

Supplemental Material

Cell-surface MHC density profiling identifies the protein instability of autoimmunity-associated HLA

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		DQB1												
		DQ2		DQ3			DQ4	DQ5			DQ6			
				DQ7	DQ8	DQ9								
		02:01	02:02	03:01	03:02	03:03	04:01	05:01	05:02	05:03	06:01	06:02	06:03	06:04
DQA1	01:01							DQ0501						
	01:02								DQ0502			DQ0602		DQ0604
	01:03										DQ0601		DQ0603	
	01:04							DQ0501	DQ0502	DQ0503				
	02:01	DQ2.2	DQ2.2	DQ7.2	DQ8.2	DQ9.2	DQ4.2							
	03:01	DQ2.3	DQ2.3	DQ7.3	DQ8.3	DQ9.3	DQ4.3							
	03:03	DQ2.3	DQ2.3	DQ7.3	DQ8.3	DQ9.3	DQ4.3							
	04:01	DQ2.4	DQ2.4	DQ7.4	DQ8.4	DQ9.4	DQ4.4							
	05:01	DQ2.5	DQ2.5	DQ7.5	DQ8.5	DQ9.5	DQ4.5							
	06:01	DQ2.6	DQ2.6	DQ7.6	DQ8.6	DQ9.6	DQ4.6							

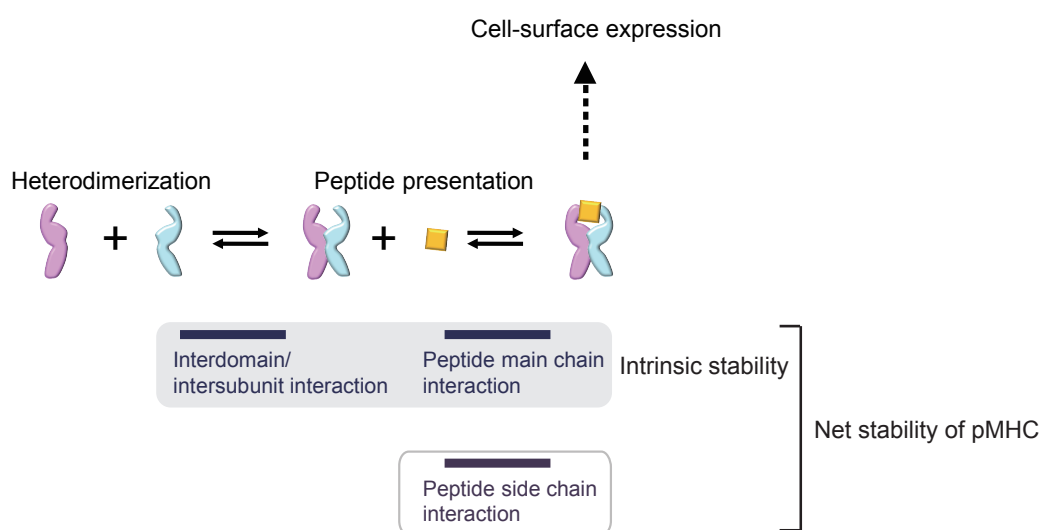
DQ5/6

DQ2/3/4

Supplemental Figure 1

Abbreviations for DQ haplotypes and HLA-DQ heterodimers.

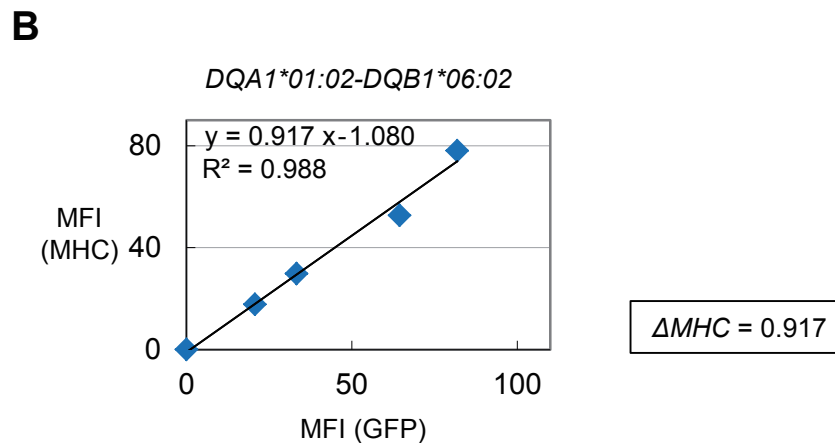
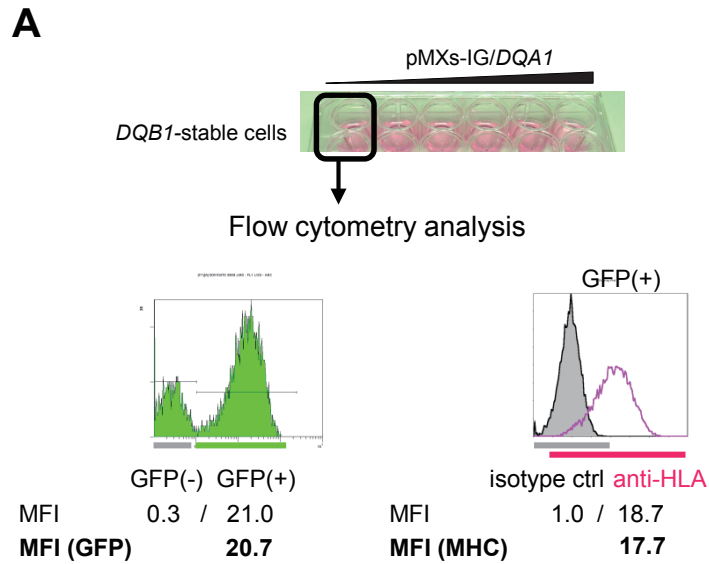
HLA-DQA1 and *-DQB1* alleles in the two distinct evolutionary sublineages (63) are designated as DQ2/3/4 (orange) and DQ5/6 (blue). Top row (yellow) shows DQ serotype name. For DQ2/3/4, DQ haplotypes and heterodimers are abbreviated using the serotype name and *HLA-DQA1* allele name (e.g., *DQA1*03-DQB1*03:02* is abbreviated as *DQ8.3*). The major DQ haplotypes in DQ5/6 in the European (133) and Japanese populations (134) are abbreviated using *HLA-DQB1* allele name (e.g., *DQA1*01:02-DQB1*06:02* is abbreviated as *DQ0602*).



Supplemental Figure 2

Mechanism that stabilizes MHC.

pMHC is formed through the assembly of the α and β subunits and interaction of α/β heterodimer with a peptide. α/β heterodimerization is mediated through interdomain and intersubunit interactions. Peptide presentation is mediated through interaction of MHC protein with peptide main chain and side chains. In this study, intrinsic MHC stability is defined as the stability of MHC protein that is stabilized through α/β heterodimerization and peptide main chain interactions.

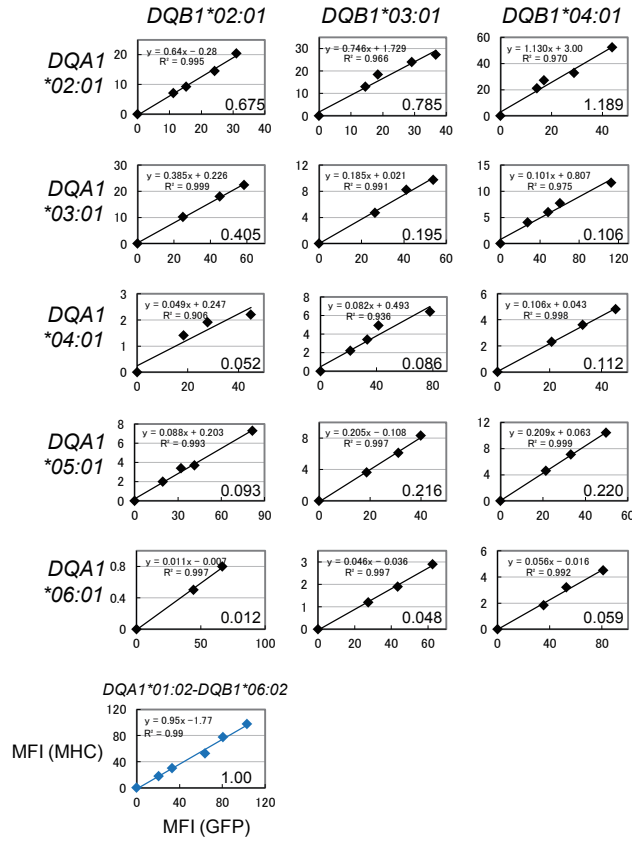


Supplemental Figure 3 Measurement of ΔMHC .

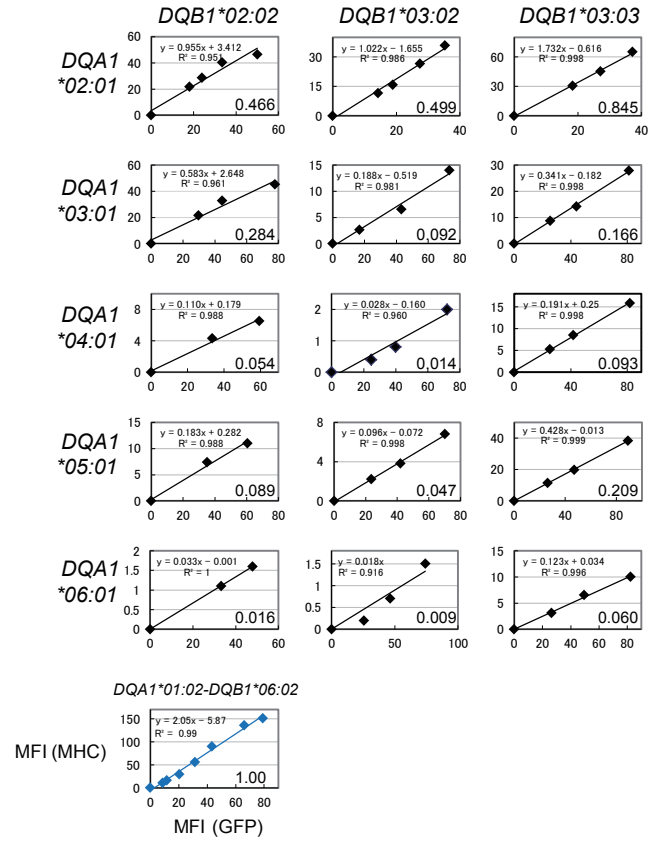
(A) HLA-DQB1-stable cell line was transduced with graded concentrations of retrovirus containing pMXs-IG/DQA1. At 48 hours after the transduction, cytosolic expression of GFP and cell-surface expression of HLA-DQ (in the GFP-positive cells) were measured by flow cytometry. MFI (GFP) represents the MFI for GFP (GFP-positive minus GFP-negative cells). MFI (MHC) represents the MFI for MHC (anti-HLA II β (WR18) minus isotype control) of GFP-positive cells.

