.

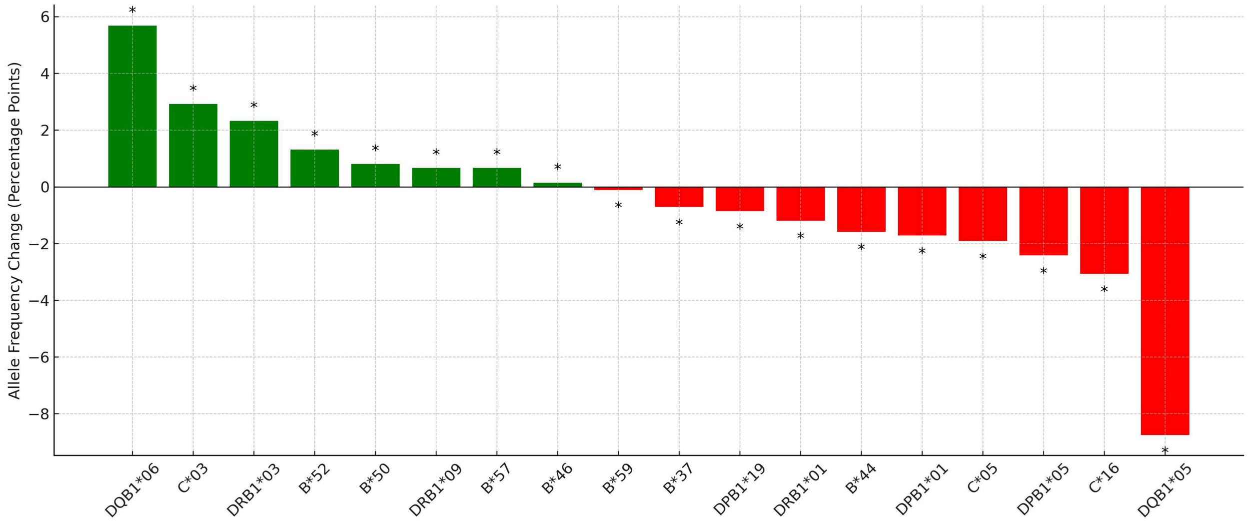

Figure 1. Statistically Significant Changes in the HLA Allele Frequencies Between the Pre- and Post-Migration Periods (2001–2011 vs. 2011–2025). The figure displays the absolute change in frequency for each allele across the two study periods. Green bars indicate alleles with increased frequency post-2011, while red bars indicate decreased frequencies. Statistically significant changes (p<0.05) are marked with an asterisk.

Genotype-specific deviations

Guo and Thompson's MCMC analysis confirmed that these deviations were due to specific homozygous genotypes, which became even more pronounced after 2011 (Supplement File 2 Appendix 6).

Selection analysis

Slatkin's homozygosity test revealed significant negative Fnd values for all loci except DPB1, indicating strong balancing selection and greater-than-expected allele diversity (e.g., DRB1 Fnd=1.73, p=0.0001; DQB1 Fnd=1.66, p=0.0120). In contrast, DPB1 showed a significant positive Fnd, indicate a different evolutionary pattern (Figure 2c, Supplement File 1 Appendix 3).

Linkage disequilibrium (LD) and haplotype dynamics

LD analysis revealed that the strong association between DRB1 and DQB1 remained stable in both periods, while LD between HLA-C and HLA-B decreased significantly after 2011 (Figure 3a, Figure 3b, Figure 3c Supplement File 1, Appendix 4). Directional relationships, such as DQB1 being a stronger predictor for DRB1 alleles, also persisted with ALD analysis (Figure 4a, Figure 4b, Figure 4c, Figure 4d; Supplement File 1, Appendix 4).

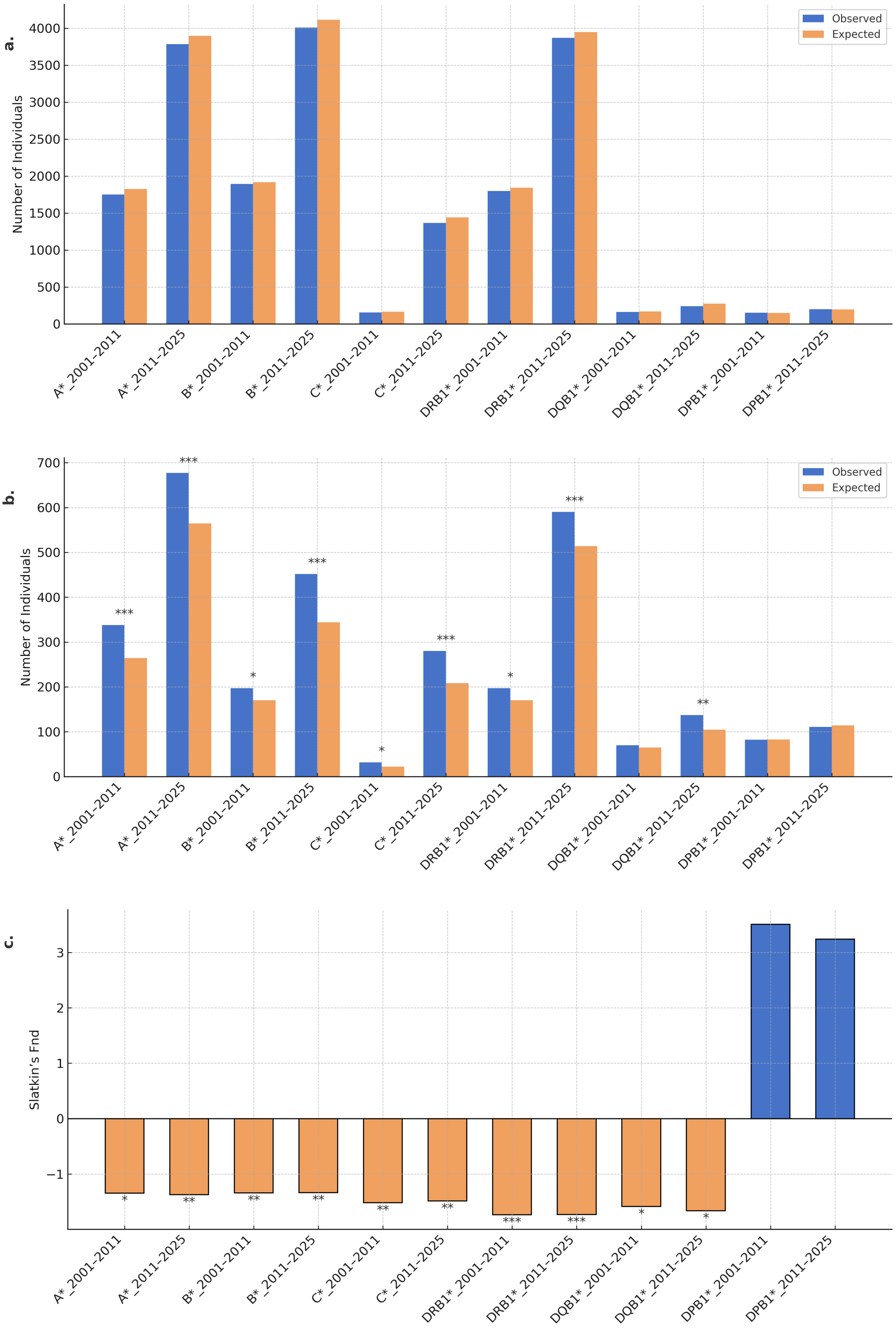

Figure 2. Summary of deviations from Hardy–Weinberg equilibrium across HLA loci for two time periods (2001–2011 and 2011–2025). a) Observed versus expected counts of heterozygotes across loci and periods. Most loci conformed to Hardy-Weinberg expectations, except for DQB1 in the second period. b) Homozygote counts revealed significant deviations from equilibrium, particularly in the second period, with notable excesses at the A, B, C, DRB1, and DQB1 loci. c) Slatkin's Fnd values from the Ewens-Watterson homozygosity test further support the presence of directional selection. Positive Fnd values are consistent with balancing selection (e.g., DPB1), whereas strongly negative values indicate directional selection at other loci. Asterisks denote statistically significant deviations ($p<0.05$, $p<0.01$, $p<0.001$).

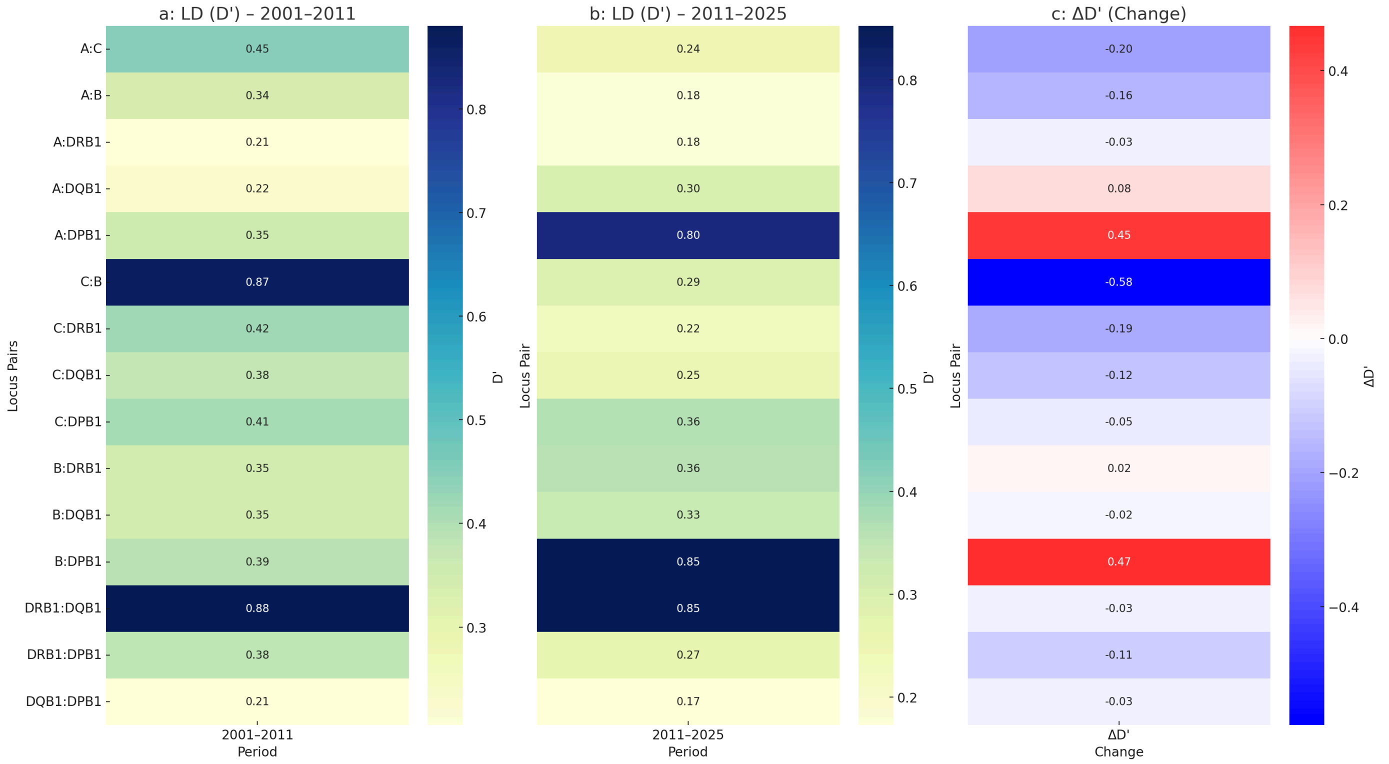

Figure 3. Temporal Changes in Linkage Disequilibrium (LD) Between HLA Locus Pairs, Displayed as Heat Maps for 2001–2011 and 2011–2025. (a) D' values for the period 2001–2011, (b) D' values for the period 2011–2025, (c) Difference between the two periods ($\Delta D' = D'_{(2011-2025)} - D'_{(2001-2011)}$) The colour scale reflects the strength of linkage (panels a and b) and the direction of change (panel c): Red tones indicate an increase in LD, blue tones indicate a decrease, and white tones represent unchanged pairs.

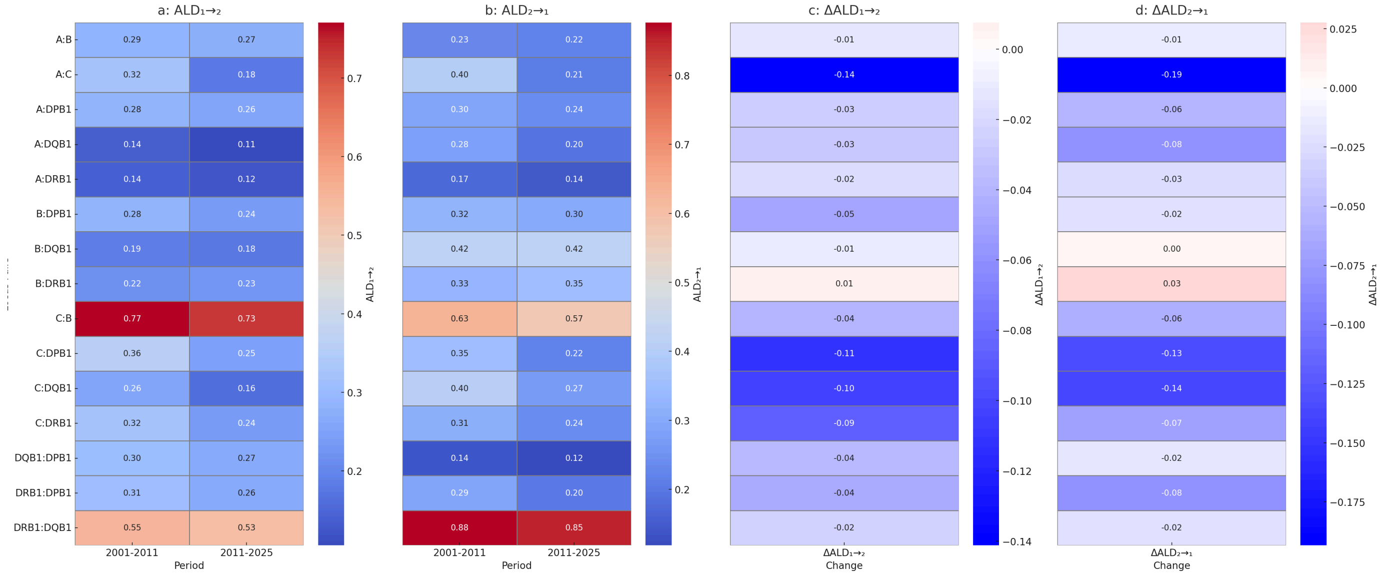

Figure 4. Heat maps consisting of four panels showing the levels of asymmetric linkage disequilibrium (ALD) between HLA locus pairs and their changes over time. a) ALD$_{1\to2}$ values for the periods 2001–2011 and 2011–2025. b) ALD$_{2\to1}$ values for the same periods. c) Inter-period differences in the ALD$_{1\to2}$ direction (ΔALD$_{1\to2}$=ALD$_{1\to2}$ [2011–2025] – ALD$_{1\to2}$ [2001–2011]). d) Inter-period differences in the ALD$_{2\to1}$ direction (ΔALD$_{2\to1}$=ALD$_{2\to1}$ [2011–2025] – ALD$_{2\to1}$ [2001–2011]). Colour scales indicate the magnitude and direction of the LD change. Warmer tones (red) indicate higher or increasing ALD values, while cooler tones (blue) represent lower or decreasing levels of disequilibrium.

Haplotype frequencies mirrored these shifts: several previously common haplotypes, such as A*30~B*51~C*16~DRB1*13, were not detected in the second period, while new haplotypes, like A*01~B*08~C*07~DRB1*03, emerged (Supplement File 1, Appendix 5; Supplement File 2, Appendix 7).

DISCUSSION

Population immunogenetics and the monitoring power of HLA

Our results confirm that HLA frequencies respond dynamically to major demographic events (Supplement File 2, Appendix 8). Although derived from a single centre, this study provides a valuable longitudinal snapshot of HLA dynamics in Central Western Anatolia during a period of significant demographic change.

Since 2011, Türkiye has experienced substantial demographic shifts, not only due to the influx of refugees—over 2.78 million Syrians under Temporary Protection and more than four million total foreign nationals as of April 2025—but also as a result of ongoing internal migration from eastern to western regions (Directorate of Migration Management, TUIK, 2024). While migrant populations were initially concentrated in border provinces, both international and internal migration have contributed to major changes in the genetic landscape of the central regions, including our study area. Although it is difficult to disentangle the effects of international versus internal migration, the pronounced Wahlund effect points to admixture with genetically more distant populations. While disentangling the precise contributions of international versus internal migration is challenging, the pronounced Wahlund effect provides clear evidence of significant population admixture. The detection of the East Asian-specific B*46 allele, which was absent in our records before 2011, provides a clear signal of external gene flow. At the same time, ongoing east-to-west internal migration has been a constant and powerful dynamic reshaping regional demographics.

Therefore, the observed population stratification and the full extent of the genetic shifts are best understood as the powerful combined result of both international gene flow and significant internal migration. (Supplement File 2, Appendix 8).The observed increases in alleles typical of Middle Eastern and Asian populations, alongside declines in European-associated alleles, closely parallel these demographic changes (7, 16-19). Notably, the rise of B*52 and the appearance of B*46 alleles point to recent gene flow from both neighbouring countries and within Türkiye itself (20). Similar impacts of migration on genetic diversity have also been reported in donor registries in Germany and South America (7, 18, 21). Indeed, the high polymorphism of MHC genes is explained by the "heterozygote advantage" hypothesis, which posits that individuals with diverse HLA alleles have a selective advantage due to their ability to respond to a broader range of pathogens. Therefore, the observed shifts in HLA frequencies are not only a reflection of demographic changes but also a dynamic indicator of the population's collective and evolving immune defence capacity (22).

HLA-A Locus: The Dynamics Behind clear Stability

Despite stable HLA-A allele frequencies between the two periods, we observed significant deviations from HWE due to excess homozygosity, especially in Group 2 (Figure 3 and Supplement File 1, Appendix 2, Appendix 3, Appendix 4). This is consistent with the introduction of new subpopulations with distinct HLA-A profiles into the donor pool, resulting in a Wahlund effect (an obvious excess of homozygotes from pooling genetically distinct groups) (23). Given that our province is among those with the lowest rates of consanguineous marriage in Türkiye—and that this rate has declined further since 2010 [(TUIK, 2024) [https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Aile-2024-53898]—the increase in homozygosity is most likely explained by population structure changes rather than consanguinity. However, because individual kinship data were not available, the potential contribution of consanguinity cannot be excluded. The Wahlund effect has previously been identified in HLA analyses of American-European populations as well (24).

HLA-B Locus: The Centre of Population Dynamics, Immunogenetic Change, and Connections

HLA-B showed the clearest combined effects of natural selection and migration. Several HLA-B allele frequencies changed markedly (with multiple Eastern-origin alleles increasing), yet overall heterozygosity at this locus remained high, reflecting ongoing balancing selection to preserve immune diversity (20, 25). The A*24~B*44 haplotype was previously reported to be the most frequent in Turks (more than three times more frequent than the other two locus combinations) and was thought to reflect an ancient founder effect (26). However, in our study, we observed a statistically significant decrease in this haplotype (Supplement File 1, Appendix 3; Supplement File 2 Appendix 7). Thus, the HLA-B locus serves as a nexus where strong historical selection and recent migratory gene flow converge, making its changes particularly informative of the population's evolving genetic landscape (27).

HLA-C Locus: The Centre of Functional, Structural, and Methodological Complexity

HLA-C exhibited complex patterns influenced by both biology and sampling. Certain allele frequencies shifted significantly (C*03 increased, whereas C*05 and C*16 declined) After 2011, a pronounced Wahlund effect was evident at HLA-C (excess homozygotes in Group 2), consistent with the introduction of subgroups (20, 28). Importantly, LD between HLA-C and HLA-B weakened substantially in the second period, indicating that many previously common C–B haplotypes were disrupted by incoming lineages. The most evolutionarily recent member of the major histocompatibility complex is HLA-C. It possesses a structure that is particularly sensitive to epigenetic modifications, such as methylation (16, 29). Thus, it may have evolved into a locus that responds more dynamically to environmental factors and selection pressures. Nonetheless, HLA-C's overall allele diversity still appears to be maintained by strong balancing selection, underscoring how this locus is shaped by both immune pressures and demographic shifts.

Class II Loci (DRB1 and DQB1): Co-evolved Asymmetric and Functional Blocks

HLA-DRB1 and -DQB1 remained tightly linked across time, preserving the long-standing DRB1-DQB1 haplotypes (5, 6, 30, 31). However, specific haplotype frequencies changed: for example, the traditionally "western DRB1*01~DQB1*05" haplotype declined significantly after 2011, while DRB1*13~DQB1*06 haplotype increased (5, 25, 28). These shifts reflect an influx of individuals in whom the former haplotype is rarer and the latter more common. Both loci continued to show evidence of balancing selection (high allele diversity), although DQB1 deviated from HWE in Group 2 due to increased homozygosity (e.g., more DQB1*05/05 genotypes) (5, 32-34), again suggesting a population substructure. Notably, several extended MHC haplotypes present before 2011 were not detected in the second period's larger cohort. While this non-detection could be a statistical artefact for haplotypes that were already at low frequencies, the change in some previously more common combinations may still underscore the impact of migration on disrupting established genetic blocks (Supplement File 2, Appendix 7). This highlights the profound impact of migration, which extends beyond single allele frequencies to reshape ancestrally inherited gene blocks. For instance, a haplotype such as A*30~B*51~C*16~DRB1*13, previously found at a 2.11% frequency, was not detected in the second period, while the A*01~B*08~C*07~DRB1*03 haplotype was identified at a 1.15% frequency despite being previously unobserved. It is important to acknowledge that the non-detection of any given haplotype can be a consequence of the sampling effects. However, a shift of this magnitude involving a relatively frequent haplotype like A*30~B*51~C*16~DRB1*13 is less likely to be a simple artefact and serves as a strong indicator of a genuine structural change in the population's immunogenetic architecture.

HLA-DPB1 locus: sensitive traces of neutral evolution and demographic mixing

HLA-DPB1 acted largely as a neutral marker of demographic change. It remained in HWE overall, and its most frequent allele (DPB1*04) remained constant, but several low-frequency DPB1 alleles were lost or sharply diminished after 2011. For instance, DPB1*01 and DPB1*19, present at ~1–2% before, were not detected in the donor pool, and DPB1*05 dropped from ~3% to <1% (35). We also observed a new linkage between DPB1 and other loci (e.g., a newfound LD between HLA-C and DPB1 in Group 2), indicating that migrants introduced novel long-range haplotypes. Because DPB1 is less subject to immune selection, such changes provide a clear genetic fingerprint of the post-2011 admixture and drift.

Direct effects on clinical transplantation: Needs and strategies that change

Shifts in HLA frequencies have practical implications for transplant donor matching (Table 2). Alleles that have become less common (such as DPB1*05) will make perfect HLA matches harder to find for patients who carry them, whereas increasing alleles (such as DQB1*06) could improve match rates for others. The observation of very rare alleles (e.g., B*46) and the loss of certain alleles (e.g., DPB1*01) highlight the need for adaptable registry strategies. Proactive donor recruitment may be required to target underrepresented alleles or ethnic groups so that the donor pool reflects the population's new genetic makeup. The National Marrow Donor Programme (NMDP) in the US has used this method successfully by running targeted campaigns for certain ethnic groups. Transplant programmes might also rely more on permissive mismatch approaches (such as tolerating certain DPB1 mismatches with careful T-cell epitope matching) to facilitate transplants when exact matches are unavailable (9, 36). Furthermore, it will be important to update donor search algorithms (37) and predictive models to account for the revised haplotype frequencies and linkage patterns; our observed LD changes indicate that algorithms based on outdated assumptions could lose efficiency in identifying optimal donors.

Disease susceptibility and public health dynamics

The increased HLA diversity is a double-edged sword for public health. While a broader HLA repertoire enhances collective immunity against emerging pathogens, it also introduces challenges such as more complex transplant matching and unpredictable shifts in disease predisposition (38) (Table 2). For instance, the increased prevalence of alleles such as B*52 may elevate the risk for certain autoimmune diseases (39), while declines in others could reduce different disease burdens. Therefore, tracking these dynamic trends is crucial for policymakers to proactively adapt health strategies, from updating donor registries and pharmacogenetic guidelines to tailoring vaccination programmes.

CONCLUSION

Over the past 25 years, the HLA gene pool of Central Western Anatolia has evolved significantly, especially following the demographic upheavals after 2011. This study documented notable shifts such as increases in alleles of Middle Eastern origin (e.g., DRB1*03, B*52, DQB1*06) and decreases in some European-associated alleles (e.g., B*44, DQB1*05). A rare East Asian allele (B*46) entered the population, and a few previously present alleles (like DPB1*01 and *19) were not detected in our donor records. These changes reflect the powerful combined effects of gene flow from incoming groups, population substructure (Wahlund effects), and ongoing natural selection and drift.

In practical terms, our findings illustrate that a population's HLA profile is a living record of its recent history. Recognising this dynamism is essential for adapting medical strategies: transplant donor registries and matching algorithms should be periodically updated to align with current immunogenetics, and public health initiatives should consider emerging HLA trends when assessing disease risk or vaccine coverage. Future research, including larger-scale, high-resolution HLA analyses in other regions and focused studies on migrant communities, will further elucidate the interplay of migration and selection on genetic landscapes. By continuously monitoring and studying HLA evolution, we can better inform medical decision-making and public health planning in an era of rapid demographic change (22)

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Appendix

Supplementary File 1

Locus	Period	Observed	Expected	Chi-square	p-value
A*	2001-2011	1751	1824.27	2.94	0.0863
A*	2011–2025	3784	3896.69	3.26	0.071
B*	2001-2011	1892	1918.9	0.38	0.5392
B*	2011–2025	4009	4117.03	2.83	0.0922
C*	2001-2011	155	164.89	0.59	0.4413
C*	2011–2025	1368	1439.47	3.55	0.0596
DRB1*	2001-2011	1799	1842.32	1.02	0.3129
DRB1*	2011–2025	3871	3947.24	1.47	0.2249
DQB1*	2001-2011	163	168.07	0.15	0.6958
DQB1*	2011–2025	240	272.5	3.88	0.049
DPB1*	2001-2011	150	149.31	0.003	0.955
DPB1*	2011–2025	199	195.91	0.05	0.8253

Appendix 1. Observed and Expected Numbers of Heterozygotes for Each HLA Locus Across Study Periods. Comparison of observed vs. expected heterozygote counts per locus, revealing deviations from Hardy-Weinberg equilibrium and potential effects of population substructure (Wahlund effect) after migration.

Locus	Period	Observed	Expected	Chi-square	p-value
A*	2001-2011	338	264.73	20.28	7e-06
A*	2011–2025	677	564.31	22.5	2e-06
B*	2001-2011	197	170.1	4.25	0.0392
B*	2011–2025	452	343.97	33.93	0.0
C*	2001-2011	32	22.11	4.42	0.0355
C*	2011–2025	280	208.53	24.5	1e-06
DRB1*	2001-2011	197	170.1	4.25	0.0392
DRB1*	2011–2025	590	513.76	11.31	0.0008
DQB1*	2001-2011	70	64.93	0.4	0.5293
DQB1*	2011–2025	137	104.5	10.1	0.0015
DPB1*	2001-2011	82	82.69	0.006	0.9395
DPB1*	2011–2025	111	114.09	0.08	0.7724

Appendix 2. Observed and Expected Numbers of Homozygotes for Each HLA Locus Across Study Periods. Observed and expected homozygote numbers and statistical test results for each locus and period, supporting findings on increased homozygosity due to demographic shifts.

Locus	Period	k	Observed F	Expected F	Variance in F	Fnd	p
A*	2001-2011	19	0.1267	0.2801	0.0130	−1.3443	0.0109*
A*	2011–2025	20	0.1265	0.2903	0.0142	−1.3728	0.0069*
B*	2001-2011	33	0.0814	0.1699	0.0044	−1.3416	0.0056*
B*	2011–2025	39	0.0771	0.1601	0.0039	−1.3381	0.0060*
C*	2001-2011	13	0.1182	0.2773	0.0109	−1.5204	0.0021**
C*	2011–2025	16	0.1265	0.3135	0.0158	−1.4854	0.0031**
DRB1*	2001-2011	13	0.1181	0.3767	0.0222	−1.7363	0.0001***
DRB1*	2011–2025	14	0.1152	0.3812	0.0236	−1.7309	0.0000****
DQB1*	2001-2011	5	0.2787	0.5768	0.0352	−1.588	0.0169*
DQB1*	2011–2025	5	0.2772	0.5981	0.0372	−1.6625	0.0120*
DPB1*	2001-2011	24	0.3564	0.1578	0.0032	3.5098	0.9896*
DPB1*	2011–2025	24	0.3680	0.1680	0.0038	3.2413	0.9867*

k: distinct alleles, Fnd:Normalized deviate of F, p: p-value of F *=significant at the 5% level, **=significant at the 1% level, ***=significant at the 0.1% level, ****=significant at the 0.01% level, *****=significant at the 0.001% level

Appendix 3. Ewens-Watterson Homozygosity Test (Slatkin’s Fnd) Results for Neutrality Assessment. Fnd values and p-values for each HLA locus and period, assessing neutrality versus selection, with significant deviations interpreted in the context of evolutionary and demographic changes.

2001-2011

Locus	D	D'	Wn	ln(L_1)	ln(L_0)	S	ALD_1_2	ALD_2_1	permus	p-value
A~C	0.00686	0.44545	0.38593	−1376.93	−1527.46	301.07	0.31955	0.40070	999	0.0000*
A~B	0.00430	0.33775	0.27116	−18132.98	−19187.46	2108.97	0.28626	0.23170	951	0.0000*
A~DRB1	0.00393	0.20643	0.15167	−16691.05	−16995.29	608.48	0.14149	0.16937	989	0.0000*
A~DQB1	0.00609	0.22324	0.28121	−1447.73	−1486.42	77.38	0.13581	0.27617	992	0.1724
A~DPB1	0.00898	0.35098	0.39607	−1484.74	−1606.73	243.97	0.28448	0.29610	998	0.0010*
C~B	0.01537	0.86723	0.70815	−1187.76	−1689.08	1002.64	0.77059	0.63335	999	0.0000*
C~DRB1	0.00666	0.41743	0.30497	−1384.87	−1517.57	265.40	0.32306	0.31150	998	0.0000*
C~DQB1	0.01179	0.37513	0.41399	−549.34	−592.33	85.97	0.26081	0.40307	998	0.0010*
C~DPB1	0.01077	0.41114	0.39482	−542.96	−606.62	127.33	0.35828	0.35157	999	0.1862
B~DRB1	0.00367	0.34585	0.31786	−17912.86	−18980.78	2135.84	0.22124	0.32614	957	0.0000*
B~DQB1	0.00631	0.34990	0.41446	−1593.70	−1688.67	189.95	0.18527	0.41784	988	0.0000*
B~DPB1	0.00645	0.38549	0.29211	−1659.35	−1811.53	304.35	0.28346	0.32298	999	0.0130*
DRB1~DQB1	0.03976	0.88010	0.82288	−1052.95	−1456.46	807.00	0.55090	0.87661	993	0.0000*
DRB1~DPB1	0.01184	0.38253	0.29865	−1474.43	−1579.31	209.75	0.30927	0.28705	998	0.0040*
DQB1~DPB1	0.01067	0.20544	0.34643	−1132.17	−1179.61	94.87	0.30479	0.13521	997	0.0371*

2011-2025

Locus pair	D	D'	Wn	ln(L_1)	ln(L_0)	S	ALD_1_2	ALD_2_1	permus	p-value
A~C	0.00379	0.24253	0.19735	−13015.13	−13444.80	859.34	0.17839	0.20735	977	0.0000*
A~B	0.00396	0.17589	0.24748	−39238.76	−41225.47	3973.43	0.27339	0.21708	962	0.0000*
A~DRB1	0.00283	0.17795	0.12859	−35765.95	−36253.75	975.61	0.12341	0.14344	998	0.0000*
A~DQB1	0.00636	0.30125	0.19373	−2384.26	−2417.95	67.38	0.10534	0.19512	995	0.3618
A~DPB1	0.00801	0.79758	0.27276	−1956.99	−2070.39	226.81	0.25685	0.23972	998	0.0100*
C~B	0.01360	0.29024	0.62157	−11344.11	−15082.22	7476.22	0.72938	0.57443	940	0.0000*
C~DRB1	0.00567	0.22395	0.22777	−12744.65	−13240.69	992.07	0.23684	0.23932	988	0.0000*
C~DQB1	0.00832	0.25035	0.25624	−2246.79	−2306.82	120.06	0.15797	0.26547	993	0.0000*
C~DPB1	0.00511	0.36494	0.27651	−1873.55	−1980.47	213.85	0.24762	0.21771	999	0.0010*

B~DRB1	0.00405	0.36124	0.31777	−38470.63	−40931.62	4921.98	0.22879	0.35378	970	0.0000*
B~DQB1	0.00781	0.33305	0.41461	−2648.98	−2798.03	298.10	0.17589	0.42229	992	0.0000*
B~DPB1	0.00456	0.85238	0.26758	−2223.11	−2385.91	325.60	0.23544	0.30308	999	0.0020*
DRB1~DQB1	0.03776	0.85238	0.79463	−1791.77	−2393.98	1204.41	0.52659	0.85461	996	0.0000*
DRB1~DPB1	0.00824	0.27229	0.27646	−1938.12	−2051.12	226.01	0.26446	0.20437	997	0.0000*
DQB1~DPB1	0.00592	0.17293	0.25910	−1469.28	−1521.89	105.21	0.26799	0.11879	996	0.0080*

Loglikelihood under linkage equilibrium [ln(L_0)], Loglikelihood obtained via the EM algorithm [ln(L_1)], D’, Hedrick’s statistic (Hedrick, 1987); Wn, Cramer’s V statistic (Cramér, 1946) for global LD; Asymetric linkage equilibrium (ALD) *significant ($p < 0.05$)

Appendix 4. Pairwise Linkage Disequilibrium (LD) and Asymmetric LD (ALD) Analyses of HLA Loci for Each Period. Pairwise LD (D, D') and ALD results for all combinations of HLA loci, presented separately for 2001–2011 and 2011–2025, demonstrating how migration and demographic changes affected genetic linkage structure in the studied population.