(B) Calculation of ΔMHC . MFI (GFP) and MFI (MHC) **(A)** were plotted to determine the increase in cell-surface MHC relative to cytosolic GFP. This value (the slope in the graph) was designated as ΔMHC . The figures show the data obtained for DQ0602.

A



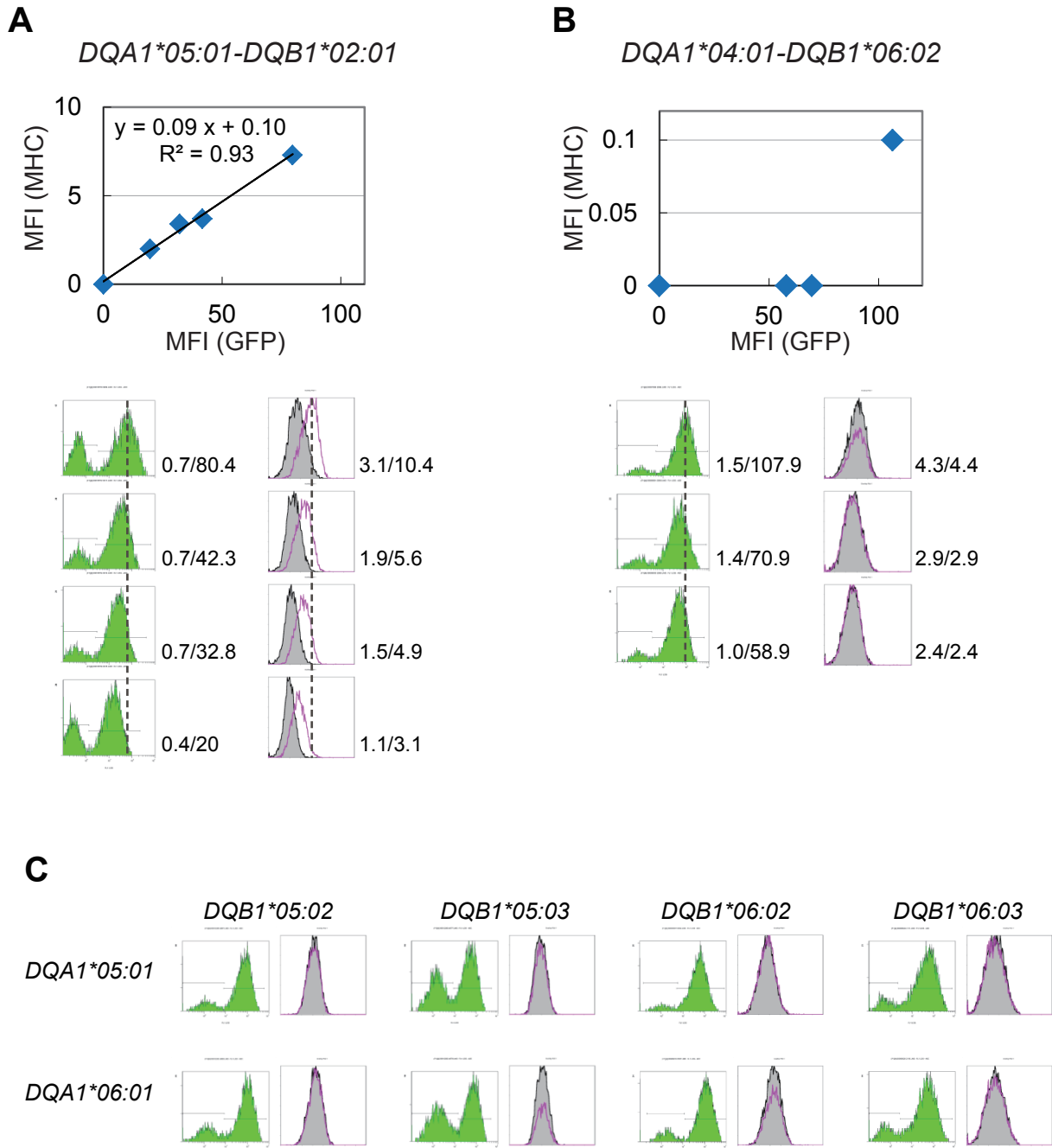
B



Supplemental Figure 4

Representative data from the ΔMHC assay.

(A, B) Representative ΔMHC data for HLA-DQB1*02:01-, *03:01-, and *04:01-stable cell lines (A) and for HLA-DQB1*02:02-, *03:02-, and *03:03-stable cell lines (B). The x- and y-axes indicate MFI (GFP) and MFI (MHC), respectively. The ΔMHC value for DQ0602 (bottom left) was used for the normalization. Numbers on the bottom right in each graph indicate ΔMHC (after normalization with DQ0602).

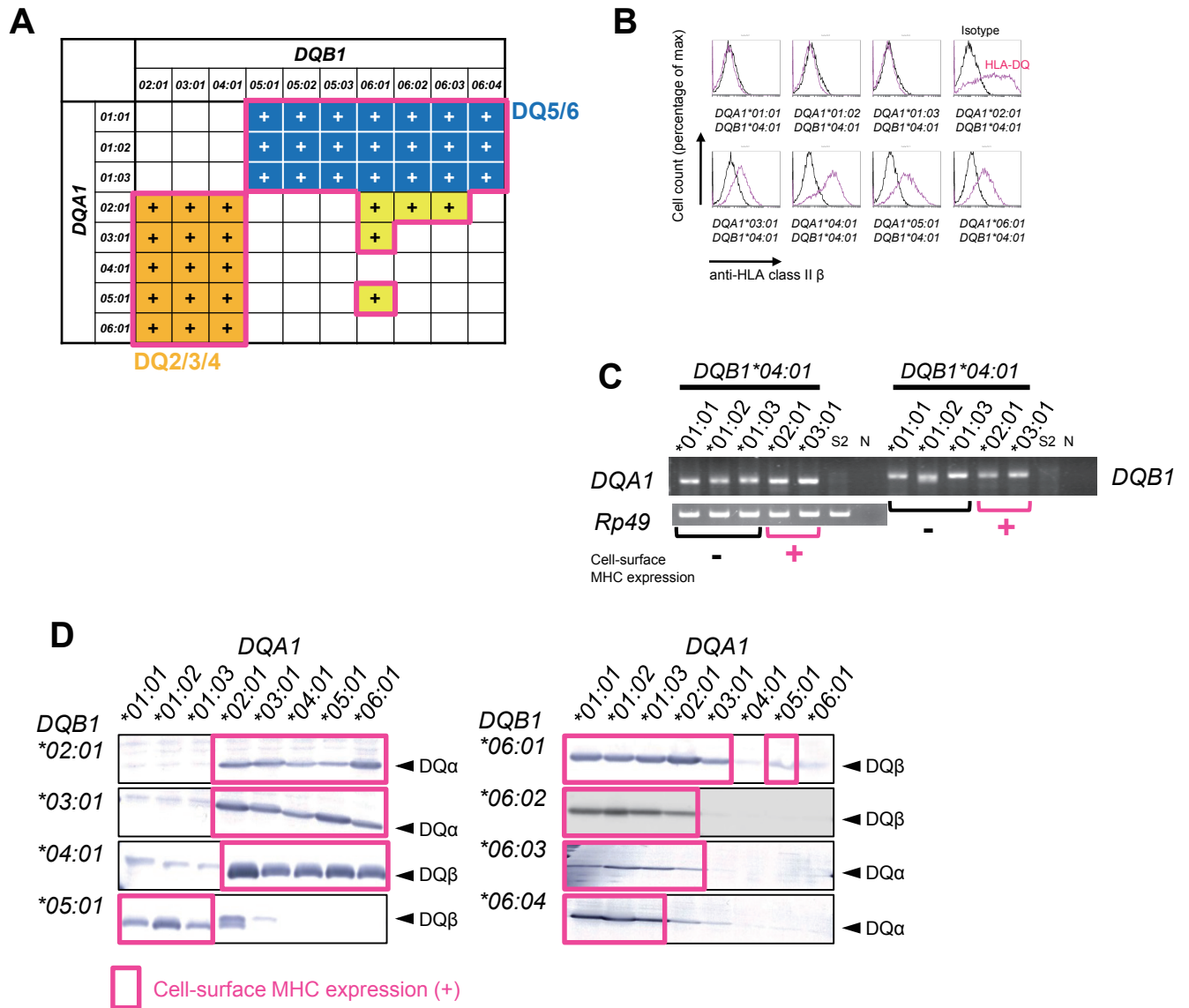


Supplemental Figure 5

Representative data from the Δ MHC assay.

(A, B) Representative flow cytometric data and calculation of Δ MHC for DQ2.5 (A) and for *DQA1*04:01-DQB1*06:02* (B). Dashed lines indicate the highest MFI levels in each sample set. Numbers indicate the MFIs for GFP-negative/-positive cells and for isotype control/anti-HLA II β (WR18).

(C) Representative flow cytometry data of the *DQA1-DQB1* alleles that did not express HLA-DQ on cell-surface. GFP (green), isotype control (black), and anti-HLA II β (WR18) (magenta).



Supplemental Figure 6

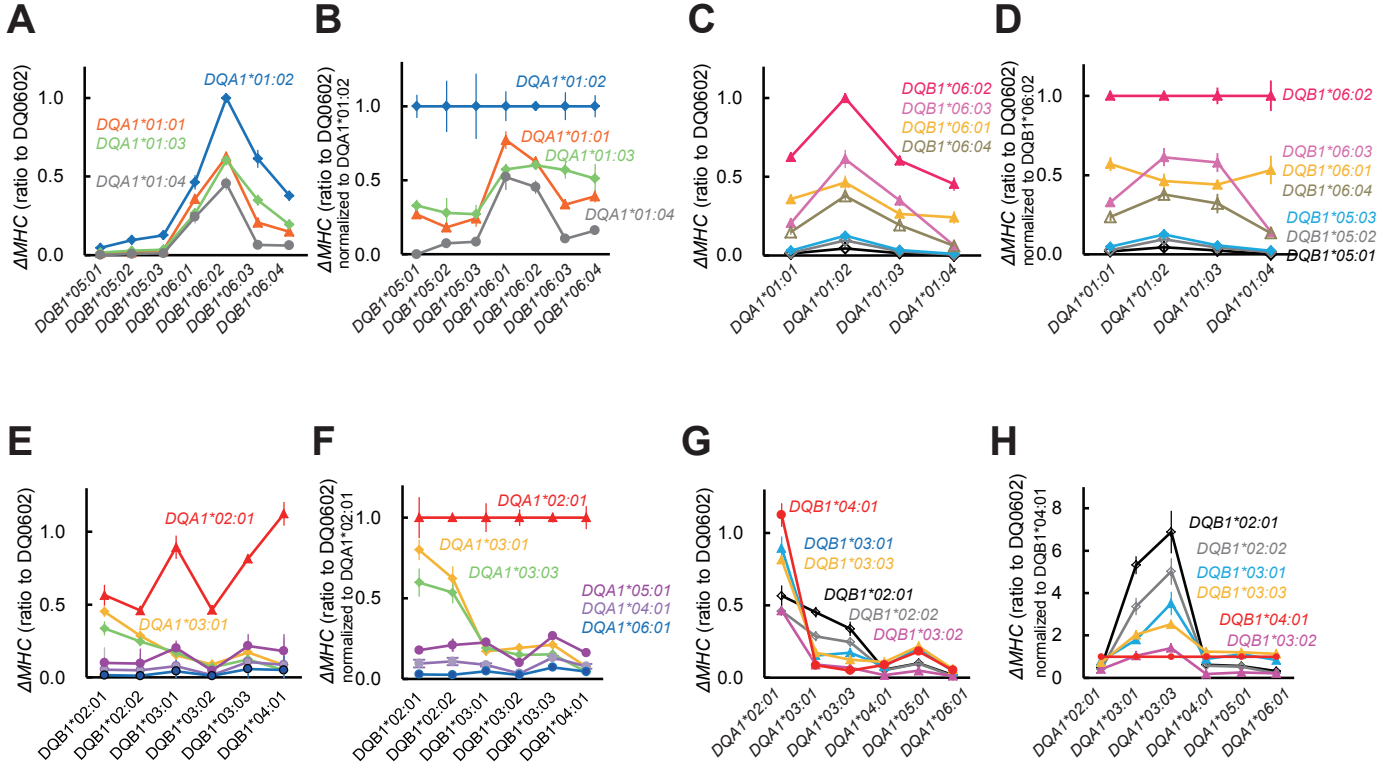
HLA-DQ protein expression on stable insect cells.

(A) HLA-DQ proteins were expressed in *Drosophila* S2 cells that were stably co-transfected with *HLA-DQA1* and *-DQB1*. Cell-surface expression of HLA-DQ proteins was analyzed by flow cytometry with anti-HLA II β mAb (WR18). Detectable (+) and undetectable expression (blank). DQ2/3/4 (orange), DQ5/6 (blue), and heterodimers that were formed between the subgroups (yellow).

(B) Representative flow cytometry data of cell-surface HLA-DQ protein expression on insect S2 cells. S2 cells were stably co-transfected with *HLA-DQB1**04:01 and various *HLA-DQA1* alleles. Anti-HLA II β (WR18) (magenta) and isotype control (black).

(C) 3' RACE profile of the stable insect cell lines that were positive (+) or negative (-) in cell-surface HLA-DQ expression. Rp49, insect ribosomal protein; S2, untransfected cells; N, negative control for 3' RACE.

(D) Affinity purification and Western blotting of HLA-DQ proteins using cell lysates of stable S2 cells. HLA-DQ proteins were purified and detected with *Strep*-tag II at the C-terminus of DQ α and with His-tag at the C-terminus of DQ β . For *HLA-DQB1**02:01-, *03:01-, *06:03-, and *06:04-stable cells, fractions that bound to Ni²⁺-NTA were detected with *Strep*-Tactin, which recognizes *Strep*-tag II. For *HLA-DQB1**04:01-, *05:01-, *06:01-, and *06:02-stable cells, fractions that bound to *Strep*-Tactin were detected with anti-His tag mAb. The boxes (magenta) indicate cell lines that expressed HLA-DQ on the cell-surface in A.

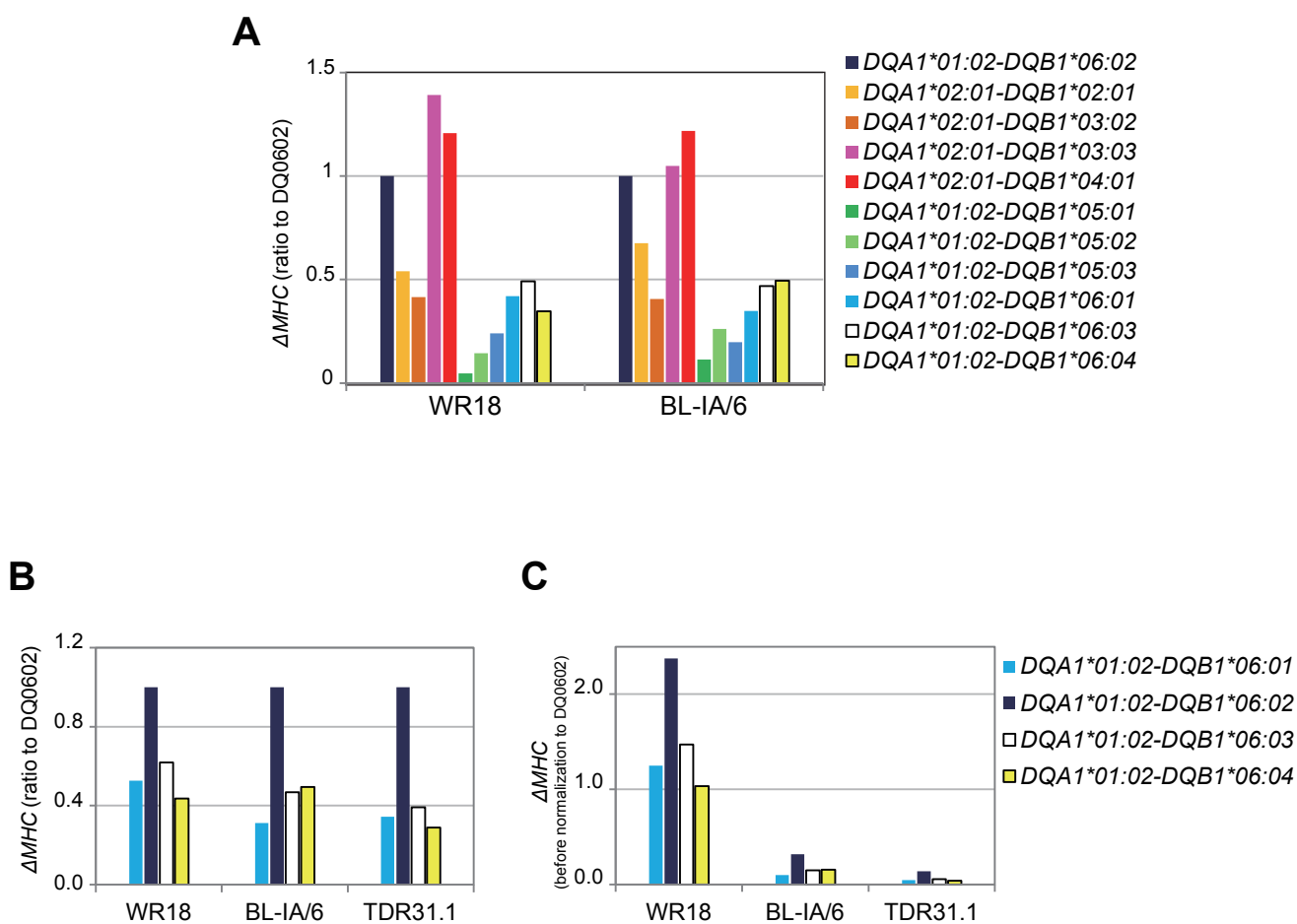


Supplemental Figure 7

Allelic hierarchy in ΔMHC within DQ5/6 and DQ2/3/4 subgroups.

(A-D) ΔMHC profiles for DQ5/6. In B and D, ΔMHC is normalized to the ΔMHC for DQ heterodimers that were formed by DQA1*01:02 (B) and DQB1*06:02 (D).

(E-H) ΔMHC profiles for DQ2/3/4. In F and H, ΔMHC is normalized to the ΔMHC for DQ heterodimers that were formed by DQA1*02:01 (F) and DQB1*04:01 (H). Error bars represent standard errors (n ≥ 3).



Supplemental Figure 8

ΔMHC measurement with various anti-HLA II mAbs.

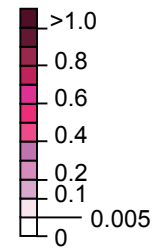
(A) ΔMHC for HLA-DQA1*01:02- and -DQA1*02:01-stable cells measured with mAb (WR18), which was used throughout in this study, and with mAb (BL-IA/6) (pan-HLA II mAb).

(B, C) ΔMHC for DQB1*06 measured with pan-HLA II mAbs (WR18, BL-IA/6, and TDR31.1).

ΔMHC (normalized to DQ0602) (B) and before normalization to DQ0602 (C). In A-C, the data are from a single experiment using cells that were prepared on the same day.