Haplotype Name	2001–2011	2011–2025	Rate Difference	P value (Exact))	Direction & Fold Change
A*01~B*35	1.87	2.62	−0.75	0.008	1.4 fold increase
A*02~B*44	3.33	2.13	1.2	0.0	1.6 fold decrease
A*11~B*35	3.09	2.1	0.99	0.001	1.5 fold decrease
A*24~B*51	1.27	2.0	−0.73	0.003	1.6 fold increase
A*02~B*07	1.63	1.18	0.45	0.04	1.4 fold decrease
A*24~B*18	1.8	1.09	0.71	0.002	1.7 fold decrease
A*11~B*52	0.68	1.05	−0.37	0.032	1.5 fold increase
A*24~B*44~	0.58	1.03	−0.45	0.009	1.8 fold increase
A*11~B*51~	1.27	0.84	0.43	0.022	1.5 fold decrease
A*03~B*35~C*04	4.57	2.49	2.08	0.027	1.8 fold decrease
A*23~B*49~C*07	4.55	1.9	2.65	0.002	2.4 fold decrease
A*02~B*51~C*15	2.91	1.46	1.45	0.046	2.0 fold decrease
A*02~B*44~C*05	2.67	0.98	1.69	0.008	2.7 fold decrease
A*30~B*51~C*16	2.41	0.02	2.39	0.0	120.5 fold decrease
A*32~B*18~C*12	1.07	0.13	0.94	0.005	8.2 fold decrease
A*01~B*18~C*12	1.07	0.0	1.07	0.0	Not observed
A*02~B*15~C*07	1.07	0.07	1.0	0.001	15.3 fold decrease
A*32~B*51~C*15	1.07	0.18	0.89	0.014	5.9 fold decrease
A*03~B*44~C*16	1.07	0.21	0.86	0.02	5.1 fold decrease
A*01~B*18~C*07	1.04	0.09	0.95	0.003	11.6 fold decrease
A*01~B*35~C*04	0.67	2.16	−1.49	0.03	3.2 fold increase
A*30~B*51~C*16~DRB1*13	2.11	0.0	2.11	0.0	Not observed
A*11~B*35~C*04~DRB1*08	1.87	0.0	1.87	0.0	Not observed
A*03~B*35~C*04~DRB1*11	1.74	0.4	1.34	0.009	4.3 fold decrease
A*03~B*35~C*04~DRB1*01	1.74	0.13	1.61	0.0	13.4 fold decrease
A*02~B*51~C*15~DRB1*11	1.6	0.36	1.24	0.007	4.4 fold decrease
A*24~B*07~C*07~DRB1*15	1.52	0.24	1.28	0.002	6.3 fold decrease

Haplotype Name	**2001–2011**	**2011–2025**	**Rate Difference**	**P value (Exact))**	**Direction & Fold Change**
A*02~B*35~C*04~DRB1*13	1.28	0.29	0.99	0.014	4.4 fold decrease
A*02~B*44~C*05~DRB1*16	1.07	0.0	1.07	0.0	Not observed
A*01~B*18~C*07~DRB1*11	1.07	0.0	1.07	0.0	Not observed
A*32~B*35~C*04~DRB1*04	1.07	0.23	0.84	0.027	4.7 fold decrease
A*02~B*39~C*12~DRB1*08	1.07	0.21	0.86	0.02	5.1 fold decrease
A*23~B*49~C*07~DRB1*15	1.07	0.21	0.86	0.02	5.1 fold decrease
A*02~B*35~C*04~DRB1*15	1.04	0.0	1.04	0.0	Not observed
A*01~B*08~C*07~DRB1*03	0.0	1.15	−1.15	0.028	New observed
A*23~B*49~C*07~DRB1*11~DQB1*03	3.32	1.08	2.24	0.041	3.1 fold decrease
A*02~B*51~C*16~DRB1*11~DQB1*03	2.17	0.0	2.17	0.002	Not observed
A*01~B*40~C*15~DRB1*14~DQB1*05	1.63	0.13	1.5	0.026	12.5 fold decrease
A*02~B*44~C*02~DRB1*16~DQB1*05	1.63	0.0	1.63	0.008	Not observed
A*03~B*08~C*07~DRB1*03~DQB1*02	1.63	0.0	1.63	0.008	Not observed
A*32~B*18~C*12~DRB1*04~DQB1*03	1.63	0.0	1.63	0.008	Not observed
A*23~B*49~C*07~DRB1*04~DQB1*03	1.58	0.0	1.58	0.008	Not observed
A*03~B*35~C*04~DRB1*11~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*24~B*07~C*07~DRB1*04~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*02~B*44~C*06~DRB1*11~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*02~B*35~C*04~DRB1*13~DQB1*06	1.09	0.0	1.09	0.039	Not observed
A*02~B*44~C*05~DRB1*01~DQB1*05	1.09	0.0	1.09	0.039	Not observed
A*01~B*57~C*06~DRB1*03~DQB1*02	1.09	0.0	1.09	0.039	Not observed
A*24~B*44~C*05~DRB1*11~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*24~B*35~C*04~DRB1*13~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*03~B*51~C*01~DRB1*01~DQB1*05	1.09	0.0	1.09	0.039	Not observed
A*24~B*50~C*06~DRB1*11~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*02~B*15~C*15~DRB1*04~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*26~B*51~C*07~DRB1*03~DQB1*02	1.09	0.0	1.09	0.039	Not observed

Haplotype Name	2001–2011	2011–2025	Rate Difference	P value (Exact))	Direction & Fold Change
A*31~B*44~C*05~DRB1*11~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*24~B*48~C*08~DRB1*04~DQB1*03	1.09	0.0	1.09	0.039	Not observed
A*11~B*35~C*04~DRB1*08~DQB1*04	1.09	0.0	1.09	0.039	Not observed
A*02~B*41~C*17~DRB1*11~DQB1*03	1.03	0.0	1.03	0.039	Not observed
A*23~B*49~C*07~DRB1*11~DQB1*03~DPB1*04	3.37	0.99	2.38	0.034	3.4 fold decrease
A*02~B*51~C*16~DRB1*11~DQB1*03~DPB1*04	1.69	0.0	1.69	0.012	Not observed
A*24~B*35~C*04~DRB1*11~DQB1*03~DPB1*02	1.69	0.0	1.69	0.012	Not observed
A*24~B*18~DRB1*11	1.13	0.61	0.52	0.003	1.9 fold decrease
A*03~C*04	4.87	2.36	2.51	0.009	2.1 fold decrease
A*23~C*07	4.81	1.98	2.83	0.001	2.4 fold decrease
A*02~C*12	4.71	2.73	1.98	0.034	1.7 fold decrease
A*30~C*16	2.35	0.28	2.07	0.0	8.4 fold decrease
A*32~C*02	1.07	0.29	0.78	0.047	3.7 fold decrease
A*33~C*15	1.07	0.05	1.02	0.001	21.4 fold decrease
A*01~C*04	0.83	2.41	−1.58	0.043	2.9 fold increase
A*03~C*12	0.0	2.36	−2.36	0.0	New observed
A*02~C*14	0.0	1.52	−1.52	0.008	New observed
A*11~C*12	0.0	1.3	−1.3	0.019	New observed
A*02~DPB1*04	19.16	12.65	6.51	0.004	1.5 fold decrease
A*24~DPB1*04	6.83	11.39	−4.56	0.012	1.7 fold increase
A*03~DPB1*02	2.5	0.85	1.65	0.025	2.9 fold decrease
A*26~DPB1*05	1.27	0.0	1.27	0.006	Not observed
A*02~DPB1*03	0.8	4.24	−3.44	0.001	5.3 fold increase
A*01~DPB1*02	0.86	4.21	−3.35	0.001	4.9 fold increase
A*26~DQB1*05	2.58	0.44	2.14	0.002	5.9 fold decrease
A*23~DQB1*05	1.65	0.34	1.31	0.026	4.9 fold decrease
A*68~DQB1*05	1.42	0.0	1.42	0.001	Not observed

Haplotype Name	**2001–2011**	**2011–2025**	**Rate Difference**	**P value (Exact))**	**Direction & Fold Change**
A*30~DQB1*06	0.0	1.14	−1.14	0.016	New observed
A*23~DQB1*06	0.0	1.07	−1.07	0.027	New observed
A*24~DRB1*11	5.34	3.94	1.4	0.0	1.4 fold decrease
A*02~DRB1*15	2.83	1.96	0.87	0.002	1.4 fold decrease
A*02~DRB1*01	1.97	1.14	0.83	0.0	1.7 fold decrease
A*01~DRB1*03	1.25	1.73	−0.48	0.035	1.4 fold increase
A*24~DRB1*13	1.24	1.8	−0.56	0.018	1.5 fold increase
A*11~DRB1*11	1.19	0.8	0.39	0.031	1.5 fold decrease
A*03~DRB1*15	0.69	1.49	−0.8	0.0	2.2 fold increase
A*24~DRB1*07	0.65	1.01	−0.36	0.046	1.6 fold increase
B*51~DPB1*04	10.02	5.85	4.17	0.014	1.7 fold decrease
B*07~DPB1*04	5.32	2.56	2.76	0.023	2.1 fold decrease
B*40~DPB1*02	1.44	0.29	1.15	0.043	5.0 fold decrease
B*44~DPB1*03	1.27	0.21	1.06	0.047	6.0 fold decrease
B*15~DPB1*19	0.86	0.0	0.86	0.033	Not observed
B*40~DPB1*04	0.8	2.63	−1.83	0.041	3.3 fold increase
B*49~DPB1*03	0.0	1.1	−1.1	0.022	New observed
B*35~DQB1*03	7.21	10.86	−3.65	0.044	1.5 fold increase
B*40~DQB1*05	2.06	0.62	1.44	0.031	3.3 fold decrease
B*44~DQB1*06	1.87	0.34	1.53	0.014	5.5 fold decrease
B*35~DQB1*04	1.46	0.0	1.46	0.001	Not observed
B*39~DQB1*05	1.37	0.13	1.24	0.014	10.5 fold decrease
B*52~DQB1*05	1.07	0.0	1.07	0.008	Not observed
B*52~DQB1*06	0.36	3.34	−2.98	0.0	9.3 fold increase
B*51~DQB1*02	0.0	1.33	−1.33	0.017	New observed
B*40~DQB1*06	0.0	1.15	−1.15	0.016	New observed
B*15~DQB1*06	0.0	0.95	−0.95	0.048	New observed

Haplotype Name	2001–2011	2011–2025	Rate Difference	P value (Exact))	Direction & Fold Change
B*18~DRB1*11	3.26	2.46	0.8	0.009	1.3 fold decrease
B*51~DRB1*11	2.77	3.68	−0.91	0.007	1.3 fold increase
B*08~DRB1*03	2.68	3.39	−0.71	0.032	1.3 fold increase
B*35~DRB1*01	2.21	1.57	0.64	0.013	1.4 fold decrease
B*50~DRB1*07	1.39	1.91	−0.52	0.037	1.4 fold increase
B*27~DRB1*11	1.13	0.63	0.5	0.004	1.8 fold decrease
B*52~DRB1*15	1.12	2.21	−1.09	0.0	2.0 fold increase
B*51~DRB1*14	0.58	1.12	−0.54	0.003	1.9 fold increase
B*55~DRB1*14	0.61	1.07	−0.46	0.008	1.8 fold increase
B*07~DRB1*11	0.58	0.99	−0.41	0.019	1.7 fold increase
C*05~B*44	4.01	2.15	1.86	0.03	1.9 fold decrease
C*16~B*51	4.01	1.59	2.42	0.003	2.5 fold decrease
C*02~B*44	1.34	0.36	0.98	0.024	3.7 fold decrease
C*03~B*15	0.0	1.3	−1.3	0.019	New observed
C*15~DPB1*04	6.57	2.47	4.1	0.009	2.7 fold decrease
C*16~DPB1*04	5.11	1.32	3.79	0.006	3.9 fold decrease
C*12~DPB1*04	3.99	9.66	−5.67	0.014	2.4 fold increase
C*04~DPB1*09	2.25	0.0	2.25	0.003	Not observed
C*06~DPB1*05	1.69	0.0	1.69	0.011	Not observed
C*03~DPB1*04	0.0	4.43	−4.43	0.002	New observed
C*06~DQB1*03	5.0	1.99	3.01	0.037	2.5 fold decrease
C*16~DQB1*06	2.17	0.28	1.89	0.016	7.8 fold decrease
C*12~DQB1*06	2.12	6.25	−4.13	0.029	2.9 fold increase
C*05~DQB1*05	1.63	0.0	1.63	0.008	Not observed
C*04~DQB1*04	1.47	0.0	1.47	0.008	Not observed
C*14~DQB1*04	1.09	0.0	1.09	0.039	Not observed
C*06~DRB1*11	2.94	0.99	1.95	0.003	3.0 fold decrease

Haplotype Name	**2001–2011**	**2011–2025**	**Rate Difference**	**P value (Exact))**	**Direction & Fold Change**
C*04~DRB1*08	2.73	0.49	2.24	0.0	5.6 fold decrease
C*16~DRB1*13	2.51	0.29	2.22	0.0	8.7 fold decrease
C*02~DRB1*16	1.87	0.7	1.17	0.028	2.7 fold decrease
C*01~DRB1*13	1.52	0.62	0.9	0.043	2.5 fold decrease
C*14~DRB1*14	1.28	0.1	1.18	0.0	12.8 fold decrease
C*05~DRB1*16	1.23	0.08	1.15	0.0	15.4 fold decrease
C*07~DRB1*13	0.64	2.68	−2.04	0.007	4.2 fold increase
C*03~DRB1*13	0.0	1.2	−1.2	0.03	New observed
C*07~DRB1*07	0.0	1.09	−1.09	0.046	New observed
C*14~DRB1*11	0.0	1.04	−1.04	0.044	New observed
DQB1*05~DPB1*04	14.48	10.46	4.02	0.048	1.4 fold decrease
DQB1*06~DPB1*04	7.98	13.49	−5.51	0.006	1.7 fold increase
DQB1*05~DPB1*05	1.72	0.0	1.72	0.001	Not observed
DQB1*02~DPB1*03	0.63	2.65	−2.02	0.018	4.2 fold increase
DQB1*03~DPB1*14	0.0	1.68	−1.68	0.006	New observed
DRB1*13~DPB1*02	0.73	4.19	−3.46	0.0	5.7 fold increase
DRB1*03~DPB1*02	0.0	1.95	−1.95	0.002	New observed
DRB1*11~DPB1*14	0.0	1.02	−1.02	0.041	New observed
DRB1*01~DQB1*05	8.8	5.44	3.36	0.025	1.6 fold decrease
DRB1*14~DQB1*05	7.73	3.81	3.92	0.005	2.0 fold decrease
DRB1*13~DQB1*06	5.79	11.13	−5.34	0.001	1.9 fold increase
DRB1*09~DQB1*03	0.0	1.33	−1.33	0.017	New observed
DRB1*01~DQB1*05~DPB1*04	5.48	3.0	2.48	0.042	1.8 fold decrease
DRB1*14~DQB1*05~DPB1*04	4.93	1.81	3.12	0.004	2.7 fold decrease
DRB1*13~DQB1*06~DPB1*04	3.43	7.28	−3.85	0.007	2.1 fold increase
DRB1*07~DQB1*02~DPB1*02	1.57	0.31	1.26	0.043	5.1 fold decrease
DRB1*13~DQB1*06~DPB1*02	1.13	3.29	−2.16	0.023	2.9 fold increase

Haplotype Name	2001–2011	2011–2025	Rate Difference	P value (Exact))	Direction & Fold Change
DRB1*03~DQB1*02~DPB1*02	0.0	2.28	−2.28	0.0	New observed
DRB1*07~DQB1*02~DPB1*03	0.0	1.16	−1.16	0.022	New observed
DRB1*11~DQB1*03~DPB1*14	0.0	0.96	−0.96	0.041	New observed

Appendix 5. Significant Haplotype Frequency Changes Between 2001–2011 and 2011–2025.. A comprehensive list of HLA haplotypes whose frequencies changed significantly between the two periods, including new, lost, and majorly shifted haplotypes, illustrating the dynamic impact of migration and population changes.