A ΔMHC (without peptide fusion)

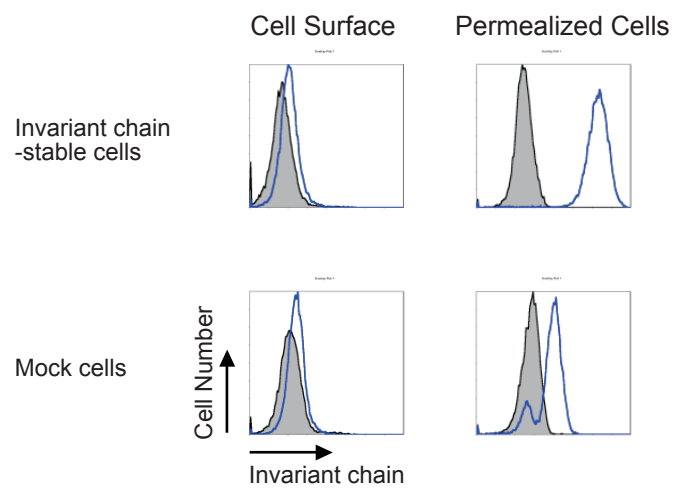
		<i>DQB1</i>					
		*02:01	*03:02	*03:03	*04:01	*05:01	*06:02
<i>DQA1</i>	*01:01					0.012	0.626
	*01:02					0.045	1.000
	*02:01	0.565	0.464	0.815	1.124		
	*03:01	0.452	0.089	0.173	0.085		
	*05:01	0.100	0.047	0.217	0.181		

Measured in the *HLA-DQB1*-stable cells ($n \geq 3$) ΔMHC
(ratio to DQ0602)**B** ΔMHC (GGS peptide fusion)

		<i>DQB1</i>					
		*02:01	*03:02	*03:03	*04:01	*05:01	*06:02
<i>DQA1</i>	*01:01					0.009	0.496
	*01:02					0.019	1.000
	*02:01	0.839	0.576	1.125	1.281		
	*03:01	0.380	0.068	0.048	0.028		
	*05:01	0.081	0.030	0.069	0.146		

Measured in the *HLA-DQA1*-stable cells ($n = 1$)**Supplemental Figure 9** **ΔMHC profiles in the absence and presence of GGS peptide.**

(**A**, **B**) ΔMHC profiles in the absence (**A**) and presence (**B**) of the model peptide (GGS). In **A**, *HLA-DQB1*-stable cells were transduced with pMXs-IG/*DQA1* (the data from Figure 2A). In **B**, *HLA-DQA1*-stable cells were transduced with pMXs-IG/*DQB1*, in which *DQB1* was expressed in fusion with the GGS peptide. $n \geq 3$ (**A**), and data from a single experiment (**B**).



Supplemental Figure 10

Construction of human invariant chain-stable cells.

Expression of human invariant chain in NIH3T3 cells that are stably transduced with human invariant chain (upper panels) and in mock cells (lower panels). Cell-surface (left panels) and intracellular staining (right panels) using anti-human invariant chain (CD74) mAb (LN2).

A

DQA1		Polymorphisms	
01:01	34	207	
01:02	E	V	
01:03	Q	M	
01:01	25 34 41	129 130	
01:03	Y E R	Q S	
01:03	F Q K	H A	
01:01	2	199	
01:04	D	T	
01:01	25 41	129 130	207
01:03	F Q K	H A	V
01:02	2	199	207
01:04	D	T	V
01:02	34	199	207
01:04	G	T	V
01:03	2 25 34 41	129 130	199
01:04	D F Q E R	H A S	A T

DQA1		DQB1							
		05:01	05:02	05:03	06:01	06:02	06:03	06:04	
01:01		0.012	0.017	0.031	0.357	0.626	0.206	0.148	
01:02		0.045	0.095	0.126	0.463	1.000	0.613	0.378	
01:01		0.012	0.017	0.031	0.357	0.626	0.206	0.148	
01:03		0.015	0.027	0.034	0.265	0.603	0.349	0.193	
01:01		0.012	0.017	0.031	0.357	0.626	0.206	0.148	
01:04		0.000	0.007	0.011	0.242	0.454	0.064	0.061	
01:02		0.045	0.095	0.126	0.463	1.000	0.613	0.378	
01:03		0.015	0.027	0.034	0.265	0.603	0.349	0.193	
01:02		0.045	0.095	0.126	0.463	1.000	0.613	0.378	
01:04		0.000	0.007	0.011	0.242	0.454	0.064	0.061	
01:03		0.015	0.027	0.034	0.265	0.603	0.349	0.193	
01:04		0.000	0.007	0.011	0.242	0.454	0.064	0.061	

B

DQB1		Polymorphisms	
05:01	57	126	
05:02	V	H	
05:01	57		
05:03	V		
05:03	D		
05:02	57	126	
05:03	S	Q	
05:01	14 26 38 70 71 74 75 77 86 116 125 130 224		
06:04	L G V G A S V R A I S R R		
05:01	14 26 38 71 74 75 77 87 116 125 224		
06:03	M L A T E L T F V G Q		
06:01	3 9 13 26 37 38 66 67 70 167 197 203		
06:02	P L A Y D V D I R H N I		
06:02	S F G L Y A E V G R S V		
06:02	9	30	
06:03	F	H	
06:02	9 30 57 70 86 87 130		
06:04	F Y D G A F		
06:04	Y H V R G Y Q		
06:03	57 70 86 87 130		
06:04	D G A F		
06:04	V R G Y Q		

DQB1		DQA1			
		01:01	01:02	01:03	01:04
05:01		0.012	0.045	0.015	0.000
05:02		0.017	0.095	0.027	0.007
05:01		0.012	0.045	0.015	0.000
05:03		0.031	0.126	0.034	0.011
05:02		0.017	0.095	0.027	0.007
05:03		0.031	0.126	0.034	0.011
05:01		0.012	0.045	0.015	0.000
06:04		0.148	0.378	0.193	0.061
05:03		0.031	0.126	0.034	0.011
06:03		0.206	0.613	0.349	0.064
06:01		0.357	0.463	0.265	0.242
06:02		0.626	1.000	0.603	0.454
06:02		0.626	1.000	0.603	0.454
06:03		0.206	0.613	0.349	0.064
06:02		0.626	1.000	0.603	0.454
06:04		0.148	0.378	0.193	0.061
06:03		0.206	0.613	0.349	0.064
06:04		0.148	0.378	0.193	0.061

$P < 0.05$

$P < 0.01$

$P < 0.001$

Supplemental Figure 11

Pairwise comparisons of amino acids and ΔMHC in DQ5/6.

(A, B) Pairwise comparisons of amino acids and ΔMHC between the representative alleles in *HLA-DQA1*01* (A) and *-DQB1*05, *06* (B). Left panels indicate amino acid variants and their relative positions (marked with horizontal bars). $\alpha 1$ domain (magenta), $\beta 1$ domain (blue), $\alpha 2$, $\beta 2$, transmembrane, and cytosolic domains (brown). Residue numbers are not to scale. Right panels indicate ΔMHC values and their differences between alleles. ΔMHC values that were significantly higher than that of other allele are painted in gray; $P < 0.05$ (light gray), $P < 0.01$ (thick gray), and $P < 0.001$ (black) (two-tailed *t*-test).

A

DQA1	Polymorphisms	DQA1	DQB1					
			02:01	02:02	03:01	03:02	03:03	04:01
02:01	25 26 47 52 54 55 76 187 F T K H L A L A Y S Q R F R V T	02:01	0.565	0.459	0.895	0.464	0.815	1.124
03:01		03:01	0.452	0.286	0.153	0.089	0.173	0.085
02:01	25 34 40 47 50 51 52 53 54 75 107 156 161 163 175 215 F E E K L F H R L I T F D I E L Y Q G C V L R Q F S I L E S K F	02:01	0.565	0.459	0.895	0.464	0.815	1.124
05:01		05:01	0.100	0.096	0.202	0.047	0.217	0.181
02:01	34 40 47 50 51 52 53 54 69 215 E E K L F H R L L L Q G C V L R Q F T F	02:01	0.565	0.459	0.895	0.464	0.815	1.124
06:01		06:01	0.016	0.011	0.043	0.011	0.058	0.051
03:01		03:01	0.452	0.286	0.153	0.089	0.173	0.085
03:03		03:03	0.337	0.246	0.172	0.069	0.124	0.049
03:01	26 34 40 47 50 51 53 55 75 76 107 156 161 163 175 187 215 S E E Q L F R R I V T F D I E T L T Q G C V L R Q A S L I L E S K A F	03:01	0.452	0.286	0.153	0.089	0.173	0.085
05:01		05:01	0.100	0.096	0.202	0.047	0.217	0.181
04:01	69 75 107 156 161 163 175 T I T F D I E L S I L E S K	04:01	0.054	0.050	0.078	0.016	0.107	0.087
05:01		05:01	0.100	0.096	0.202	0.047	0.217	0.181
04:01	25 Y F	04:01	0.054	0.050	0.078	0.016	0.107	0.087
06:01		06:01	0.016	0.011	0.043	0.011	0.058	0.051
05:01	25 69 75 107 156 161 163 175 Y L S I L E S K F T I F D I E	05:01	0.100	0.096	0.202	0.047	0.217	0.181
06:01		06:01	0.016	0.011	0.043	0.011	0.058	0.051

B

DQB1	Polymorphisms	DQB1	DQA1					
			02:01	03:01	03:02	04:01	05:01	06:01
02:01		02:01	0.565	0.452	0.337	0.054	0.100	0.016
02:02		02:02	0.459	0.286	0.246	0.050	0.096	0.011
02:01	28 30 37 38 46 47 52 55 66 67 71 74 75 77 140 182 185 S S I V E F L L D I K A V R A S T T Y Y A V Y P P E V T E L T T N I	02:01	0.565	0.452	0.337	0.054	0.100	0.016
03:02		03:02	0.464	0.089	0.069	0.016	0.047	0.011
02:01	9 23 26 28 30 37 38 46 47 52 55 56 57 70 71 74 77 140 182 185 Y R L S S I V E F L L P A R K A R A S T F L G T Y Y A V Y P R L D E D S T T N I	02:01	0.565	0.452	0.337	0.054	0.100	0.016
04:01		04:01	1.124	0.085	0.049	0.087	0.181	0.051
03:01	13 26 45 57 167 185 A Y E D H T G L G A R I	03:01	0.895	0.153	0.172	0.078	0.202	0.043
03:02		03:02	0.464	0.089	0.069	0.016	0.047	0.011
03:01	13 26 45 167 185 A Y E H T G L G R I	03:01	0.895	0.153	0.172	0.078	0.202	0.043
03:03		03:03	0.815	0.173	0.124	0.107	0.217	0.058
03:02	57 A D	03:02	0.464	0.089	0.069	0.016	0.047	0.011
03:03		03:03	0.815	0.173	0.124	0.107	0.217	0.058
03:03	9 23 26 55 56 66 67 70 71 74 75 Y R L P P E V R T E L F L G R L D I E D S V	03:03	0.815	0.173	0.124	0.107	0.217	0.058
04:01		04:01	1.124	0.085	0.049	0.087	0.181	0.051