Supplementary File 2

Period	Genotype	(observed/expected)	[Chen's pval]	[diff pval]
2001-2011	A*01+A*01	(39/23.912039)	0.0023**	0.0023**
2001-2011	A*02+A*02	(155/132.444232)	0.0143*	0.0143*
2001-2011	A*03+A*02	(97/116.077549)	0.0395*	0.0498*
2001-2011	A*24+A*24	(62/46.897559)	0.0133*	0.0133*
2001-2011	A*25+A*01	(0/4.386549)	0.0289*	0.0289*
2001-2011	A*25+A*11	(7/3.140258)	0.0375*	0.0383*
2001-2011	A*25+A*24	(12/6.143131)	0.0082**	0.0082**
2001-2011	A*29+A*01	(4/9.842987)	0.0312*	0.0357*
2001-2011	A*30+A*26	(1/8.021063)	0.0033**	0.0033**
2001-2011	A*30+A*30	(8/2.413116)	0.0069**	0.0069**
2001-2011	A*31+A*03	(13/7.503112)	0.0456*	0.0472*
2001-2011	A*31+A*29	(5/1.497367)	0.0102*	0.0110*
2001-2011	A*32+A*24	(19/30.865486)	0.0229*	0.0229*
2001-2011	A*32+A*26	(19/11.636190)	0.0333*	0.0333*
2001-2011	A*32+A*32	(15/5.078506)	0.0000*****	0.0000*****
2001-2011	A*66+A*30	(3/0.815701)	0.0464*	0.0498*
2001-2011	A*68+A*34	(1/0.082336)	0.0374*	0.0757
2001-2011	A*69+A*03	(0/2.537817)	0.0399*	0.1004
2001-2011	A*74+A*68	(1/0.082336)	0.0385*	0.0735
2001-2011	A*74+A*69	(1/0.011010)	0.0117*	0.0124*
2001-2011	c*03+c*02	(2/0.411765)	0.0459*	0.0590
2001-2011	c*04+c*04	(11/6.364973)	0.0335*	0.0335*
2001-2011	c*06+c*06	(5/2.033422)	0.0389*	0.0389*
2001-2011	c*15+c*07	(11/6.331551)	0.0413*	0.0415*
2001-2011	c*17+c*16	(3/0.601604)	0.0068**	0.0165*
2001-2011	B*13+B*13	(9/2.728698)	0.0168*	0.0168*

Period	Genotype	(observed/expected)	[Chen's pval]	[diff pval]
2001-2011	B*27+B*18	(16/9.316419)	0.0206*	0.0210*
2001-2011	B*35+B*08	(18/28.685974)	0.0378*	0.0378*
2001-2011	B*35+B*18	(67/50.296075)	0.0127*	0.0158*
2001-2011	B*38+B*18	(3/10.260651)	0.0231*	0.0243*
2001-2011	B*38+B*38	(7/3.179631)	0.0254*	0.0254*
2001-2011	B*39+B*39	(4/0.553375)	0.0026**	0.0026**
2001-2011	B*40+B*18	(4/10.827190)	0.0243*	0.0412*
2001-2011	B*40+B*35	(22/32.893250)	0.0452*	0.0460*
2001-2011	B*41+B*38	(0/4.330541)	0.0293*	0.0293*
2001-2011	B*44+B*15	(19/11.353758)	0.0108*	0.0182*
2001-2011	B*44+B*40	(23/14.573480)	0.0098**	0.0107*
2001-2011	B*46+B*38	(1/0.039014)	0.0417*	0.0436*
2001-2011	B*47+B*41	(2/0.185974)	0.0114*	0.0114*
2001-2011	B*48+B*48	(1/0.080900)	0.0494*	0.0494*
2001-2011	B*49+B*07	(1/9.020345)	0.0003***	0.0003***
2001-2011	B*49+B*49	(9/3.418023)	0.0118*	0.0118*
2001-2011	B*50+B*07	(13/6.351604)	0.0154*	0.0169*
2001-2011	B*50+B*38	(12/4.642652)	0.0035**	0.0045**
2001-2011	B*51+B*08	(28/19.135950)	0.0436*	0.0441*
2001-2011	B*52+B*08	(8/3.159406)	0.0039**	0.0057**
2001-2011	B*52+B*39	(5/1.432264)	0.0218*	0.0218*
2001-2011	B*55+B*44	(21/12.709430)	0.0103*	0.0170*
2001-2011	B*56+B*38	(2/0.312111)	0.0352*	0.0352*
2001-2011	B*56+B*44	(2/0.677836)	0.0222*	0.1317
2001-2011	B*57+B*38	(7/2.340833)	0.0067**	0.0093**
2001-2011	B*58+B*44	(11/6.269986)	0.0166*	0.0347*
2001-2011	B*58+B*48	(3/0.460507)	0.0041**	0.0041**

Period	Genotype	(observed/expected)	[Chen's pval]	[diff pval]
2001-2011	B*59+B*13	(2/0.180708)	0.0128*	0.0148*
2001-2011	DRB1*04+DRB1*04	(67/50.407013)	0.0047**	0.0047**
2001-2011	DRB1*07+DRB1*07	(25/16.472116)	0.0292*	0.0292*
2001-2011	DRB1*10+DRB1*08	(9/2.869794)	0.0015**	0.0015**
2001-2011	DRB1*11+DRB1*09	(14/7.573001)	0.0106*	0.0139*
2001-2011	DRB1*13+DRB1*04	(52/70.367879)	0.0168*	0.0171*
2001-2011	DRB1*13+DRB1*07	(52/40.225706)	0.0499*	0.0499*
2001-2011	DRB1*13+DRB1*08	(5/11.818334)	0.0356*	0.0362*
2001-2011	DRB1*14+DRB1*01	(11/20.254667)	0.0257*	0.0258*
2001-2011	DRB1*14+DRB1*11	(39/55.823839)	0.0118*	0.0118*
2001-2011	DRB1*14+DRB1*13	(42/27.973672)	0.0060**	0.0060**
2001-2011	DRB1*15+DRB1*03	(35/25.156774)	0.0354*	0.0375*
2001-2011	DRB1*15+DRB1*09	(0/3.225227)	0.0362*	0.0654
2001-2011	DRB1*15+DRB1*13	(58/41.743657)	0.0080**	0.0085**
2001-2011	DRB1*16+DRB1*08	(1/5.974390)	0.0460*	0.0472*
2001-2011	DPB1*17+DPB1*04	(11/7.368534)	0.0371*	0.0474*
2001-2011	DPB1*18+DPB1*09	(1/0.034483)	0.0334*	0.0334*
2001-2011	DPB1*22+DPB1*13	(1/0.019397)	0.0120*	0.0122*
2001-2011	DPB1*23+DPB1*05	(1/0.064655)	0.0376*	0.0458*
2001-2011	DPB1*23+DPB1*17	(1/0.056034)	0.0317*	0.0365*
2001-2011	DPB1*26+DPB1*06	(1/0.012931)	0.0034**	0.0034**
2001-2011	DPB1*61+DPB1*05	(1/0.032328)	0.0447*	0.0494*
2001-2011	DPB1*84+DPB1*19	(1/0.008621)	0.0100**	0.0106*
2001-2011	DPB1*91+DPB1*09	(1/0.017241)	0.0235*	0.0252*
2011-2025	A*02+A*02	(304/266.330419)	0.0014**	0.0014**
2011-2025	A*11+A*11	(40/26.219233)	0.0007***	0.0007***
2011-2025	A*23+A*03	(46/34.797579)	0.0320*	0.0335*

Period	Genotype	(observed/expected)	[Chen's pval]	[diff pval]
2011-2025	A*24+A*01	(128/157.732459)	0.0000*****	0.0000*****
2011-2025	A*24+A*03	(133/158.482851)	0.0215*	0.0215*
2011-2025	A*25+A*24	(7/14.107375)	0.0376*	0.0395*
2011-2025	A*26+A*01	(44/60.666330)	0.0135*	0.0135*
2011-2025	A*26+A*26	(26/14.863540)	0.0042**	0.0042**
2011-2025	A*30+A*30	(14/5.316297)	0.0031**	0.0031**
2011-2025	A*31+A*25	(4/1.443398)	0.0481*	0.0539
2011-2025	A*31+A*26	(2/7.907980)	0.0277*	0.0278*
2011-2025	A*31+A*31	(4/1.051838)	0.0240*	0.0240*
2011-2025	A*32+A*02	(79/96.514234)	0.0532	0.0483*
2011-2025	A*32+A*24	(76/59.280991)	0.0281*	0.0281*
2011-2025	A*36+A*26	(2/0.288612)	0.0311*	0.0311*
2011-2025	A*66+A*01	(11/5.065344)	0.0042**	0.0049**
2011-2025	A*66+A*03	(0/5.089442)	0.0117*	0.0135*
2011-2025	A*68+A*01	(62/38.048980)	0.0003***	0.0003***
2011-2025	A*68+A*03	(23/38.229993)	0.0022**	0.0022**
2011-2025	A*68+A*26	(30/18.644362)	0.0209*	0.0210*
2011-2025	A*68+A*30	(3/11.150415)	0.0162*	0.0162*
2011-2025	A*69+A*11	(0/4.906523)	0.0325*	0.0345*
2011-2025	A*69+A*68	(6/2.316969)	0.0260*	0.0318*
2011-2025	A*74+A*68	(2/0.108608)	0.0021**	0.0027**
2011-2025	c*01+c*01	(6/2.643204)	0.0499*	0.0499*
2011-2025	c*04+c*04	(83/62.524879)	0.0032**	0.0032**
2011-2025	c*07+c*07	(101/75.184466)	0.0000*****	0.0000*****
2011-2025	c*08+c*04	(10/24.542476)	7.2e-5****	1.1e-5****
2011-2025	c*08+c*07	(36/26.912621)	0.0427*	0.0428*
2011-2025	c*12+c*12	(41/27.271845)	0.0027**	0.0027**

Period	Genotype	(observed/expected)	[Chen's pval]	[diff pval]
2011-2025	c*14+c*08	(10/4.969660)	0.0132*	0.0184*
2011-2025	c*15+c*12	(16/28.686893)	0.0083**	0.0083**
2011-2025	c*15+c*14	(16/8.795510)	0.0060**	0.0090**
2011-2025	c*17+c*14	(5/2.169296)	0.0250*	0.0692
2011-2025	c*18+c*03	(4/0.936893)	0.0100**	0.0110*
2011-2025	B*13+B*13	(13/6.554808)	0.0459*	0.0459*
2011-2025	B*37+B*07	(10/5.432751)	0.0337*	0.0465*
2011-2025	B*37+B*13	(0/4.101547)	0.0198*	0.0210*
2011-2025	B*37+B*35	(29/19.452365)	0.0249*	0.0307*
2011-2025	B*38+B*27	(6/13.021520)	0.0491*	0.0495*
2011-2025	B*38+B*38	(19/9.056490)	0.0010**	0.0010**
2011-2025	B*39+B*14	(12/3.366174)	0.0000*****	0.0000*****
2011-2025	B*45+B*14	(3/0.644586)	0.0431*	0.0492*
2011-2025	B*45+B*40	(3/1.053127)	0.0386*	0.0458*
2011-2025	B*46+B*35	(8/2.545169)	0.0000*****	0.0000*****
2011-2025	B*47+B*14	(2/0.167115)	0.0052**	0.0087**
2011-2025	B*47+B*37	(3/0.083950)	0.0000*****	0.0000*****
2011-2025	B*48+B*35	(2/9.635284)	0.0075**	0.0090**
2011-2025	B*49+B*49	(20/7.022865)	0.0000*****	0.0000*****
2011-2025	B*50+B*38	(8/14.688635)	0.0339*	0.0339*
2011-2025	B*50+B*40	(26/12.715535)	0.0021**	0.0021**
2011-2025	B*50+B*50	(19/5.955839)	0.0000*****	0.0000*****
2011-2025	B*51+B*07	(77/58.592468)	0.0215*	0.0269*
2011-2025	B*51+B*41	(16/27.032728)	0.0132*	0.0137*
2011-2025	B*51+B*51	(101/74.631024)	0.0019**	0.0019**
2011-2025	B*53+B*13	(6/1.494956)	0.0071**	0.0072**
2011-2025	B*53+B*14	(3/0.931069)	0.0446*	0.0625

Period	Genotype	(observed/expected)	[Chen's pval]	[diff pval]
2011-2025	B*53+B*40	(4/1.521184)	0.0378*	0.0475*
2011-2025	B*54+B*35	(4/1.454382)	0.0318*	0.0322*
2011-2025	B*56+B*56	(2/0.076720)	0.0050**	0.0050**
2011-2025	B*57+B*08	(17/7.901704)	0.0029**	0.0046**
2011-2025	B*57+B*39	(6/2.955279)	0.0424*	0.0822
2011-2025	B*57+B*48	(3/1.110850)	0.0092**	0.0739
2011-2025	B*58+B*44	(17/9.703430)	0.0011**	0.0023**
2011-2025	B*58+B*52	(11/4.820108)	0.0042**	0.0042**
2011-2025	B*59+B*50	(1/0.036539)	0.0220*	0.0220*
2011-2025	B*73+B*38	(2/0.315400)	0.0363*	0.0363*
2011-2025	B*73+B*58	(1/0.110625)	0.0420*	0.0965
2011-2025	B*83+B*07	(2/0.101547)	0.0011**	0.0014**
2011-2025	DRB1*01+DRB1*01	(31/19.773369)	0.0107*	0.0107*
2011-2025	DRB1*04+DRB1*03	(87/113.249271)	0.0022**	0.0028**
2011-2025	DRB1*07+DRB1*03	(98/76.591571)	0.0081**	0.0081**
2011-2025	DRB1*09+DRB1*04	(27/19.209370)	0.0393*	0.0470*
2011-2025	DRB1*13+DRB1*09	(7/15.469626)	0.0328*	0.0368*
2011-2025	DRB1*13+DRB1*10	(31/21.357319)	0.0248*	0.0267*
2011-2025	DRB1*13+DRB1*11	(184/210.687066)	0.0425*	0.0425*
2011-2025	DRB1*13+DRB1*13	(84/59.454158)	0.0155*	0.0155*
2011-2025	DRB1*14+DRB1*01	(55/38.015467)	0.0014**	0.0014**
2011-2025	DRB1*14+DRB1*12	(0/8.383883)	0.0032**	0.0032**
2011-2025	DRB1*15+DRB1*01	(43/59.586416)	0.0210*	0.0210*
2011-2025	DRB1*15+DRB1*15	(56/44.890439)	0.0495*	0.0495*
2011-2025	DRB1*16+DRB1*08	(17/9.434768)	0.0137*	0.0139*
2011-2025	DRB1*16+DRB1*09	(11/6.353060)	0.0417*	0.0575
2011-2025	DQB1*04+DQB1*03	(13/7.836870)	0.0195*	0.0201*

Period	**Genotype**	**(observed/expected)**	**[Chen's pval]**	**[diff pval]**
2011-2025	DQB1*05+DQB1*03	(43/54.858090)	0.0467*	0.0369*
2011-2025	DQB1*05+DQB1*05	(22/11.730106)	0.0006***	0.0006***
2011-2025	DQB1*06+DQB1*06	(28/17.188992)	0.0010***	0.0010***
2011-2025	DPB1*11+DPB1*05	(1/0.016129)	0.0146*	0.0147*
2011-2025	DPB1*129+DPB1*10	(1/0.014516)	0.0110*	0.0110*
2011-2025	DPB1*13+DPB1*02	(0/2.558065)	0.0489*	0.0696

Appendix 6. Guo and Thompson MCMC Analysis Results for Hardy–Weinberg equilibrium at Each Locus. The results of MCMC-based Hardy–Weinberg equilibrium testing for all HLA loci and both periods support the statistical robustness of the equilibrium assessments.