$P < 0.05$

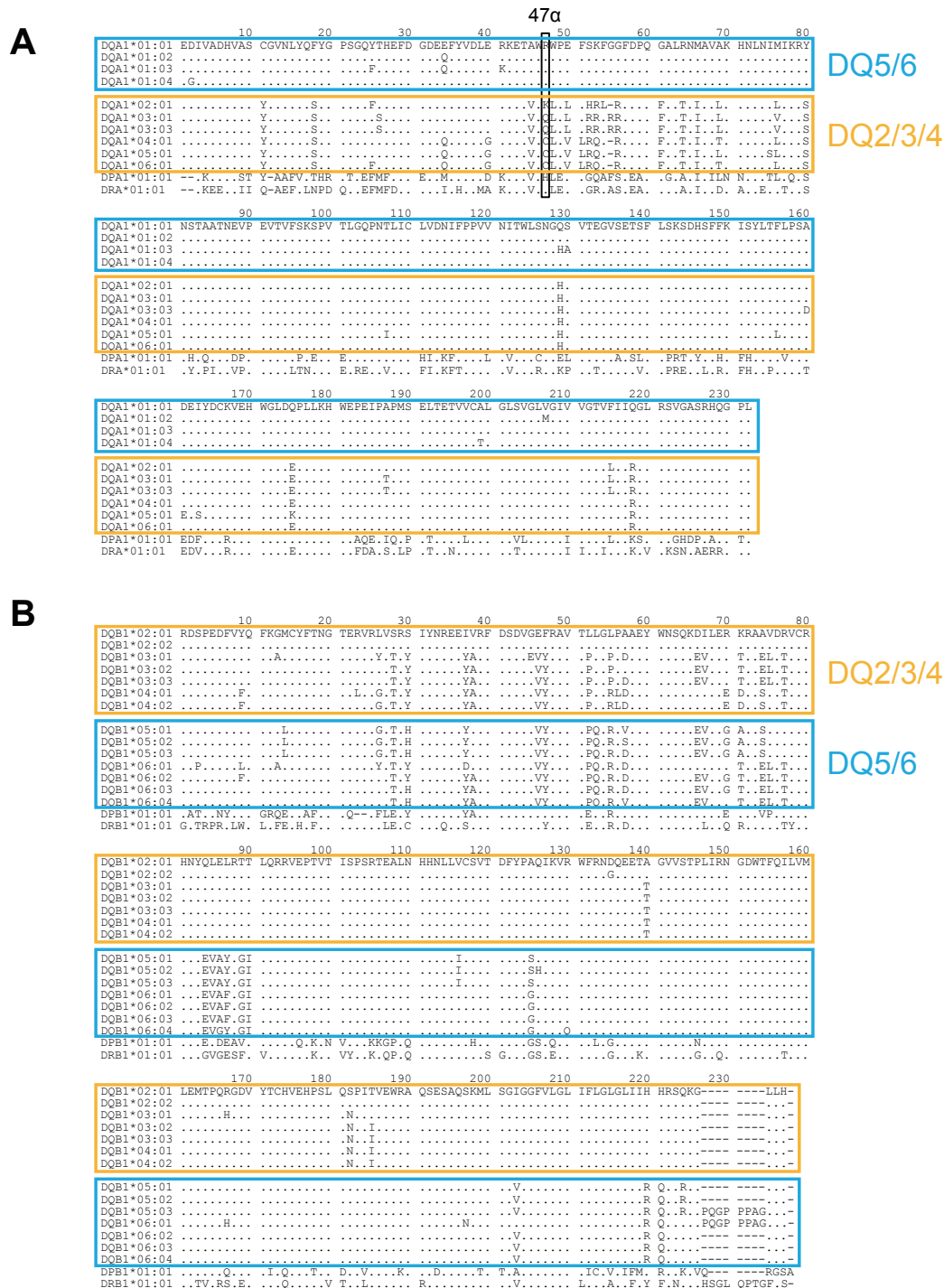
$P < 0.01$

$P < 0.001$

Supplemental Figure 12

Pairwise comparisons of amino acids and ΔMHC in DQ2/3/4.

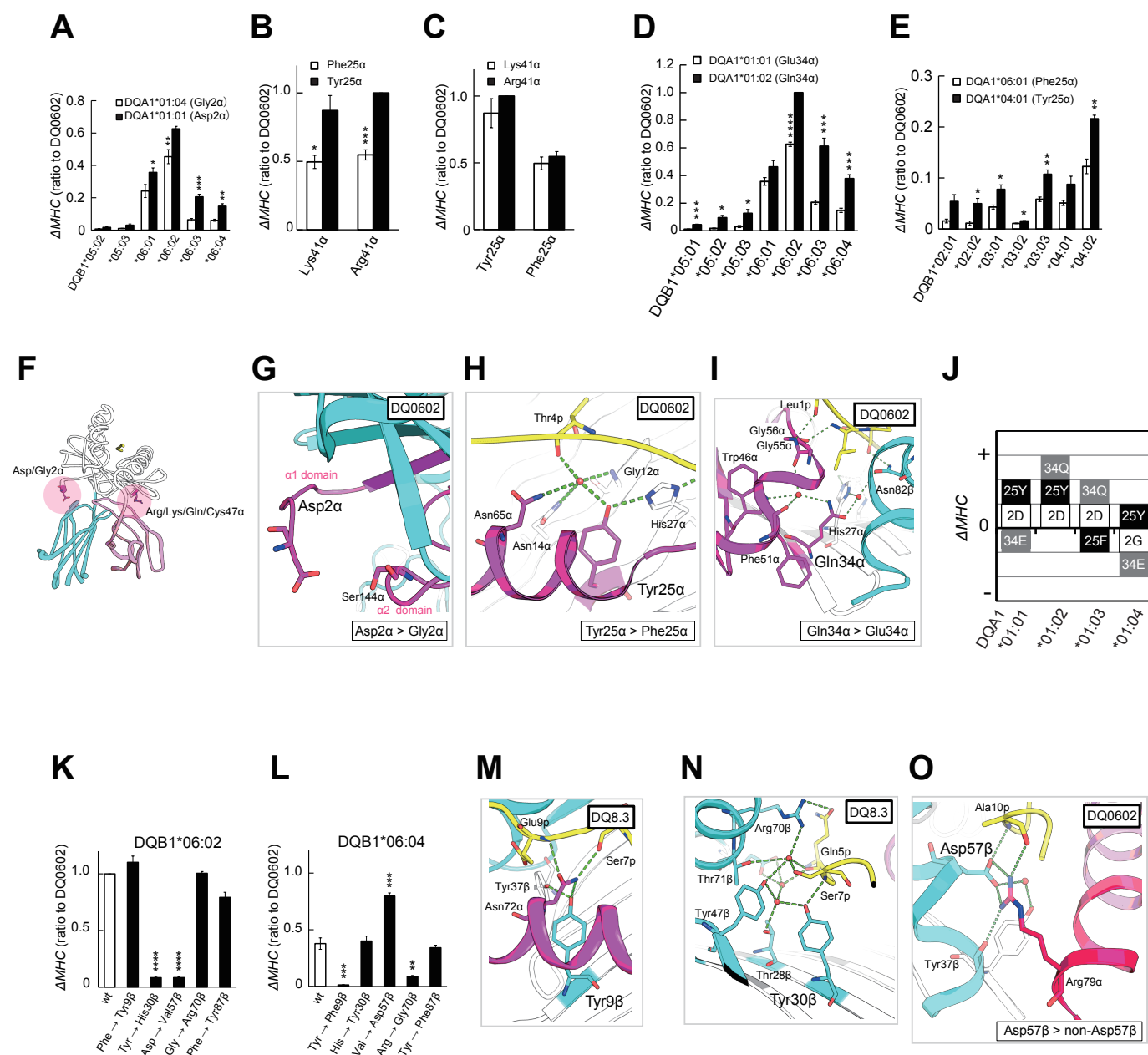
(A, B) Pairwise comparisons of amino acids and ΔMHC between the representative alleles in *HLA-DQA1*02-*06* (A) and *-DQB1*02-*04* (B). Left panels indicate amino acid variants and their relative positions (marked with horizontal bars). $\alpha 1$ domain (magenta), $\beta 1$ domain (blue), and $\alpha 2$, $\beta 2$, transmembrane, and cytosolic domains (brown). Residue numbers are not to scale. Right panels indicate ΔMHC values and their differences between alleles. ΔMHC values that were significantly higher than that of other allele are painted in gray; $P < 0.05$ (light gray), $P < 0.01$ (thick gray), and $P < 0.001$ (black) (two-tailed t -test).



Supplemental Figure 13

Amino acid sequence alignments for the representative *HLA-DQ* alleles.

(A, B) Alignments of amino acid sequences for *HLA-DQA1* (A) and *-DQB1* (B). Residues are numbered according to mature DQα (DQA1) and DQβ (DQB1) protein sequences. DQ2/3/4 (orange) and DQ5/6 (blue). Variants at 47α are boxed (black). Dots indicate the residues that are identical to *HLA-DQA1*01:01* or *-DQB1*02:01*. - indicates a deletion.



Supplemental Figure 14

Supplemental Figure 14

Effects of polymorphisms on ΔMHC .

(A) Comparison of ΔMHC values between DQA1*01:01 and DQA1*01:04, which differ at Asp/Gly2 α and Ala/Thr199 α (Supplemental Figure 11A).

(B, C) Effects of variants Phe/Tyr25 α **(B)** and Lys/Arg41 α **(C)** on ΔMHC . 25 α and 41 α in DQA1*01:02 were substituted using mutagenesis. ΔMHC were measured in the presence of DQB1*06:02.

(D) Comparisons of ΔMHC values between DQA1*01:01 and DQA1*01:02, which differ at 34 α .

(E) Comparisons of ΔMHC values between DQA1*04:01 and DQA1*06:01, which differ at 25 α .

(F) Location of Asp2 α and Arg47 α in the structure of DQ0602 (PDB: 1uvq (70)).

(G) The side chain of Asp2 α in DQ0602 points to Ser144 α (α 2 domain), with an Asp2 α O δ 1-Ser144 α O γ distance of 4.3 Å (PDB: 1uvq (70)), indicating that an H-bond mediated by a water molecule may be formed between Asp2 α and Ser144 α . The large B-factor at the side chain atoms of Asp2 α suggests the conformational diversity of Asp2 α . In the protein structure of DQ8.3, the side chain of Asp2 α orients toward the β 2 domain (PDB: 2nna (69)).

(H) Tyr25 α in DQA1*01:02 forms H-bonds with the conserved His27 α and a water molecule. The water molecule further interacts with the conserved Gly12 α N, Asn14 α , Asn65 α , and Thr4p O (PDB: 1uvq (70)). Tyr25 α in DQA1*03 and *05 also form H-bonds with conserved residues and with p4 N and O (69, 72, 73).