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*02~B*51	4,44	5,23	−0,79	1,2	0,052	decrease
A*24~B*35	4,1	3,65	0,45	1,1	0,22	increase
A*03~B*35	2,89	2,91	−0,02	1	1	stabil
A*01~B*35	1,87	2,62	−0,75	1,4	0,008	decrease
A*02~B*35	2,92	2,49	0,43	1,2	0,161	increase
A*02~B*44	3,33	2,13	1,2	1,6	0	increase
A*11~B*35	3,09	2,1	0,99	1,5	0,001	increase
A*26~B*38	1,63	2,03	−0,4	1,2	0,131	decrease
A*24~B*51	1,27	2	−0,73	1,6	0,003	decrease
A*02~B*18	1,39	1,83	−0,44	1,3	0,069	decrease
A*03~B*07	1,26	1,39	−0,13	1,1	0,569	decrease
A*01~B*08	1,48	1,37	0,11	1,1	0,633	increase
A*02~B*50	1,36	1,32	0,04	1	0,87	stabil
A*23~B*49	1,5	1,29	0,21	1,2	0,331	increase
A*32~B*35	1,29	1,26	0,03	1	0,933	stabil
A*02~B*27	1,03	1,26	−0,23	1,2	0,298	decrease
A*33~B*14	1,19	1,26	−0,07	1,1	0,865	decrease
A*02~B*40	1,25	1,23	0,02	1	0,933	stabil
A*01~B*57	0,97	1,21	−0,24	1,2	0,289	decrease
A*02~B*07	1,63	1,18	0,45	1,4	0,04	increase
A*03~B*51	1,41	1,1	0,31	1,3	0,143	increase
A*24~B*18	1,8	1,09	0,71	1,7	0,002	increase
A*11~B*52	0,68	1,05	−0,37	1,5	0,032	decrease
A*24~B*44	0,58	1,03	−0,45	1,8	0,009	decrease
A*01~B*51	0,9	1,02	−0,12	1,1	0,635	decrease
A*30~B*13	1,18	1,01	0,17	1,2	0,411	increase
A*02~B*15	1,25	0,98	0,27	1,3	0,202	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*24~B*07	0,88	0,94	−0,06	1,1	0,845	decrease
A*11~B*51	1,27	0,84	0,43	1,5	0,022	increase
A*02~B*41	1,15	0,93	0,22	1,2	0,258	increase
A*03~B*44	1,13	0,91	0,22	1,2	0,253	increase
A*24~B*55	1,07	0,78	0,29	1,4	0,107	increase
A*03~B*35~C*04	4,57	2,49	2,08	1,8	0,027	increase
A*23~B*49~C*07	4,55	1,9	2,65	2,4	0,002	increase
A*02~B*35~C*04	4,06	3,11	0,95	1,3	0,35	increase
A*11~B*35~C*04	2,94	1,77	1,17	1,7	0,11	increase
A*02~B*51~C*15	2,91	1,46	1,45	2	0,046	increase
A*02~B*44~C*05	2,67	0,98	1,69	2,7	0,008	increase
A*26~B*38~C*12	2,41	1,25	1,16	1,9	0,093	increase
A*30~B*51~C*16	2,41	0,02	2,39	120,5	0	increase
A*24~B*35~C*04	2,19	3,36	−1,17	1,5	0,279	decrease
A*24~B*07~C*07	1,87	0,9	0,97	2,1	0,094	increase
A*02~B*39~C*12	1,6	0,64	0,96	2,5	0,05	increase
A*32~B*35~C*04	1,6	1,15	0,45	1,4	0,448	increase
A*30~B*13~C*06	1,6	0,97	0,63	1,6	0,273	increase
A*02~B*50~C*06	1,44	1,17	0,27	1,2	0,798	increase
A*02~B*41~C*17	1,34	0,66	0,68	2	0,188	increase
A*33~B*14~C*08	1,34	1,27	0,07	1,1	0,81	increase
A*01~B*51~C*14	1,26	0,48	0,78	2,6	0,055	increase
A*32~B*18~C*12	1,07	0,13	0,94	8,2	0,005	increase
A*02~B*13~C*06	1,07	0,56	0,51	1,9	0,285	increase
A*01~B*18~C*12	1,07	0	1,07	inf	0	increase
A*01~B*57~C*06	1,07	1,11	−0,04	1	1	stabil
A*02~B*15~C*07	1,07	0,07	1	15,3	0,001	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*32~B*51~C*15	1,07	0,18	0,89	5,9	0,014	increase
A*03~B*44~C*16	1,07	0,21	0,86	5,1	0,02	increase
A*01~B*37~C*06	1,07	0,59	0,48	1,8	0,299	increase
A*01~B*18~C*07	1,04	0,09	0,95	11,6	0,003	increase
A*03~B*07~C*07	0,88	1,3	−0,42	1,5	0,621	decrease
A*02~B*38~C*12	0,8	1,02	−0,22	1,3	1	decrease
A*01~B*35~C*04	0,67	2,16	−1,49	3,2	0,03	decrease
A*02~B*18~C*07	0,56	1,51	−0,95	2,7	0,165	decrease
A*02~B*51~C*14	0,53	1,67	−1,14	3,2	0,119	decrease
A*02~B*07~C*07	0,29	1,42	−1,13	4,9	0,086	decrease
A*01~B*08~C*07	0,27	1,3	−1,03	4,8	0,125	decrease
A*23~B*49~C*07~DRB1*11	2,14	1,02	1,12	2,1	0,069	increase
A*30~B*51~C*16~DRB1*13	2,11	0	2,11	inf	0	increase
A*11~B*35~C*04~DRB1*08	1,87	0	1,87	inf	0	increase
A*03~B*35~C*04~DRB1*11	1,74	0,4	1,34	4,3	0,009	increase
A*03~B*35~C*04~DRB1*01	1,74	0,13	1,61	13,4	0	increase
A*02~B*51~C*15~DRB1*11	1,6	0,36	1,24	4,4	0,007	increase
A*24~B*07~C*07~DRB1*15	1,52	0,24	1,28	6,3	0,002	increase
A*30~B*13~C*06~DRB1*07	1,34	0,72	0,62	1,9	0,211	increase
A*02~B*35~C*04~DRB1*13	1,28	0,29	0,99	4,4	0,014	increase
A*03~B*44~C*16~DRB1*04	1,07	0,34	0,73	3,1	0,058	increase
A*02~B*44~C*05~DRB1*16	1,07	0	1,07	inf	0	increase
A*01~B*18~C*07~DRB1*11	1,07	0	1,07	inf	0	increase
A*32~B*35~C*04~DRB1*04	1,07	0,23	0,84	4,7	0,027	increase
A*02~B*39~C*12~DRB1*08	1,07	0,21	0,86	5,1	0,02	increase
A*02~B*13~C*06~DRB1*07	1,07	0,58	0,49	1,8	0,285	increase
A*23~B*49~C*07~DRB1*15	1,07	0,21	0,86	5,1	0,02	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*02~B*35~C*04~DRB1*15	1,04	0	1,04	inf	0	increase
A*02~B*35~C*04~DRB1*11	0,53	1,51	−0,98	2,8	0,165	decrease
A*24~B*35~C*04~DRB1*11	0,53	1,28	−0,75	2,4	0,314	decrease
A*01~B*08~C*07~DRB1*03	0	1,15	−1,15	inf	0,028	decrease
A*23~B*49~C*07~DRB1*11~DQB1*03	3,32	1,08	2,24	3,1	0,041	increase
A*02~B*13~C*06~DRB1*07~DQB1*02	2,17	0,94	1,23	2,3	0,243	increase
A*03~B*07~C*07~DRB1*15~DQB1*06	2,17	0,81	1,36	2,7	0,117	increase
A*02~B*51~C*16~DRB1*11~DQB1*03	2,17	0	2,17	inf	0,002	increase
A*01~B*40~C*15~DRB1*14~DQB1*05	1,63	0,13	1,5	12,5	0,026	increase
A*02~B*51~C*15~DRB1*11~DQB1*03	1,63	0,81	0,82	2	0,393	increase
A*30~B*13~C*06~DRB1*07~DQB1*02	1,63	0,4	1,23	4,1	0,097	increase
A*02~B*44~C*02~DRB1*16~DQB1*05	1,63	0	1,63	inf	0,008	increase
A*03~B*08~C*07~DRB1*03~DQB1*02	1,63	0	1,63	inf	0,008	increase
A*32~B*18~C*12~DRB1*04~DQB1*03	1,63	0	1,63	inf	0,008	increase
A*23~B*49~C*07~DRB1*04~DQB1*03	1,58	0	1,58	inf	0,008	increase
A*03~B*35~C*04~DRB1*11~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*24~B*07~C*07~DRB1*04~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*02~B*44~C*06~DRB1*11~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*02~B*35~C*04~DRB1*13~DQB1*06	1,09	0	1,09	inf	0,039	increase
A*02~B*51~C*15~DRB1*14~DQB1*05	1,09	0,13	0,96	8,4	0,102	increase
A*02~B*44~C*05~DRB1*01~DQB1*05	1,09	0	1,09	inf	0,039	increase
A*01~B*57~C*06~DRB1*03~DQB1*02	1,09	0	1,09	inf	0,039	increase
A*02~B*07~C*07~DRB1*15~DQB1*06	1,09	0,81	0,28	1,3	0,662	increase
A*02~B*35~C*04~DRB1*11~DQB1*03	1,09	3,25	−2,16	3	0,138	decrease
A*24~B*44~C*05~DRB1*11~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*24~B*35~C*04~DRB1*13~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*02~B*18~C*07~DRB1*11~DQB1*03	1,09	0,27	0,82	4	0,178	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*03~B*51~C*01~DRB1*01~DQB1*05	1,09	0	1,09	inf	0,039	increase
A*24~B*50~C*06~DRB1*11~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*02~B*15~C*15~DRB1*04~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*26~B*51~C*07~DRB1*03~DQB1*02	1,09	0	1,09	inf	0,039	increase
A*31~B*44~C*05~DRB1*11~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*24~B*48~C*08~DRB1*04~DQB1*03	1,09	0	1,09	inf	0,039	increase
A*11~B*35~C*04~DRB1*08~DQB1*04	1,09	0	1,09	inf	0,039	increase
A*24~B*35~C*04~DRB1*11~DQB1*03	1,09	1,94	−0,85	1,8	0,751	decrease
A*02~B*41~C*17~DRB1*11~DQB1*03	1,03	0	1,03	inf	0,039	increase
A*02~B*35~C*04~DRB1*04~DQB1*03	0,54	1,56	−1,02	2,9	0,483	decrease
A*01~B*35~C*04~DRB1*13~DQB1*06	0	1,47	−1,47	inf	0,134	decrease
A*01~B*08~C*07~DRB1*03~DQB1*02	0	1,21	−1,21	inf	0,218	decrease
A*24~B*08~C*07~DRB1*03~DQB1*02	0	1,21	−1,21	inf	0,218	decrease
A*11~B*52~C*12~DRB1*15~DQB1*06	0,54	1,17	−0,63	2,2	0,696	decrease
A*33~B*14~C*08~DRB1*01~DQB1*05	0,54	1,08	−0,54	2	1	decrease
A*24~B*49~C*07~DRB1*11~DQB1*03	0	1,08	−1,08	inf	0,368	decrease
A*02~B*50~C*06~DRB1*07~DQB1*02	0	1,08	−1,08	inf	0,368	decrease
A*23~B*49~C*07~DRB1*11~DQB1*03~DPB1*04	3,37	0,99	2,38	3,4	0,034	increase
A*02~B*51~C*16~DRB1*11~DQB1*03~DPB1*04	1,69	0	1,69	inf	0,012	increase
A*24~B*35~C*04~DRB1*11~DQB1*03~DPB1*02	1,69	0	1,69	inf	0,012	increase
A*02~B*35~C*04~DRB1*11~DQB1*03~DPB1*04	1,69	3,42	−1,73	2	0,323	decrease
A*02~B*51~C*15~DRB1*11~DQB1*03~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*01~B*40~C*15~DRB1*14~DQB1*05~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*03~B*35~C*04~DRB1*16~DQB1*05~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*02~B*44~C*05~DRB1*01~DQB1*05~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*23~B*49~C*07~DRB1*04~DQB1*03~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*26~B*38~C*12~DRB1*03~DQB1*02~DPB1*04	1,12	0	1,12	inf	0,051	increase

Haplotype Name	**2001-2011**	**2011-2025**	**Rate Difference**	**Fold Change**	**P value (Exact))**	**Direction**
A*24~B*35~C*04~DRB1*13~DQB1*03~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*24~B*18~C*07~DRB1*15~DQB1*06~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*03~B*07~C*07~DRB1*15~DQB1*06~DPB1*01	1,12	0	1,12	inf	0,051	increase
A*02~B*52~C*12~DRB1*15~DQB1*05~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*03~B*51~C*01~DRB1*01~DQB1*05~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*02~B*15~C*15~DRB1*04~DQB1*03~DPB1*02	1,12	0	1,12	inf	0,051	increase
A*24~B*50~C*06~DRB1*11~DQB1*02~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*26~B*49~C*07~DRB1*15~DQB1*05~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*26~B*08~C*07~DRB1*03~DQB1*02~DPB1*04	1,12	0,99	0,13	1,1	1	increase
A*03~B*08~C*07~DRB1*03~DQB1*02~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*24~B*48~C*08~DRB1*04~DQB1*03~DPB1*02	1,12	0	1,12	inf	0,051	increase
A*02~B*13~C*06~DRB1*07~DQB1*02~DPB1*02	1,12	0	1,12	inf	0,051	increase
A*30~B*13~C*06~DRB1*07~DQB1*02~DPB1*05	1,12	0	1,12	inf	0,051	increase
A*11~B*35~C*04~DRB1*08~DQB1*04~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*01~B*44~C*07~DRB1*11~DQB1*03~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*02~B*51~C*07~DRB1*14~DQB1*05~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*02~B*50~C*06~DRB1*11~DQB1*03~DPB1*04	1,12	0	1,12	inf	0,051	increase
A*01~B*35~C*04~DRB1*13~DQB1*06~DPB1*04	0	1,49	−1,49	inf	0,221	decrease
A*11~B*52~C*12~DRB1*15~DQB1*06~DPB1*04	0	1,01	−1,01	inf	0,346	decrease
A*24~B*35~C*04~DRB1*11~DQB1*03~DPB1*04	0	0,99	−0,99	inf	0,346	decrease
A*24~B*35~DRB1*11	1,82	1,5	0,32	1,2	0,18	increase
A*02~B*51~DRB1*11	1,24	1,47	−0,23	1,2	0,338	decrease
A*24~B*18~DRB1*11	1,13	0,61	0,52	1,9	0,003	increase
A*02~B*51~DRB1*04	1,12	1,18	−0,06	1,1	0,794	decrease
A*01~B*08~DRB1*03	1,11	1,13	−0,02	1	0,929	stabil
A*33~B*14~DRB1*01	0,99	0,9	0,09	1,1	0,625	increase
A*01~B*35~DRB1*11	0,98	1,09	−0,11	1,1	0,646	decrease

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*03~B*35~DRB1*11	0,96	0,66	0,3	1,5	0,083	increase
A*02~B*50~DRB1*07	0,92	0,94	−0,02	1	0,922	stabil
A*02~B*18~DRB1*11	0,87	1,03	−0,16	1,2	0,392	decrease
A*03~C*04	4,87	2,36	2,51	2,1	0,009	increase
A*23~C*07	4,81	1,98	2,83	2,4	0,001	increase
A*02~C*12	4,71	2,73	1,98	1,7	0,034	increase
A*02~C*07	4,63	5,67	−1,04	1,2	0,407	decrease
A*02~C*04	3,8	3,36	0,44	1,1	0,653	increase
A*11~C*04	3,48	2,67	0,81	1,3	0,402	increase
A*02~C*06	3,37	2,04	1,33	1,7	0,089	increase
A*01~C*07	3,32	2,88	0,44	1,2	0,745	increase
A*01~C*06	3,07	2,3	0,77	1,3	0,283	increase
A*26~C*12	2,81	1,58	1,23	1,8	0,134	increase
A*24~C*04	2,65	3,48	−0,83	1,3	0,546	decrease
A*02~C*05	0,26	0	0	0	1	stabil
A*30~C*16	2,35	0,28	2,07	8,4	0	increase
A*24~C*07	2,25	3,01	−0,76	1,3	0,419	decrease
A*02~C*15	2,17	2,05	0,12	1,1	0,851	increase
A*32~C*12	1,84	1,21	0,63	1,5	0,325	increase
A*02~C*16	1,71	1,07	0,64	1,6	0,303	increase
A*02~C*17	1,6	0,69	0,91	2,3	0,112	increase
A*30~C*06	1,6	1,18	0,42	1,4	0,455	increase
A*24~C*14	1,5	0,71	0,79	2,1	0,112	increase
A*03~C*07	1,47	2,28	−0,81	1,6	0,575	decrease
A*01~C*15	1,36	1,15	0,21	1,2	0,798	increase
A*33~C*08	1,34	1,45	−0,11	1,1	1	decrease
A*32~C*04	1,34	1,42	−0,08	1,1	1	decrease