(I) Gln34 α in DQA1*01:02 contributes to the H-bond network along with residues that are conserved in DQ5/6 (His27 α , Trp46 α , Phe51 α O, Gly55 α O, and Asn82 β) and water molecules (PDB: 1uvq (70)). A significant decrease in ΔMHC by the replacement of Gln34 α to Glu34 α **(D)** suggests that the change of the amide group (Gln34 α) to the carboxyl group (Glu34 α) weakens water-mediated H-bond network. In DQ2/3/4, stabilization/destabilization of HLA-DQ protein by Gln/Glu34 α may differ from that in DQ5/6 because the H-bond network in DQ2/3/4 is formed by direct interactions of Gln/Glu34 α with residues that are unique to DQ2/3/4 (69, 72, 73).

(J) Combination of stabilizing effects of Asp2 α (2D), Tyr25 α (25Y), and Gln34 α (34Q) explain the allelic hierarchy in ΔMHC among the DQA1*01 allele products.

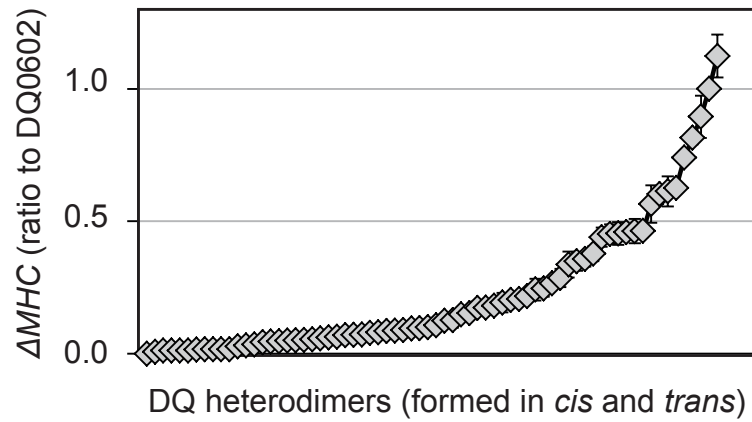
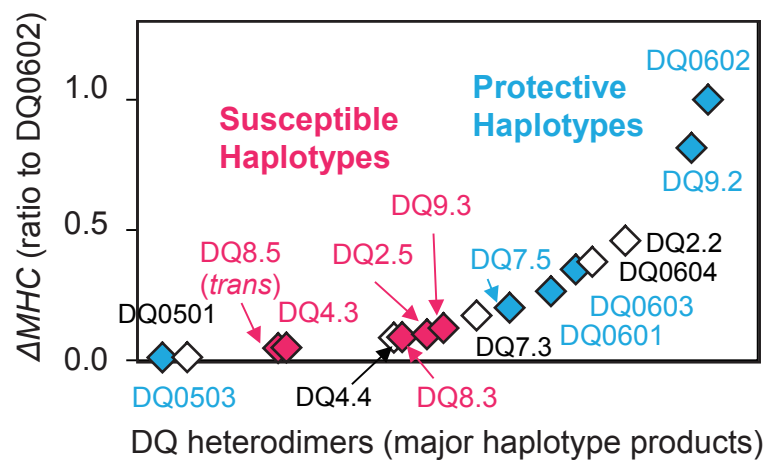
(K, L) ΔMHC values of the mutant DQB1*06:02 **(K)** and *06:04 **(L)** that were substituted at residues that differed between the two alleles. The ΔMHC values were measured in the presence of DQA1*01:02.

(M) Tyr9 β forms H-bonds with Tyr37 β and Asn72 α in DQ8.3. Asn72 α further interacts with Ser7p O and Glu9p N of the peptide (PDB: 2nna (69)).

(N) Tyr30 β in DQ8.3 forms H-bonds with Ser7p N and with Tyr47 β and Thr28 β via a water molecule. These H-bonds constitute a part of H-bond network in the peptide-binding groove (PDB: 2nna (69)). These H-bonds are also formed in DQ0602 (PDB: 1uvq (70)).

(O) Asp57 β in DQ0602 forms H-bonds/salt bridges with Arg79 α and also interacts with Tyr37 β and peptide main chain (PDB: 1uvq (70)).

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ (two-tailed t -test) in all of the graphs. The error bars represent the standard errors ($n \geq 3$). DQ α (magenta), DQ β (blue), bound peptide (yellow), water molecules (red spheres), and distances of < 3.4 Å (green dots).

A**B****Supplemental Figure 15****Allelic hierarchy of ΔMHC among the *HLA-DQ* allele products.**

(A, B) ΔMHC profiles for all of the *HLA-DQ* heterodimers that were analyzed in this study **(A)** and for the major *DQ* haplotype products (haplotype frequency > 0.03) in European (133) and Japanese populations (134) **(B)**. *DQ* haplotypes that are susceptible (magenta), protective (blue), and neutral to T1D.

Supplemental Table 1 ΔMHC profile for the major *HLA-DQ* allele products.

<i>DQB1</i>															
	<i>*02:01</i>	<i>*02:02</i>	<i>*03:01</i>	<i>*03:02</i>	<i>*03:03</i>	<i>*04:01</i>	<i>*05:01</i>	<i>*05:02</i>	<i>*05:03</i>	<i>*06:01</i>	<i>*06:02</i>	<i>*06:03</i>	<i>*06:04</i>	mock	
<i>DQA1</i>	<i>*01:01</i>	n. d.	n. d.	n. d.	n. d.	n. d.		0.012 ±0.001	0.017 ±0.003	0.031 ±0.007	0.357 ±0.028	0.626 ±0.015	0.206 ±0.016	0.148 ±0.016	n. d.
	<i>*01:02</i>	n. d.	n. d.	n. d.	n. d.	n. d.		0.045 ±0.004	0.095 ±0.016	0.126 ±0.028	0.463 ±0.046	1.000 ±0.057	0.613 ±0.028	0.378 ±0.028	n. d.
	<i>*01:03</i>	n. d.	n. d.	n. d.	n. d.	n. d.		0.015 ±0.002	0.027 ±0.010	0.034 ±0.008	0.265 ±0.014	0.603 ±0.031	0.349 ±0.036	0.193 ±0.037	n. d.
	<i>*01:04</i>	n. d.	n. d.	n. d.	n. d.	n. d.		0 (*) ±0.003	0.007 ±0.001	0.011 ±0.001	0.242 ±0.041	0.454 ±0.043	0.064 ±0.008	0.061 ±0.007	n. d.
	<i>*02:01</i>	0.565 ±0.071	0.459 ±0.004	0.895 ±0.080	0.464 ±0.024	0.815 ±0.024	1.124 ±0.081	n. d.	n. d.	n. d.	0.74 ±0.011	0.440 ±0.036	0.072 ±0.019	n. d.	n. d.
	<i>*03:01</i>	0.452 ±0.036	0.286 ±0.035	0.153 ±0.014	0.089 ±0.004	0.173 ±0.004	0.085 ±0.011	n. d.	n. d.	n. d.	0.081 ±0.012	0 (*)	n. d.	n. d.	n. d.
	<i>*03:02</i>	0.337 ±0.049	0.246 ±0.031	0.172 ±0.027	0.069 ±0.003	0.124 ±0.001	0.049 ±0.004	n. d.	n. d.	n. d.	0.071 ±0.006	n. d.	n. d.	n. d.	n. d.
	<i>*04:01</i>	0.054 ±0.013	0.050 ±0.010	0.078 ±0.009	0.016 ±0.001	0.107 ±0.008	0.087 ±0.016	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
	<i>*05:01</i>	0.100 ±0.007	0.096 ±0.019	0.202 ±0.010	0.047 ±0.002	0.217 ±0.014	0.181 ±0.021	n. d.	n. d.	n. d.	0.017 ±0.002	n. d.	n. d.	n. d.	n. d.
	<i>*06:01</i>	0.016 ±0.004	0.011 ±0.004	0.043 ±0.004	0.011 ±0.001	0.058 ±0.004	0.051 ±0.005	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
	mock	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	-

Numbers indicate ΔMHC (normalized to DQ0602) ±standard errors. n. d., below threshold. Asterisks indicate the expression observed at a sub-threshold level.

Supplemental Table 2 Association of amino acid variants in DQ2/3/4 with Δ MHC.

Amino acid residue (DQA1*02-*06)	Variant	<i>P</i>	Amino acid residue (DQB1*02-*04)	Variant	<i>P</i>
25a	F/Y	1.14E-02	9β	Y/F	0.68
26a	T/S	0.58	13β	G/A	0.73
34a	E/Q	5.94E-04	23β	R/L	0.68
40a	E/G	5.94E-04	26β	Y vs. GL	0.73
47a	K vs. QC	4.40E-11		G vs. YL	0.68
	Q vs. KC	0.58		L vs. YG	0.55
	C vs. KQ	5.94E-04	28β	S/T	0.99
50a	L/V	5.94E-04	30β	S/Y	0.99
51a	F/L	5.94E-04	37β	I/Y	0.99
52a	H/R	4.40E-11	38β	V/A	0.99
53a	R/Q	5.94E-04	45β	G/E	0.73
54a	L/F	4.40E-11	46β	E/V	0.99
55a	del/R	0.58	47β	F/Y	0.99
69a	L/T	4.00E-03	52β	L/P	0.99
75a	I/S	0.42	55β	P vs. LR	0.75
76a	L/V	0.58		R vs. LP	0.68
107a	T/I	0.42		L vs. PR	0.99
156a	F/L	0.42	56β	P/L	0.68
160a	A/D	0.58	57β	A/D	0.44
161a	D/E	0.42	66β	D/E	0.75
163a	I/S	0.42	67β	I/V	0.75
175a	E/K	0.42	70β	R/E	0.68
187a	A/T	0.58	71β	T vs. DK	0.75
215a	L/F	5.94E-04		D vs. KT	0.68
				K vs. DT	0.99
			74β	E vs. AS	0.75
				S vs. AE	0.68
				A vs. ES	0.99
			75β	V/L	0.75
			77β	R/T	0.99
			135β	D/G	0.76
			140β	A/T	0.99
			167β	H/R	0.73
			182β	S/N	0.99
			185β	T/I	0.78

Tested by the two-tailed *t*-test. The strongest associations are indicated in bold.

Supplemental Table 3 The *dn* and *ds* for codons in *HLA-DQA1*.