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*01~C*14	1,15	0,43	0,72	2,7	0,103	increase
A*32~C*02	1,07	0,29	0,78	3,7	0,047	increase
A*33~C*15	1,07	0,05	1,02	21,4	0,001	increase
A*01~C*04	0,83	2,41	−1,58	2,9	0,043	decrease
A*03~C*12	0	2,36	−2,36	inf	0	decrease
A*02~C*03	0,8	1,77	−0,97	2,2	0,204	decrease
A*24~C*12	0,59	1,67	−1,08	2,8	0,119	decrease
A*03~C*06	0,48	1,53	−1,05	3,2	0,165	decrease
A*02~C*14	0	1,52	−1,52	inf	0,008	decrease
A*11~C*12	0	1,3	−1,3	inf	0,019	decrease
A*11~C*07	0,27	1,28	−1,01	4,7	0,122	decrease
A*02~C*01	0,29	1,14	−0,85	3,9	0,176	decrease
A*24~C*03	0,53	1,05	−0,52	2	0,58	decrease
A*24~C*01	0,91	1,04	−0,13	1,1	1	decrease
A*26~C*07	0,96	1,02	−0,06	1,1	0,792	decrease
A*02~C*02	0,64	0,94	−0,3	1,5	0,573	decrease
A*24~C*06	0,72	0,91	−0,19	1,3	1	decrease
A*24~C*15	0,86	0,9	−0,04	1	1	stabil
A*02~DPB1*04	19,16	12,65	6,51	1,5	0,004	increase
A*24~DPB1*04	6,83	11,39	−4,56	1,7	0,012	decrease
A*02~DPB1*02	6,29	3,68	2,61	1,7	0,062	increase
A*03~DPB1*04	5,5	6,92	−1,42	1,3	0,451	decrease
A*01~DPB1*04	5,26	5,16	0,1	1	1	increase
A*11~DPB1*04	4,89	5,39	−0,5	1,1	0,89	decrease
A*26~DPB1*04	3,81	3,02	0,79	1,3	0,501	increase
A*23~DPB1*04	2,76	1,74	1,02	1,6	0,299	increase
A*68~DPB1*04	2,74	1,71	1,03	1,6	0,299	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*32~DPB1*04	2,5	2,87	−0,37	1,1	0,852	decrease
A*03~DPB1*02	2,5	0,85	1,65	2,9	0,025	increase
A*24~DPB1*02	1,47	2,52	−1,05	1,7	0,288	decrease
A*30~DPB1*04	1,38	2,16	−0,78	1,6	0,359	decrease
A*01~DPB1*03	1,36	0,6	0,76	2,3	0,341	increase
A*33~DPB1*04	1,29	1,32	−0,03	1	1	stabil
A*26~DPB1*05	1,27	0	1,27	inf	0,006	increase
A*24~DPB1*03	1,14	1,97	−0,83	1,7	0,327	decrease
A*11~DPB1*02	1,08	1,98	−0,9	1,8	0,327	decrease
A*02~DPB1*03	0,8	4,24	−3,44	5,3	0,001	decrease
A*01~DPB1*02	0,86	4,21	−3,35	4,9	0,001	decrease
A*33~DPB1*02	0,86	1,74	−0,88	2	0,294	decrease
A*03~DPB1*03	0,45	1,08	−0,63	2,4	0,315	decrease
A*29~DPB1*04	0,32	1,03	−0,71	3,2	0,478	decrease
A*03~DPB1*13	0,56	1,02	−0,46	1,8	0,74	decrease
A*02~DQB1*03	12,12	10,82	1,3	1,1	0,577	increase
A*02~DQB1*05	6,33	4,31	2,02	1,5	0,107	increase
A*02~DQB1*06	5,88	4,2	1,68	1,4	0,22	increase
A*24~DQB1*03	5,71	8,69	−2,98	1,5	0,06	decrease
A*03~DQB1*03	4,66	3,87	0,79	1,2	0,465	increase
A*02~DQB1*02	4,42	4,02	0,4	1,1	0,661	increase
A*03~DQB1*05	3,71	2,98	0,73	1,2	0,505	increase
A*01~DQB1*03	2,83	3,97	−1,14	1,4	0,338	decrease
A*11~DQB1*03	2,68	2,71	−0,03	1	1	stabil
A*24~DQB1*05	2,58	2,25	0,33	1,1	0,704	increase
A*26~DQB1*05	2,58	0,44	2,14	5,9	0,002	increase
A*33~DQB1*05	2,53	1,43	1,1	1,8	0,194	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*01~DQB1*06	2,51	2,57	−0,06	1	1	stabil
A*26~DQB1*03	2,49	2,4	0,09	1	0,851	stabil
A*23~DQB1*03	2,42	1,39	1,03	1,7	0,182	increase
A*24~DQB1*06	2,15	4,39	−2,24	2	0,054	decrease
A*32~DQB1*03	2,08	1,74	0,34	1,2	0,666	increase
A*01~DQB1*02	2,02	2,29	−0,27	1,1	0,839	decrease
A*03~DQB1*02	1,72	2,39	−0,67	1,4	0,542	decrease
A*01~DQB1*05	1,7	1,71	−0,01	1	1	stabil
A*23~DQB1*05	1,65	0,34	1,31	4,9	0,026	increase
A*11~DQB1*05	1,63	1,63	0	1	1	stabil
A*30~DQB1*03	1,61	1,88	−0,27	1,2	1	decrease
A*32~DQB1*05	1,48	0,73	0,75	2	0,262	increase
A*68~DQB1*05	1,42	0	1,42	inf	0,001	increase
A*11~DQB1*02	1,31	1,55	−0,24	1,2	0,809	decrease
A*03~DQB1*06	1,29	1,84	−0,55	1,4	0,497	decrease
A*30~DQB1*02	1,24	1,1	0,14	1,1	0,785	increase
A*01~DQB1*04	1,03	0,2	0,83	5,2	0,113	increase
A*11~DQB1*06	1,03	2,48	−1,45	2,4	0,091	decrease
A*31~DQB1*03	0,92	0,72	0,2	1,3	0,738	increase
A*26~DQB1*02	0,71	1,21	−0,5	1,7	0,552	decrease
A*68~DQB1*06	0,39	1,18	−0,79	3	0,222	decrease
A*30~DQB1*06	0	1,14	−1,14	inf	0,016	decrease
A*23~DQB1*06	0	1,07	−1,07	inf	0,027	decrease
A*29~DQB1*03	0,84	1,06	−0,22	1,3	1	decrease
A*24~DQB1*02	0,67	1,01	−0,34	1,5	0,547	decrease
A*68~DQB1*02	0,36	0,95	−0,59	2,6	0,496	decrease
A*24~DRB1*11	5,34	3,94	1,4	1,4	0	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
A*02~DRB1*11	4,01	4,38	−0,37	1,1	0,378	decrease
A*02~DRB1*04	3,43	3,8	−0,37	1,1	0,345	decrease
A*01~DRB1*11	2,89	2,85	0,04	1	0,866	stabil
A*02~DRB1*15	2,83	1,96	0,87	1,4	0,002	increase
A*02~DRB1*13	2,79	2,72	0,07	1	0,863	stabil
A*03~DRB1*04	2,72	2,31	0,41	1,2	0,162	increase
A*02~DRB1*16	2,36	1,9	0,46	1,2	0,098	increase
A*02~DRB1*07	2,34	2,59	−0,25	1,1	0,436	decrease
A*24~DRB1*04	2,28	2,15	0,13	1,1	0,654	increase
A*02~DRB1*01	1,97	1,14	0,83	1,7	0	increase
A*03~DRB1*11	1,9	1,85	0,05	1	0,89	stabil
A*02~DRB1*03	1,81	1,92	−0,11	1,1	0,731	decrease
A*11~DRB1*15	1,7	1,42	0,28	1,2	0,249	increase
A*01~DRB1*07	1,57	1,3	0,27	1,2	0,201	increase
A*26~DRB1*04	1,51	1,33	0,18	1,1	0,424	increase
A*02~DRB1*14	1,46	1,41	0,05	1	0,813	stabil
A*32~DRB1*11	1,46	1,62	−0,16	1,1	0,499	decrease
A*24~DRB1*15	1,34	1,39	−0,05	1	0,872	stabil
A*01~DRB1*13	1,3	1,5	−0,2	1,2	0,386	decrease
A*01~DRB1*03	1,25	1,73	−0,48	1,4	0,035	decrease
A*24~DRB1*13	1,24	1,8	−0,56	1,5	0,018	decrease
A*11~DRB1*11	1,19	0,8	0,39	1,5	0,031	increase
A*03~DRB1*13	1,16	1,14	0,02	1	1	stabil
A*11~DRB1*04	1,13	0,93	0,2	1,2	0,299	increase
A*23~DRB1*11	1,07	1,05	0,02	1	1	stabil
A*26~DRB1*11	0,99	1,2	−0,21	1,2	0,288	decrease
A*03~DRB1*15	0,69	1,49	−0,8	2,2	0	decrease

Haplotype Name	**2001-2011**	**2011-2025**	**Rate Difference**	**Fold Change**	**P value (Exact))**	**Direction**
A*01~DRB1*04	0,96	1,27	−0,31	1,3	0,138	decrease
A*03~DRB1*01	0,86	1,23	−0,37	1,4	0,061	decrease
A*24~DRB1*14	0,88	1,2	−0,32	1,4	0,126	decrease
A*03~DRB1*03	0,95	1,03	−0,08	1,1	0,778	decrease
A*33~DRB1*01	0,97	1,01	−0,04	1	0,925	stabil
A*24~DRB1*07	0,65	1,01	−0,36	1,6	0,046	decrease
A*01~DRB1*15	0,67	1	−0,33	1,5	0,059	decrease
A*11~DRB1*07	0,68	0,99	−0,31	1,5	0,072	decrease
A*03~DRB1*07	0,69	0,97	−0,28	1,4	0,133	decrease
B*35~DPB1*04	11,79	12,84	−1,05	1,1	0,643	decrease
B*51~DPB1*04	10,02	5,85	4,17	1,7	0,014	increase
B*07~DPB1*04	5,32	2,56	2,76	2,1	0,023	increase
B*44~DPB1*04	5,11	4,66	0,45	1,1	0,776	increase
B*18~DPB1*04	3,56	3,32	0,24	1,1	1	increase
B*35~DPB1*02	2,72	4,74	−2,02	1,7	0,152	decrease
B*49~DPB1*04	2,44	3,82	−1,38	1,6	0,224	decrease
B*38~DPB1*04	2,41	2,6	−0,19	1,1	1	decrease
B*08~DPB1*04	2,18	2,76	−0,58	1,3	0,694	decrease
B*55~DPB1*04	2,16	2,24	−0,08	1	1	stabil
B*51~DPB1*02	1,96	1,37	0,59	1,4	0,462	increase
B*35~DPB1*03	1,87	2,4	−0,53	1,3	0,68	decrease
B*18~DPB1*02	1,83	1,39	0,44	1,3	0,807	increase
B*39~DPB1*04	1,51	0,42	1,09	3,6	0,109	increase
B*40~DPB1*02	1,44	0,29	1,15	5	0,043	increase
B*50~DPB1*04	1,4	0,44	0,96	3,2	0,183	increase
B*13~DPB1*02	1,38	0,52	0,86	2,7	0,183	increase
B*44~DPB1*03	1,27	0,21	1,06	6	0,047	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
B*13~DPB1*17	1,27	0,97	0,3	1,3	0,771	increase
B*27~DPB1*04	1,19	1,77	−0,58	1,5	0,626	decrease
B*52~DPB1*04	1,08	2,13	−1,05	2	0,235	decrease
B*44~DPB1*02	1,08	0,61	0,47	1,8	0,509	increase
B*57~DPB1*04	1,08	1,68	−0,6	1,6	0,602	decrease
B*51~DPB1*03	1,03	0,48	0,55	2,1	0,299	increase
B*13~DPB1*04	1,01	1,66	−0,65	1,6	0,602	decrease
B*15~DPB1*04	0,97	1,95	−0,98	2	0,204	decrease
B*15~DPB1*19	0,86	0	0,86	inf	0,033	increase
B*40~DPB1*04	0,8	2,63	−1,83	3,3	0,041	decrease
B*07~DPB1*02	0,82	1,84	−1,02	2,2	0,294	decrease
B*52~DPB1*02	0,37	1,56	−1,19	4,2	0,081	decrease
B*58~DPB1*04	0,5	1,15	−0,65	2,3	0,315	decrease
B*15~DPB1*02	0,39	1,11	−0,72	2,8	0,315	decrease
B*49~DPB1*03	0	1,1	−1,1	inf	0,022	decrease
B*35~DQB1*03	7,21	10,86	−3,65	1,5	0,044	decrease
B*51~DQB1*03	6,74	4,46	2,28	1,5	0,116	increase
B*35~DQB1*05	5,47	5,7	−0,23	1	1	decrease
B*44~DQB1*03	4,36	2,88	1,48	1,5	0,201	increase
B*13~DQB1*02	4,18	2,43	1,75	1,7	0,088	increase
B*18~DQB1*03	3,56	3,7	−0,14	1	1	decrease
B*51~DQB1*05	3,26	2,02	1,24	1,6	0,187	increase
B*51~DQB1*06	3,03	2,28	0,75	1,3	0,456	increase
B*07~DQB1*05	2,94	1,27	1,67	2,3	0,054	increase
B*08~DQB1*02	2,55	3,55	−1	1,4	0,403	decrease
B*07~DQB1*06	2,53	1,79	0,74	1,4	0,419	increase
B*49~DQB1*03	2,4	2,81	−0,41	1,2	0,716	decrease

Haplotype Name	**2001-2011**	**2011-2025**	**Rate Difference**	**Fold Change**	**P value (Exact))**	**Direction**
B*35~DQB1*06	2,34	3,24	−0,9	1,4	0,482	decrease
B*40~DQB1*05	2,06	0,62	1,44	3,3	0,031	increase
B*07~DQB1*03	1,91	2,93	−1,02	1,5	0,351	decrease
B*44~DQB1*06	1,87	0,34	1,53	5,5	0,014	increase
B*18~DQB1*05	1,74	0,74	1	2,4	0,17	increase
B*50~DQB1*02	1,72	1,64	0,08	1	1	stabil
B*57~DQB1*03	1,72	0,7	1,02	2,5	0,092	increase
B*44~DQB1*05	1,61	0,56	1,05	2,9	0,068	increase
B*35~DQB1*02	1,55	2,23	−0,68	1,4	0,404	decrease
B*35~DQB1*04	1,46	0	1,46	inf	0,001	increase
B*14~DQB1*05	1,46	1,42	0,04	1	1	stabil
B*27~DQB1*03	1,42	1,62	−0,2	1,1	1	decrease
B*39~DQB1*05	1,37	0,13	1,24	10,5	0,014	increase
B*55~DQB1*05	1,35	0,41	0,94	3,3	0,093	increase
B*27~DQB1*06	1,31	1,07	0,24	1,2	0,785	increase
B*15~DQB1*03	1,2	2,15	−0,95	1,8	0,377	decrease
B*44~DQB1*02	1,18	1,9	−0,72	1,6	0,497	decrease
B*40~DQB1*03	1,16	1,33	−0,17	1,1	0,794	decrease
B*49~DQB1*06	1,12	1,51	−0,39	1,3	0,617	decrease
B*52~DQB1*05	1,07	0	1,07	inf	0,008	increase
B*41~DQB1*03	1,07	0,72	0,35	1,5	0,519	increase
B*50~DQB1*03	1,07	0,57	0,5	1,9	0,315	increase
B*38~DQB1*03	1,05	1,66	−0,61	1,6	0,617	decrease
B*55~DQB1*03	1,05	1,29	−0,24	1,2	0,794	decrease
B*18~DQB1*06	1,05	0,8	0,25	1,3	0,757	increase
B*49~DQB1*05	0,97	1,11	−0,14	1,1	1	decrease
B*52~DQB1*06	0,36	3,34	−2,98	9,3	0	decrease

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
B*38~DQB1*06	0,82	1,84	−1,02	2,2	0,222	decrease
B*51~DQB1*02	0	1,33	−1,33	inf	0,017	decrease
B*40~DQB1*06	0	1,15	−1,15	inf	0,016	decrease
B*41~DQB1*02	0,43	1,14	−0,71	2,7	0,222	decrease
B*15~DQB1*06	0	0,95	−0,95	inf	0,048	decrease
B*35~DRB1*11	5,32	5,32	0	1	1	stabil
B*18~DRB1*11	3,26	2,46	0,8	1,3	0,009	increase
B*51~DRB1*04	3	2,44	0,56	1,2	0,069	increase
B*51~DRB1*11	2,77	3,68	−0,91	1,3	0,007	decrease
B*35~DRB1*04	2,71	2,92	−0,21	1,1	0,535	decrease
B*08~DRB1*03	2,68	3,39	−0,71	1,3	0,032	decrease
B*13~DRB1*07	2,4	2,49	−0,09	1	0,763	stabil
B*35~DRB1*01	2,21	1,57	0,64	1,4	0,013	increase
B*35~DRB1*14	2,13	1,88	0,25	1,1	0,344	increase
B*35~DRB1*13	2,09	1,84	0,25	1,1	0,339	increase
B*44~DRB1*04	2,03	1,86	0,17	1,1	0,495	increase
B*51~DRB1*13	1,87	1,6	0,27	1,2	0,276	increase
B*07~DRB1*15	1,67	1,8	−0,13	1,1	0,669	decrease
B*44~DRB1*11	1,58	1,51	0,07	1	0,761	stabil
B*50~DRB1*07	1,39	1,91	−0,52	1,4	0,037	decrease
B*49~DRB1*11	1,35	1,61	−0,26	1,2	0,283	decrease
B*14~DRB1*01	1,29	1,51	−0,22	1,2	0,346	decrease
B*35~DRB1*15	1,27	1,15	0,12	1,1	0,604	increase
B*38~DRB1*13	1,23	1,07	0,16	1,1	0,477	increase
B*51~DRB1*15	1,13	1,2	−0,07	1,1	0,794	decrease
B*27~DRB1*11	1,13	0,63	0,5	1,8	0,004	increase
B*44~DRB1*07	1,13	1,03	0,1	1,1	0,648	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
B*52~DRB1*15	1,12	2,21	−1,09	2	0	decrease
B*18~DRB1*15	1,01	0,8	0,21	1,3	0,267	increase
B*40~DRB1*04	0,95	0,78	0,17	1,2	0,302	increase
B*51~DRB1*14	0,58	1,12	−0,54	1,9	0,003	decrease
B*55~DRB1*14	0,61	1,07	−0,46	1,8	0,008	decrease
B*15~DRB1*13	0,74	1,06	−0,32	1,4	0,084	decrease
B*07~DRB1*11	0,58	0,99	−0,41	1,7	0,019	decrease
C*04~B*35	16,58	16,22	0,36	1	0,825	increase
C*07~B*49	6,68	4,48	2,2	1,5	0,07	increase
C*15~B*51	5,86	4,48	1,38	1,3	0,241	increase
C*14~B*51	4,55	3,28	1,27	1,4	0,226	increase
C*07~B*07	4,52	4,55	−0,03	1	1	stabil
C*05~B*44	4,01	2,15	1,86	1,9	0,03	increase
C*06~B*50	4,01	2,79	1,22	1,4	0,193	increase
C*16~B*51	4,01	1,59	2,42	2,5	0,003	increase
C*12~B*38	3,48	3,67	−0,19	1,1	1	decrease
C*12~B*18	3,18	2,3	0,88	1,4	0,283	increase
C*06~B*13	2,94	3,43	−0,49	1,2	0,762	decrease
C*07~B*18	2,43	2,78	−0,35	1,1	0,867	decrease
C*07~B*08	2,14	4,18	−2,04	2	0,068	decrease
C*12~B*39	1,87	1,23	0,64	1,5	0,331	increase
C*01~B*55	1,87	1,7	0,17	1,1	0,832	increase
C*16~B*44	1,87	1,43	0,44	1,3	0,494	increase
C*17~B*41	1,82	1,52	0,3	1,2	0,513	increase
C*08~B*14	1,6	2,67	−1,07	1,7	0,298	decrease
C*07~B*15	1,6	1,49	0,11	1,1	0,822	increase
C*06~B*37	1,34	0,97	0,37	1,4	0,42	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
C*03~B*55	1,34	1,09	0,25	1,2	0,604	increase
C*02~B*44	1,34	0,36	0,98	3,7	0,024	increase
C*12~B*52	1,34	3	−1,66	2,2	0,07	decrease
C*04~B*44	1,07	1,02	0,05	1	0,792	stabil
C*07~B*58	1,07	0,73	0,34	1,5	0,523	increase
C*06~B*57	1,07	1,73	−0,66	1,6	0,519	decrease
C*08~B*48	1,07	0,79	0,28	1,4	0,54	increase
C*02~B*40	1,07	0,39	0,68	2,7	0,087	increase
C*03~B*40	0,8	2,35	−1,55	2,9	0,059	decrease
C*02~B*27	0,8	1,9	−1,1	2,4	0,151	decrease
C*12~B*35	0,53	1,61	−1,08	3	0,118	decrease
C*03~B*15	0	1,3	−1,3	inf	0,019	decrease
C*07~DPB1*04	16,46	12,5	3,96	1,3	0,209	increase
C*04~DPB1*04	7,75	12,89	−5,14	1,7	0,085	decrease
C*15~DPB1*04	6,57	2,47	4,1	2,7	0,009	increase
C*06~DPB1*04	5,34	4,67	0,67	1,1	0,694	increase
C*16~DPB1*04	5,11	1,32	3,79	3,9	0,006	increase
C*07~DPB1*02	4,78	4	0,78	1,2	0,672	increase
C*12~DPB1*02	4,44	3,37	1,07	1,3	0,5	increase
C*12~DPB1*04	3,99	9,66	−5,67	2,4	0,014	decrease
C*05~DPB1*04	2,7	1,01	1,69	2,7	0,077	increase
C*01~DPB1*04	2,47	3,06	−0,59	1,2	0,8	decrease
C*06~DPB1*02	2,36	1,8	0,56	1,3	0,755	increase
C*04~DPB1*02	2,3	5,42	−3,12	2,4	0,105	decrease
C*04~DPB1*09	2,25	0	2,25	inf	0,003	increase
C*14~DPB1*04	2,19	0,69	1,5	3,2	0,081	increase
C*04~DPB1*03	1,74	2,03	−0,29	1,2	1	decrease

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
C*06~DPB1*05	1,69	0	1,69	inf	0,011	increase
C*14~DPB1*03	1,63	0,75	0,88	2,2	0,389	increase
C*07~DPB1*03	1,18	2,52	−1,34	2,1	0,387	decrease
C*03~DPB1*03	1,12	0,39	0,73	2,9	0,22	increase
C*06~DPB1*10	1,12	0,31	0,81	3,6	0,22	increase
C*17~DPB1*04	1,12	0	1,12	inf	0,051	increase
C*08~DPB1*02	1,12	1,19	−0,07	1,1	1	decrease
C*15~DPB1*01	1,12	0	1,12	inf	0,051	increase
C*03~DPB1*04	0	4,43	−4,43	inf	0,002	decrease
C*02~DPB1*04	0,79	2,25	−1,46	2,8	0,212	decrease
C*08~DPB1*04	0	1,72	−1,72	inf	0,128	decrease
C*15~DPB1*02	0	1,57	−1,57	inf	0,128	decrease
C*06~DPB1*17	0,56	0,98	−0,42	1,8	1	decrease
C*07~DQB1*03	8,97	8,13	0,84	1,1	0,765	increase
C*04~DQB1*03	8,26	10,82	−2,56	1,3	0,343	decrease
C*06~DQB1*02	7,5	4,72	2,78	1,6	0,139	increase
C*07~DQB1*06	5,76	4,47	1,29	1,3	0,437	increase
C*06~DQB1*03	5	1,99	3,01	2,5	0,037	increase
C*07~DQB1*02	4,89	4,58	0,31	1,1	0,845	increase
C*12~DQB1*05	4,29	2,1	2,19	2	0,116	increase
C*07~DQB1*05	4,13	3,06	1,07	1,3	0,367	increase
C*15~DQB1*03	4,08	2,8	1,28	1,5	0,341	increase
C*05~DQB1*03	3,8	1,75	2,05	2,2	0,093	increase
C*15~DQB1*05	3,53	1,44	2,09	2,5	0,123	increase
C*12~DQB1*03	3,32	5,51	−2,19	1,7	0,262	decrease
C*16~DQB1*03	3,26	1,37	1,89	2,4	0,106	increase
C*02~DQB1*05	2,72	1,13	1,59	2,4	0,15	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
C*04~DQB1*06	2,66	3,91	−1,25	1,5	0,519	decrease
C*04~DQB1*05	2,17	5,04	−2,87	2,3	0,111	decrease
C*16~DQB1*06	2,17	0,28	1,89	7,8	0,016	increase
C*12~DQB1*06	2,12	6,25	−4,13	2,9	0,029	decrease
C*14~DQB1*06	1,79	0,54	1,25	3,3	0,145	increase
C*05~DQB1*05	1,63	0	1,63	inf	0,008	increase
C*04~DQB1*04	1,47	0	1,47	inf	0,008	increase
C*01~DQB1*06	1,41	1,55	−0,14	1,1	1	decrease
C*03~DQB1*05	1,36	0,36	1	3,8	0,26	increase
C*03~DQB1*03	1,36	2,56	−1,2	1,9	0,403	decrease
C*14~DQB1*05	1,25	0,38	0,87	3,3	0,26	increase
C*04~DQB1*02	1,2	2,87	−1,67	2,4	0,286	decrease
C*01~DQB1*05	1,2	0,26	0,94	4,6	0,178	increase
C*14~DQB1*04	1,09	0	1,09	inf	0,039	increase
C*08~DQB1*03	1,09	0,57	0,52	1,9	0,341	increase
C*14~DQB1*03	0,76	1,21	−0,45	1,6	0,696	decrease
C*17~DQB1*03	0,71	1,16	−0,45	1,6	0,696	decrease
C*01~DQB1*03	0,71	1,6	−0,89	2,3	0,483	decrease
C*08~DQB1*05	0,54	1,24	−0,7	2,3	0,696	decrease
C*06~DQB1*05	0	1,81	−1,81	inf	0,083	decrease
C*03~DQB1*02	0	1,67	−1,67	inf	0,138	decrease
C*03~DQB1*06	0	1,43	−1,43	inf	0,134	decrease
C*06~DQB1*06	0	1,23	−1,23	inf	0,218	decrease
C*02~DQB1*03	0	1,2	−1,2	inf	0,218	decrease
C*07~DRB1*11	5,7	5,23	0,47	1,1	0,714	increase
C*06~DRB1*07	4,49	4,39	0,1	1	0,894	increase
C*04~DRB1*11	4,09	5,41	−1,32	1,3	0,327	decrease

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
C*07~DRB1*15	4,01	3,41	0,6	1,2	0,549	increase
C*07~DRB1*03	3,32	3,74	−0,42	1,1	0,771	decrease
C*12~DRB1*04	3,21	2,15	1,06	1,5	0,197	increase
C*07~DRB1*04	2,97	1,56	1,41	1,9	0,06	increase
C*06~DRB1*11	2,94	0,99	1,95	3	0,003	increase
C*04~DRB1*08	2,73	0,49	2,24	5,6	0	increase
C*16~DRB1*13	2,51	0,29	2,22	8,7	0	increase
C*15~DRB1*11	2,49	1,59	0,9	1,6	0,281	increase
C*12~DRB1*11	2,41	2,31	0,1	1	0,856	increase
C*04~DRB1*01	2,38	1,98	0,4	1,2	0,559	increase
C*04~DRB1*13	2,09	2,47	−0,38	1,2	0,86	decrease
C*04~DRB1*04	1,9	3,57	−1,67	1,9	0,097	decrease
C*02~DRB1*16	1,87	0,7	1,17	2,7	0,028	increase
C*16~DRB1*04	1,87	1,28	0,59	1,5	0,338	increase
C*15~DRB1*15	1,66	1,13	0,53	1,5	0,441	increase
C*15~DRB1*04	1,63	1,44	0,19	1,1	0,818	increase
C*04~DRB1*07	1,58	0,98	0,6	1,6	0,273	increase
C*15~DRB1*14	1,55	0,75	0,8	2,1	0,124	increase
C*14~DRB1*04	1,55	0,7	0,85	2,2	0,112	increase
C*01~DRB1*13	1,52	0,62	0,9	2,5	0,043	increase
C*12~DRB1*16	1,44	0,49	0,95	2,9	0,055	increase
C*12~DRB1*15	1,44	3,09	−1,65	2,1	0,052	decrease
C*14~DRB1*14	1,28	0,1	1,18	12,8	0	increase
C*07~DRB1*08	1,26	0,49	0,77	2,6	0,055	increase
C*05~DRB1*16	1,23	0,08	1,15	15,4	0	increase
C*05~DRB1*11	1,15	0,69	0,46	1,7	0,348	increase
C*06~DRB1*16	1,07	0,53	0,54	2	0,273	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
C*04~DRB1*16	1,07	0,38	0,69	2,8	0,072	increase
C*04~DRB1*15	1,04	1,72	−0,68	1,7	0,519	decrease
C*12~DRB1*14	0,99	1,34	−0,35	1,4	0,814	decrease
C*07~DRB1*01	0,99	0,83	0,16	1,2	0,55	increase
C*07~DRB1*13	0,64	2,68	−2,04	4,2	0,007	decrease
C*08~DRB1*01	0,75	1,86	−1,11	2,5	0,207	decrease
C*12~DRB1*13	0,75	1,7	−0,95	2,3	0,275	decrease
C*06~DRB1*03	0,75	1,56	−0,81	2,1	0,363	decrease
C*03~DRB1*13	0	1,2	−1,2	inf	0,03	decrease
C*07~DRB1*07	0	1,09	−1,09	inf	0,046	decrease
C*04~DRB1*14	0,72	1,06	−0,34	1,5	1	decrease
C*14~DRB1*11	0	1,04	−1,04	inf	0,044	decrease
DQB1*03~DPB1*04	25,65	23,24	2,41	1,1	0,389	increase
DQB1*05~DPB1*04	14,48	10,46	4,02	1,4	0,048	increase
DQB1*06~DPB1*04	7,98	13,49	−5,51	1,7	0,006	decrease
DQB1*02~DPB1*04	7,54	8,27	−0,73	1,1	0,734	decrease
DQB1*03~DPB1*02	6,78	7,36	−0,58	1,1	0,81	decrease
DQB1*05~DPB1*02	4,43	3,22	1,21	1,4	0,416	increase
DQB1*06~DPB1*02	3,46	5,5	−2,04	1,6	0,143	decrease
DQB1*03~DPB1*03	3,39	3,93	−0,54	1,2	0,747	decrease
DQB1*02~DPB1*02	1,85	3,08	−1,23	1,7	0,174	decrease
DQB1*02~DPB1*17	1,83	1,12	0,71	1,6	0,44	increase
DQB1*05~DPB1*05	1,72	0	1,72	inf	0,001	increase
DQB1*04~DPB1*04	1,3	0,73	0,57	1,8	0,341	increase
DQB1*06~DPB1*03	1,26	0,83	0,43	1,5	0,544	increase
DQB1*05~DPB1*10	1,24	0,77	0,47	1,6	0,544	increase
DQB1*03~DPB1*13	1,11	1,09	0,02	1	1	stabil

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
DQB1*03~DPB1*05	0,98	0,81	0,17	1,2	1	increase
DQB1*02~DPB1*03	0,63	2,65	−2,02	4,2	0,018	decrease
DQB1*03~DPB1*14	0	1,68	−1,68	inf	0,006	decrease
DQB1*05~DPB1*03	0,87	1,4	−0,53	1,6	0,416	decrease
DQB1*05~DPB1*09	0,83	0,98	−0,15	1,2	1	decrease
DRB1*11~DPB1*04	16,21	14,21	2	1,1	0,391	increase
DRB1*04~DPB1*04	6,53	6,18	0,35	1,1	0,899	increase
DRB1*01~DPB1*04	5,62	3,15	2,47	1,8	0,067	increase
DRB1*13~DPB1*04	5,52	7,97	−2,45	1,4	0,148	decrease
DRB1*15~DPB1*04	5,06	5,74	−0,68	1,1	0,689	decrease
DRB1*03~DPB1*04	4,96	6,18	−1,22	1,2	0,428	decrease
DRB1*14~DPB1*04	4,25	2,55	1,7	1,7	0,125	increase
DRB1*04~DPB1*02	3,97	3,63	0,34	1,1	0,871	increase
DRB1*16~DPB1*04	3,23	2,48	0,75	1,3	0,457	increase
DRB1*15~DPB1*02	3,21	3,08	0,13	1	0,862	increase
DRB1*11~DPB1*02	2,35	1,68	0,67	1,4	0,382	increase
DRB1*07~DPB1*04	2,28	4,32	−2,04	1,9	0,095	decrease
DRB1*07~DPB1*17	2,13	1,13	1	1,9	0,219	increase
DRB1*08~DPB1*04	2,05	1,77	0,28	1,2	0,663	increase
DRB1*07~DPB1*02	2,05	0,94	1,11	2,2	0,129	increase
DRB1*11~DPB1*03	1,96	1,79	0,17	1,1	0,825	increase
DRB1*01~DPB1*02	1,36	1,44	−0,08	1,1	1	decrease
DRB1*14~DPB1*02	1,31	1,23	0,08	1,1	1	increase
DRB1*04~DPB1*03	1,08	2,27	−1,19	2,1	0,166	decrease
DRB1*04~DPB1*05	0,86	0,65	0,21	1,3	0,73	increase
DRB1*13~DPB1*02	0,73	4,19	−3,46	5,7	0	decrease
DRB1*03~DPB1*02	0	1,95	−1,95	inf	0,002	decrease