<i>HLA-DQA1</i>	<i>ps</i>	<i>pn</i>	<i>pn-ps</i>	<i>ds</i>	<i>dn</i>	<i>ds/dn</i>	<i>dn-ds</i>	<i>P</i> (<i>ps</i> and <i>pn</i>)	<i>P</i> (<i>ds</i> and <i>dn</i>)
18α	0.000	0.212	0.212	0.000	0.249	0.000	0.249	5.18E-09	5.18E-09
19α	0.429	0.000	-0.429	0.636	0.000	NA	-0.636	1.47E-03	NA
21α	0.000	0.071	0.071	0.000	0.075	0.000	0.075	1.47E-03	1.47E-03
23α	0.143	0.000	-0.143	0.158	0.000	NA	-0.158	1.47E-03	NA
25α	0.000	0.165	0.165	0.000	0.186	0.000	0.186	3.57E-08	3.57E-08
26α	0.000	0.061	0.061	0.000	0.064	0.000	0.064	1.47E-03	1.47E-03
32α	1.484	0.000	-1.484	NA	0.000	NA	NA	5.18E-09	NA
34α	0.000	0.165	0.165	0.000	0.186	0.000	0.186	3.57E-08	3.57E-08
36α	0.791	0.000	-0.791	NA	0.000	NA	NA	1.82E-05	NA
40α	0.000	0.231	0.231	0.000	0.276	0.000	0.276	1.11E-09	1.11E-09
41α	0.000	0.057	0.057	0.000	0.059	0.000	0.059	1.47E-03	1.47E-03
44α	0.000	0.071	0.071	0.000	0.075	0.000	0.075	1.47E-03	1.47E-03
45α	0.000	0.247	0.247	0.000	0.300	0.000	0.300	5.18E-09	5.18E-09
47α	0.302	0.502	0.200	0.387	0.830	0.466	0.443	1.63E-11	NA
48α	0.000	0.185	0.185	0.000	0.213	0.000	0.213	5.18E-09	5.18E-09
50α	0.420	0.433	0.012	0.616	0.645	0.956	0.029	1.03E-02	NA
51α	0.000	0.231	0.231	0.000	0.276	0.000	0.276	1.11E-09	1.11E-09
52α	0.169	0.336	0.167	0.192	0.445	0.431	0.253	3.92E-04	NA
53α	0.154	0.280	0.127	0.172	0.351	0.490	0.179	9.68E-02	NA
54α	0.000	0.061	0.061	0.000	0.064	0.000	0.064	1.47E-03	1.47E-03
59α	0.000	0.078	0.078	0.000	0.082	0.000	0.082	1.47E-03	1.47E-03
60α	1.484	0.000	-1.484	NA	0.000	NA	NA	5.18E-09	NA
61α	0.000	0.424	0.424	0.000	0.625	0.000	0.625	5.18E-09	NA
64α	0.000	0.228	0.228	0.000	0.272	0.000	0.272	5.18E-09	5.18E-09
66α	0.000	0.185	0.185	0.000	0.213	0.000	0.213	5.18E-09	5.18E-09
67α	0.143	0.000	-0.143	0.158	0.000	NA	-0.158	1.47E-03	NA
68α	0.440	0.000	-0.440	0.662	0.000	NA	-0.662	3.57E-08	NA
69α	0.000	0.658	0.658	0.000	1.573	0.000	1.573	5.17E-12	NA
71α	1.583	0.000	-1.583	NA	0.000	NA	NA	1.63E-09	NA
75α	0.879	0.176	-0.703	NA	0.200	NA	NA	3.57E-08	NA
76α	0.000	0.258	0.258	0.000	0.317	0.000	0.317	2.39E-10	2.39E-10
77α	0.000	0.066	0.066	0.000	0.069	0.000	0.069	9.82E-04	9.82E-04
79α	0.000	0.061	0.061	0.000	0.064	0.000	0.064	9.82E-04	9.82E-04

HLA-DQA1 (14 alleles) were used for analysis. NA, not applicable (codons that showed *ps* ≥ 0.75 or *pn* ≥ 0.75, and codons that showed *dn* = 0, see Methods). Differences between *ps* and *pn*, or *ds* and *dn* were tested by the Wilcoxon signed-rank test.

Supplemental Table 4 The *dn* and *ds* for codons in ape *DQA1*.

Ape <i>DQA1</i>	<i>ps</i>	<i>pn</i>	<i>pn-ps</i>	<i>ds</i>	<i>dn</i>	<i>ds/dn</i>	<i>dn-ds</i>	<i>P</i> (<i>ps</i> and <i>pn</i>)	<i>P</i> (<i>ds</i> and <i>dn</i>)
18α	0.000	0.081	0.081	0.000	0.086	0.000	0.086	1.68E-07	1.68E-07
21α	0.086	0.104	0.018	0.092	0.112	0.818	0.020	1.09E-02	NA
22α	0.000	0.043	0.043	0.000	0.044	0.000	0.044	1.32E-04	1.32E-04
23α	0.337	0.000	-0.337	0.447	0.000	NA	-0.447	3.53E-12	NA
25α	0.000	0.148	0.148	0.000	0.165	0.000	0.165	5.28E-14	5.28E-14
26α	0.000	0.043	0.043	0.000	0.044	0.000	0.044	1.32E-04	1.32E-04
32α	1.563	0.000	-1.563	NA	0.000	NA	NA	5.69E-18	NA
34α	0.000	0.229	0.229	0.000	0.273	0.000	0.273	8.98E-21	8.98E-21
36α	1.579	0.000	-1.579	NA	0.000	NA	NA	3.90E-18	NA
40α	0.000	0.144	0.144	0.000	0.160	0.000	0.160	3.53E-12	3.53E-12
41α	0.000	0.076	0.076	0.000	0.080	0.000	0.080	1.68E-07	1.68E-07
45α	0.000	0.168	0.168	0.000	0.191	0.000	0.191	3.53E-12	3.53E-12
47α	0.218	0.530	0.313	0.257	0.921	0.279	0.664	1.43E-23	NA
48α	0.000	0.112	0.112	0.000	0.122	0.000	0.122	5.14E-11	5.14E-11
50α	0.540	0.514	-0.026	0.955	0.867	1.102	-0.088	2.74E-01	NA
51α	0.302	0.254	-0.048	0.386	0.310	1.244	-0.076	2.41E-01	NA
52α	0.213	0.326	0.112	0.251	0.427	0.587	0.176	1.12E-02	NA
53α	0.311	0.471	0.161	0.401	0.742	0.540	0.342	5.00E-09	NA
54α	0.000	0.040	0.040	0.000	0.041	0.000	0.041	1.32E-04	1.32E-04
57α	0.000	0.037	0.037	0.000	0.038	0.000	0.038	1.32E-04	1.32E-04
59α	0.337	0.000	-0.337	0.447	0.000	NA	-0.447	3.53E-12	NA
60α	1.516	0.000	-1.516	NA	0.000	NA	NA	1.78E-17	NA
61α	0.118	0.411	0.292	0.129	0.595	0.217	0.466	1.12E-06	NA
62α	0.268	0.000	-0.268	0.332	0.000	NA	-0.332	5.15E-10	NA
64α	0.295	0.206	-0.088	0.374	0.241	1.550	-0.133	5.62E-02	NA
66α	0.474	0.215	-0.258	0.749	0.254	2.949	-0.495	2.26E-05	NA
67α	0.101	0.092	-0.009	0.109	0.099	1.102	-0.010	1.42E-02	NA
68α	0.619	0.410	-0.209	1.308	0.594	2.204	-0.715	2.61E-04	NA
69α	0.014	0.676	0.663	0.014	1.742	0.008	1.728	2.30E-26	NA
71α	1.437	0.148	-1.289	NA	0.165	NA	NA	8.88E-16	NA
72α	0.300	0.037	-0.263	0.383	0.038	9.960	-0.345	6.47E-03	NA
74α	0.000	0.071	0.071	0.000	0.075	0.000	0.075	1.68E-07	1.68E-07
75α	0.900	0.259	-0.641	NA	0.318	NA	NA	6.66E-16	NA
76α	0.000	0.257	0.257	0.000	0.314	0.000	0.314	1.87E-19	1.87E-19
78α	0.268	0.071	-0.197	0.332	0.075	4.452	-0.258	6.61E-01	NA
79α	0.000	0.081	0.081	0.000	0.086	0.000	0.086	1.68E-07	1.68E-07

DQA1 alleles of ape (*Gogo-DQA1*, *Patr-DQA1*, *Hyla-DQA1*, and *Popy-DQA1*, total 20 alleles) were used for the analysis. NA, not applicable (codons that showed *ps* ≥ 0.75 or *pn* ≥ 0.75, and codons that showed *dn* = 0, see Methods). Differences between *ps* and *pn*, or *ds* and *dn* were tested by the Wilcoxon signed-rank test.

Supplemental Table 5 Frequency of *HLA-DQ* haplotypes in T1D cases and controls.