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
DRB1*07~DPB1*03	0,71	1,16	−0,45	1,6	0,53	decrease
DRB1*15~DPB1*03	0,67	1,16	−0,49	1,7	0,53	decrease
DRB1*03~DPB1*03	0,28	1,06	−0,78	3,8	0,148	decrease
DRB1*11~DPB1*14	0	1,02	−1,02	inf	0,041	decrease
DRB1*11~DQB1*03	22,53	20,05	2,48	1,1	0,311	increase
DRB1*04~DQB1*03	10,92	12,49	−1,57	1,1	0,467	decrease
DRB1*15~DQB1*06	9,44	8,86	0,58	1,1	0,759	increase
DRB1*01~DQB1*05	8,8	5,44	3,36	1,6	0,025	increase
DRB1*14~DQB1*05	7,73	3,81	3,92	2	0,005	increase
DRB1*07~DQB1*02	7,73	7,28	0,45	1,1	0,823	increase
DRB1*03~DQB1*02	6,44	9,26	−2,82	1,4	0,086	decrease
DRB1*13~DQB1*06	5,79	11,13	−5,34	1,9	0,001	decrease
DRB1*16~DQB1*05	4,51	4,38	0,13	1	1	increase
DRB1*10~DQB1*05	3	1,72	1,28	1,7	0,162	increase
DRB1*13~DQB1*03	2,15	1,74	0,41	1,2	0,666	increase
DRB1*15~DQB1*05	2,15	1,37	0,78	1,6	0,353	increase
DRB1*07~DQB1*03	1,93	2,14	−0,21	1,1	1	decrease
DRB1*04~DQB1*04	1,74	1,1	0,64	1,6	0,438	increase
DRB1*08~DQB1*04	1,48	1,29	0,19	1,1	0,806	increase
DRB1*08~DQB1*03	1,09	1,34	−0,25	1,2	0,794	decrease
DRB1*12~DQB1*03	1,07	1,06	0,01	1	1	stabil
DRB1*04~DQB1*06	0,21	0,4	−0,19	1,9	1	decrease
DRB1*11~DQB1*06	0,21	0,27	−0,06	1,3	1	decrease
DRB1*04~DQB1*02	0,21	0,38	−0,17	1,8	1	decrease
DRB1*13~DQB1*05	0,21	0,13	0,08	1,6	1	increase
DRB1*09~DQB1*03	0	1,33	−1,33	inf	0,017	decrease
DRB1*11~DQB1*05	0	0,33	−0,33	inf	0,527	decrease

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
DRB1*08~DQB1*06	0	0,42	−0,42	inf	0,291	decrease
DRB1*04~DQB1*05	0	0,2	−0,2	inf	0,527	decrease
DRB1*07~DQB1*06	0	0,13	−0,13	inf	1	decrease
DRB1*08~DQB1*05	0	0,13	−0,13	inf	1	decrease
DRB1*03~DQB1*05	0	0,13	−0,13	inf	1	decrease
DRB1*03~DQB1*06	0	0,13	−0,13	inf	1	decrease
DRB1*03~DQB1*03	0	0,29	−0,29	inf	0,527	decrease
DRB1*01~DQB1*03	0	0,13	−0,13	inf	1	decrease
DRB1*11~DQB1*03~DPB1*04	16,04	14,61	1,43	1,1	0,549	increase
DRB1*04~DQB1*03~DPB1*04	5,83	4,85	0,98	1,2	0,494	increase
DRB1*01~DQB1*05~DPB1*04	5,48	3	2,48	1,8	0,042	increase
DRB1*03~DQB1*02~DPB1*04	5,02	5,11	−0,09	1	1	stabil
DRB1*14~DQB1*05~DPB1*04	4,93	1,81	3,12	2,7	0,004	increase
DRB1*15~DQB1*06~DPB1*04	3,93	5,39	−1,46	1,4	0,311	decrease
DRB1*04~DQB1*03~DPB1*02	3,8	3,63	0,17	1	0,871	increase
DRB1*13~DQB1*06~DPB1*04	3,43	7,28	−3,85	2,1	0,007	decrease
DRB1*16~DQB1*05~DPB1*04	3	2,93	0,07	1	1	stabil
DRB1*07~DQB1*02~DPB1*04	2,59	3,47	−0,88	1,3	0,48	decrease
DRB1*11~DQB1*03~DPB1*02	2,43	0,9	1,53	2,7	0,084	increase
DRB1*15~DQB1*06~DPB1*02	2,2	2,69	−0,49	1,2	0,693	decrease
DRB1*11~DQB1*03~DPB1*03	2,11	1,63	0,48	1,3	0,649	increase
DRB1*07~DQB1*02~DPB1*17	1,93	1,14	0,79	1,7	0,314	increase
DRB1*13~DQB1*03~DPB1*04	1,74	0,42	1,32	4,1	0,063	increase
DRB1*07~DQB1*02~DPB1*02	1,57	0,31	1,26	5,1	0,043	increase
DRB1*01~DQB1*05~DPB1*02	1,39	1,56	−0,17	1,1	0,801	decrease
DRB1*14~DQB1*05~DPB1*02	1,35	1,01	0,34	1,3	0,771	increase
DRB1*15~DQB1*06~DPB1*03	1,15	0,62	0,53	1,9	0,509	increase

Haplotype Name	2001-2011	2011-2025	Rate Difference	Fold Change	P value (Exact))	Direction
DRB1*13~DQB1*06~DPB1*02	1,13	3,29	−2,16	2,9	0,023	decrease
DRB1*08~DQB1*04~DPB1*04	1,09	0,21	0,88	5,2	0,09	increase
DRB1*10~DQB1*05~DPB1*04	1,02	0,65	0,37	1,6	0,509	increase
DRB1*08~DQB1*03~DPB1*04	0,87	1,11	−0,24	1,3	0,766	decrease
DRB1*03~DQB1*02~DPB1*02	0	2,28	−2,28	inf	0	decrease
DRB1*04~DQB1*03~DPB1*03	0,37	1,86	−1,49	5	0,05	decrease
DRB1*03~DQB1*02~DPB1*03	0,28	1,4	−1,12	5	0,05	decrease
DRB1*07~DQB1*02~DPB1*03	0	1,16	−1,16	inf	0,022	decrease
DRB1*11~DQB1*03~DPB1*14	0	0,96	−0,96	inf	0,041	decrease

Appendix 7. All Detected HLA Haplotype Frequencies and Their Changes Over Time Complete list of all HLA haplotypes identified in the donor pool, with their frequencies in both periods and statistical analysis of changes.

	2001-2011			**2011-2025**			
Allele Name	Allele Counts	Total Allele count	Frequencies	Allele Counts	Total Allele count	Frequencies	p_exact
A*01	447	4178	0.1070	1051	8922	0.1178	0.0724
A*02	1052	4178	0.2518	2180	8922	0.2443	0.3610
A*03	461	4178	0.1103	1056	8922	0.1184	0.1870
A*11	320	4178	0.0766	684	8922	0.0767	10.000
A*23	146	4178	0.0349	294	8922	0.0330	0.5670
A*24	626	4178	0.1498	1339	8922	0.1501	0.9790
A*25	41	4178	0.0098	94	8922	0.0105	0.7810
A*26	236	4178	0.0565	515	8922	0.0577	0.8090
A*29	92	4178	0.0220	169	8922	0.0189	0.2540
A*30	142	4178	0.0340	308	8922	0.0345	0.9180
A*31	68	4178	0.0163	137	8922	0.0154	0.7060
A*32	206	4178	0.0493	395	8922	0.0443	0.2100
A*33	117	4178	0.0280	260	8922	0.0291	0.7370
A*34	2	4178	0.0005	0	8922	0.0000	0.1020
A*36	1	4178	0.0002	5	8922	0.0006	0.6720
A*66	24	4178	0.0057	43	8922	0.0048	0.5120
A*68	172	4178	0.0412	323	8922	0.0362	0.1690
A*69	23	4178	0.0055	64	8922	0.0072	0.3000
A*74	2	4178	0.0005	3	8922	0.0003	0.6570
B*07	223	4178	0.0534	453	8922	0.0508	0.525000
B*08	150	4178	0.0359	377	8922	0.0423	0.086100
B*13	151	4178	0.0361	342	8922	0.0383	0.555000
B*14	81	4178	0.0194	213	8922	0.0239	0.114000
B*15	134	4178	0.0321	318	8922	0.0356	0.305000
B*18	263	4178	0.0629	524	8922	0.0587	0.344000
B*27	148	4178	0.0354	289	8922	0.0324	0.375000

	2001-2011			2011-2025			
B*35	799	4178	0.1912	1622	8922	0.1818	0.201000
B*37	80	4178	0.0191	107	8922	0.0120	0.001960
B*38	163	4178	0.0390	402	8922	0.0451	0.117000
B*39	68	4178	0.0163	141	8922	0.0158	0.823000
B*40	172	4178	0.0412	348	8922	0.0390	0.565000
B*41	111	4178	0.0266	209	8922	0.0234	0.275000
B*42	0	4178	0.0000	1	8922	0.0001	1.000.000
B*44	354	4178	0.0847	614	8922	0.0688	0.001420
B*45	6	4178	0.0014	27	8922	0.0030	0.095700
B*46	1	4178	0.0002	14	8922	0.0016	0.048200
B*47	7	4178	0.0017	7	8922	0.0008	0.158000
B*48	26	4178	0.0062	53	8922	0.0059	0.904000
B*49	169	4178	0.0404	354	8922	0.0397	0.848000
B*50	119	4178	0.0285	326	8922	0.0365	0.017300
B*51	533	4178	0.1276	1154	8922	0.1293	0.801000
B*52	88	4178	0.0211	305	8922	0.0342	0.000028
B*53	22	4178	0.0053	39	8922	0.0044	0.493000
B*54	7	4178	0.0017	8	8922	0.0009	0.267000
B*55	150	4178	0.0359	292	8922	0.0327	0.350000
B*56	8	4178	0.0019	37	8922	0.0041	0.053000
B*57	60	4178	0.0144	187	8922	0.0210	0.008830
B*58	74	4178	0.0177	141	8922	0.0158	0.418000
B*59	5	4178	0.0012	1	8922	0.0001	0.014500
B*73	3	4178	0.0007	7	8922	0.0008	1.000.000
B*82	0	4178	0.0000	1	8922	0.0001	1.000.000
B*83	0	4178	0.0000	2	8922	0.0002	1.000.000
C*01	13	374	0.0348	132	3296	0.0400	0.77900

	2001-2011			2011-2025			
C*02	14	374	0.0374	116	3296	0.0352	0.76900
C*03	11	374	0.0294	193	3296	0.0586	0.01690
C*04	69	374	0.1845	642	3296	0.1948	0.67900
C*05	16	374	0.0428	78	3296	0.0237	0.03630
C*06	39	374	0.1043	336	3296	0.1019	0.85700
C*07	74	374	0.1979	704	3296	0.2136	0.50500
C*08	10	374	0.0267	126	3296	0.0382	0.31300
C*12	43	374	0.1150	424	3296	0.1286	0.51200
C*14	19	374	0.0508	130	3296	0.0394	0.27100
C*15	32	374	0.0856	223	3296	0.0677	0.19800
C*16	25	374	0.0668	119	3296	0.0361	0.00694
C*17	9	374	0.0241	55	3296	0.0167	0.29500
C*18	0	374	0.0000	16	3296	0.0049	0.39700
DRB1*01	328	4178	0.0785	594	8922	0.0666	0.01400000
DRB1*03	273	4178	0.0653	790	8922	0.0885	0.00000482
DRB1*04	649	4178	0.1553	1279	8922	0.1434	0.07200000
DRB1*07	371	4178	0.0888	865	8922	0.0970	0.14000000
DRB1*08	109	4178	0.0261	199	8922	0.0223	0.19400000
DRB1*09	35	4178	0.0084	134	8922	0.0150	0.00152000
DRB1*10	110	4178	0.0263	185	8922	0.0207	0.05000000
DRB1*11	904	4178	0.2164	1825	8922	0.2046	0.12200000
DRB1*12	74	4178	0.0177	131	8922	0.0147	0.19900000
DRB1*13	453	4178	0.1084	1030	8922	0.1154	0.24900000
DRB1*14	258	4178	0.0618	571	8922	0.0640	0.64400000
DRB1*15	385	4178	0.0921	895	8922	0.1003	0.14700000
DRB1*16	229	4178	0.0548	423	8922	0.0474	0.07040000
DQB1*02	67	466	0.1438	130	754	0.1724	0.201000

	2001-2011			**2011-2025**			
DQB1*03	188	466	0.4034	311	754	0.4125	0.765000
DQB1*04	15	466	0.0322	19	754	0.0252	0.479000
DQB1*05	123	466	0.2639	133	754	0.1764	0.000378
DQB1*06	73	466	0.1567	161	754	0.2135	0.016500
DPB1*01	8	464	0.0172	0	620	0.0000	0.00109
DPB1*02	76	464	0.1638	122	620	0.1968	0.17700
DPB1*03	32	464	0.0690	58	620	0.0935	0.15000
DPB1*04	263	464	0.5668	350	620	0.5645	0.95100
DPB1*05	15	464	0.0323	5	620	0.0081	0.00493
DPB1*06	2	464	0.0043	1	620	0.0016	0.57900
DPB1*08	1	464	0.0022	0	620	0.0000	0.42800
DPB1*09	8	464	0.0172	10	620	0.0161	100.000
DPB1*10	8	464	0.0172	9	620	0.0145	0.80700
DPB1*105	0	464	0.0000	5	620	0.0081	0.07500
DPB1*11	1	464	0.0022	2	620	0.0032	100.000
DPB1*129	0	464	0.0000	1	620	0.0016	100.000
DPB1*13	9	464	0.0194	13	620	0.0210	100.000
DPB1*131	0	464	0.0000	2	620	0.0032	0.51000
DPB1*14	6	464	0.0129	12	620	0.0194	0.47800
DPB1*15	4	464	0.0086	9	620	0.0145	0.41600
DPB1*16	0	464	0.0000	1	620	0.0016	100.000
DPB1*17	13	464	0.0280	8	620	0.0129	0.07940
DPB1*18	2	464	0.0043	0	620	0.0000	0.18300
DPB1*19	4	464	0.0086	0	620	0.0000	0.03330
DPB1*22	1	464	0.0022	0	620	0.0000	0.42800
DPB1*23	2	464	0.0043	3	620	0.0048	100.000
DPB1*26	3	464	0.0065	0	620	0.0000	0.07810

	2001-2011			**2011-2025**			
DPB1*36	1	464	0.0022	1	620	0.0016	100.000
DPB1*45	0	464	0.0000	1	620	0.0016	100.000
DPB1*47	0	464	0.0000	2	620	0.0032	0.51000
DPB1*503	0	464	0.0000	1	620	0.0016	100.000
DPB1*51	0	464	0.0000	2	620	0.0032	0.51000
DPB1*61	1	464	0.0022	0	620	0.0000	0.42800
DPB1*66	2	464	0.0043	0	620	0.0000	0.18300
DPB1*70	0	464	0.0000	1	620	0.0016	100.000
DPB1*805	0	464	0.0000	1	620	0.0016	100.000
DPB1*84	1	464	0.0022	0	620	0.0000	0.42800
DPB1*91	1	464	0.0022	0	620	0.0000	0.42800

Appendix 8. Comprehensive List of HLA Allele Frequencies and Statistical P-Values in 2001-2011 and 2011-2025. Full dataset of all detected HLA allele frequencies for both study periods, including statistical significance of temporal changes (p-values), providing the raw data for allele-based analyses.