DQ haplotypes	47α-57β ΔMHC	Swedish				Japanese			
		Case 2n=	Control 2n=	OR (95% CI)	Pc	Case 2n=	Control 2n=	OR (95% CI)	Pc
		1280 (%)	976 (%)			1090 (%)	792 (%)		
<i>DQA1*02-DQB1*02</i>	K-non D	0.46	46	51	0.68 (0.45-1.02)	0 (0.0)	0 (0.0)		
			(3.6)	(5.2)					
<i>DQA1*05-DQB1*02</i>	C-non D	0.10	353	118	2.77 (2.20-3.48)	5.5E-18	0 (0.0)	0 (0.0)	
			(27.6)	(12.1)					
<i>DQA1*03-DQB1*03:01</i>	Q-D	0.17	56	63	0.66 (0.46-0.96)	0.51	0 (0.0)	0 (0.0)	
			(4.4)	(6.5)					
<i>DQA1*05-DQB1*03:01</i>	C-D	0.20	29	80	0.26 (0.17-0.40)	1.4E-09	16	39	0.29 (0.16-0.52) 1.4E-04
			(2.3)	(8.2)			(1.5)	(4.9)	
<i>DQA1*06-DQB1*03:01</i>	C-D	0.04	0	1			2	14	0.10 (0.02-0.45) 2.9E-03
			(0.0)	(0.1)			(0.2)	(1.8)	
<i>DQA1*03-DQB1*03:02</i>	Q-non D	0.09	504	138	3.94 (3.19-4.88)	2.6E-38	113	73	1.14 (0.84-1.55)
			(39.4)	(14.1)			(10.4)	(9.2)	
<i>DQA1*02-DQB1*03:03</i>	K-D	0.82	7	36	0.14 (0.06-0.32)	1.2E-06	0	0 (0.0)	
			(0.5)	(3.7)			(0.0)		
<i>DQA1*03-DQB1*03:03</i>	Q-D	0.12	19	17	0.85 (0.44-1.64)		309	117	2.28 (1.80-2.89) 4.8E-11
			(1.5)	(1.7)			(28.3)	(14.8)	
<i>DQA1*03-DQB1*04:01</i>	Q-D	0.05	0	0			321	96	3.03 (2.36-3.89) 5.2E-18
			(0.0)	(0.0)			(29.4)	(12.1)	
<i>DQA1*04-DQB1*04:02</i>	C-D	0.09	52	39	1.02 (0.67-1.55)		7	19	0.26 (0.11-0.63) 0.016
			(4.1)	(4.0)			(0.6)	(2.4)	
<i>DQA1*01:01-DQB1*05:01</i>	R-non D	0.01	97	101	0.71 (0.53-0.95)	0.38	46	57	0.57 (0.38-0.85) 6.6E-02
			(7.6)	(10.3)			(4.2)	(7.2)	
<i>DQA1*01:04-DQB1*05:01</i>	R-non D	0.00	0	9			0 (0.0)	0 (0.0)	
			(0.0)	(1.0)					
<i>DQA1*01:02-DQB1*05:02</i>	R-non D	0.10	5	4			0 (0.0)	0 (0.0)	
			(0.4)	(0.4)					
<i>DQA1*01:04-DQB1*05:02</i>	R-non D	0.01	0	0			2	12	0.12 (0.03-0.54) 0.012
			(0.0)	(0.0)			(0.2)	(1.5)	
<i>DQA1*01:04-DQB1*05:03</i>	R-D	0.01	1	29	0.03	5.0E-08	10	37	0.19 (0.09-0.38) 3.3E-06
			(0.1)	(3.0)	(0.003-0.19)		(0.9)	(4.7)	
<i>DQA1*01:03-DQB1*06:01</i>	R-D	0.27	1	1			76	146	0.33 (0.25-0.45) 3.6E-13
			(0.1)	(0.1)			(7.0)	(18.4)	
<i>DQA1*01:02-DQB1*06:02</i>	R-D	1.00	10	140	0.05 (0.03-0.09)	2.6E-36	24	59	0.28 (0.17-0.45) 5.7E-07
			(0.8)	(14.3)			(2.2)	(7.4)	
<i>DQA1*01:03-DQB1*06:03</i>	R-D	0.35	35	86	0.29 (0.19-0.44)	3.9E-09	0 (0.0)	0 (0.0)	
			(0.8)	(8.8)					
<i>DQA1*01:02-DQB1*06:04</i>	R-non D	0.38	63	58	0.82 (0.57-1.18)		87	42	1.55 (1.06-2.27) 0.30
			(4.9)	(5.9)			(8.0)	(5.3)	
Unknown/Others			2	5			77	81	
			(0.2)	(0.5)			(7.1)	(10.2)	

Case-control data reported for the Swedish (77, 78) and Japanese populations (10). The *DQA1-DQB1* haplotypes were estimated from the *DRB1-DQB1* haplotypes (Methods). Polymorphisms at 47 α and 57 β are indicated in one-letter amino acid code. The ΔMHC of *DQB1*04:02* were assumed identical with that of *DQB1*04:01*. The *P*_c values were calculated by the chi-square test with Bonferroni correction.

Supplemental Table 6 Association of amino acid variants in *HLA-DQA1* with susceptibility to T1D.

<i>DQA1</i>	Amino acids	Swedish						Japanese					
		Case (2n = 1280)	Control (2n = 976)	OR	95% low	95% high	<i>P</i>	Case (2n = 1090)	Control (2n = 792)	OR	95% low	95% high	<i>P</i>
2a	D (vs. G)	1277	933	19.62	6.07	63.43	3.77E-12	1001	662	2.21	1.66	2.94	3.60E-08
11a	Y (vs. C)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
18a	S (vs. F)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
25a	Y (vs. F)	1189	796	2.95	2.26	3.86	2.34E-16	935	551	2.64	2.10	3.31	1.64E-17
26a	S (vs. T)	579	218	2.87	2.38	3.46	1.78E-29	743	286	3.79	3.12	4.59	2.90E-43
34a	E (vs. Q)	730	444	1.59	1.34	1.88	5.47E-08	801	392	2.83	2.33	3.43	1.47E-26
40a	E (vs. G)	844	733	0.64	0.53	0.77	2.58E-06	988	639	2.32	1.77	3.04	4.58E-10
	G (vs. E)	434	238	1.59	1.32	1.92	9.63E-07	25	72	0.23	0.15	0.37	4.57E-11
41a	R (vs. K)	1242	884	3.40	2.31	5.01	6.99E-11	937	565	2.46	1.95	3.10	6.05E-15
45a	V (vs. A)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
47a	KQC (vs. R)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	RQC (vs. K)	1225	884	2.32	1.64	3.27	1.01E-06	1013	711	1.50	1.08	2.08	1.46E-02
	Q (vs. RKC)	579	218	2.87	2.38	3.46	1.78E-29	743	286	3.79	3.12	4.59	2.90E-43
	C (vs. RKQ)	434	238	1.59	1.32	1.92	9.63E-07	25	72	0.23	0.15	0.37	4.57E-11
	QC (vs. RK)	1013	456	4.33	3.60	5.20	1.15E-57	768	358	2.89	2.39	3.50	2.62E-28
	RQ (vs. KC)	791	646	0.83	0.69	0.98	3.16E-02	988	639	2.32	1.77	3.04	4.58E-10
	KQ (vs. RC)	632	305	2.15	1.80	2.55	4.91E-18	743	286	3.79	3.12	4.59	2.90E-43
48a	L (vs. W)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
50a	LV (vs. E)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	L (vs. EV)	632	305	2.15	1.80	2.55	4.91E-18	743	286	3.79	3.12	4.59	2.90E-43
	V (vs. EL)	434	238	1.59	1.32	1.92	9.63E-07	25	72	0.23	0.15	0.37	4.57E-11
51a	F (vs. L)	844	733	0.64	0.53	0.77	2.58E-06	988	639	2.32	1.77	3.04	4.58E-10
	L (vs. F)	434	238	1.59	1.32	1.92	9.63E-07	25	72	0.23	0.15	0.37	4.57E-11
52a	HR (vs. S)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	RS (vs. H)	1225	884	2.32	1.64	3.27	1.01E-06	1013	711	1.50	1.08	2.08	1.46E-02
	R (vs. SH)	1013	456	4.33	3.60	5.20	1.15E-57	768	358	2.89	2.39	3.50	2.62E-28
53a	RQ (vs. K)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	R (vs. KQ)	632	305	2.15	1.80	2.55	4.91E-18	743	286	3.79	3.12	4.59	2.90E-43
	Q (vs. RK)	434	238	1.59	1.32	1.92	9.63E-07	25	72	0.23	0.15	0.37	4.57E-11
54a	F (vs. L)	1225	884	2.32	1.64	3.27	1.01E-06	1013	711	1.50	1.08	2.08	1.46E-02
55a	del, R (vs. G)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	GR (vs. del)	791	646	0.83	0.69	0.98	3.16E-02	988	639	2.32	1.77	3.04	4.58E-10
	R (vs. G, del)	579	218	2.87	2.38	3.46	1.78E-29	743	286	3.79	3.12	4.59	2.90E-43
56a	R (vs. G)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
61a	F (vs. G)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
64a	T (vs. R)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
66a	I (vs. M)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
69a	LT (vs. A)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	L (vs. AT)	1014	503	3.58	2.98	4.31	8.41E-44	759	325	3.29	2.72	3.99	2.83E-35
	AL (vs. T)	1226	931	1.10	0.73	1.64	6.53E-01	1004	678	1.96	1.46	2.64	6.18E-06
75a	I (vs. S)	896	773	0.61	0.50	0.75	8.02E-07	997	672	1.91	1.44	2.55	7.64E-06
76a	LV (vs. M)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	L (vs. MV)	487	325	1.23	1.03	1.46	1.99E-02	25	72	0.23	0.15	0.37	4.57E-11

	V (vs. ML)	579	218	2.87	2.38	3.46	1.78E-29	743	286	3.79	3.12	4.59	2.90E-43
80a	S (vs. Y)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
107a	T (vs. I)	896	773	0.61	0.50	0.75	8.02E-07	997	672	1.91	1.44	2.55	7.64E-06
	I (vs. T)	382	198	1.67	1.37	2.03	2.66E-07	16	39	0.29	0.16	0.52	1.11E-05
129a	H (vs. Q)	1102	630	3.40	2.77	4.18	3.31E-33	844	504	1.96	1.60	2.40	5.61E-11
130a	S (vs. A)	1242	884	3.40	2.31	5.01	6.99E-11	937	565	2.46	1.95	3.10	6.05E-15
156a	F (vs. L)	896	773	0.61	0.50	0.75	8.02E-07	997	672	1.91	1.44	2.55	7.64E-06
	L (vs. F)	382	198	1.67	1.37	2.03	2.66E-07	16	39	0.29	0.16	0.52	1.11E-05
161a	D (vs. A)	896	773	0.61	0.50	0.75	8.02E-07	997	672	1.91	1.44	2.55	7.64E-06
	E (vs. D)	382	198	1.67	1.37	2.03	2.66E-07	16	39	0.29	0.16	0.52	1.11E-05
163a	I (vs. S)	896	773	0.61	0.50	0.75	8.02E-07	997	672	1.91	1.44	2.55	7.64E-06
	S (vs. I)	382	198	1.67	1.37	2.03	2.66E-07	16	39	0.29	0.16	0.52	1.11E-05
175a	EK (vs. Q)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	E (vs. QK)	684	345	2.10	1.77	2.49	1.27E-17	752	319	3.30	2.72	3.99	2.08E-35
	K (vs. QE)	382	198	1.67	1.37	2.03	2.66E-07	16	39	0.29	0.16	0.52	1.11E-05
187a	T (vs. A)	579	218	2.87	2.38	3.46	1.78E-29	743	286	3.79	3.12	4.59	2.90E-43
	A (vs. T)	699	753	0.36	0.30	0.43	1.64E-28	270	425	0.28	0.23	0.35	1.25E-37
199a	A (vs. T)	1277	933	19.62	6.07	63.43	3.77E-12	1001	662	2.21	1.66	2.94	3.60E-08
207a	V (vs. M)	1200	769	4.04	3.07	5.31	4.36E-26	902	610	1.43	1.14	1.80	2.01E-03
215a	L (vs. F)	632	305	2.15	1.80	2.55	4.91E-18	743	286	3.79	3.12	4.59	2.90E-43
	F (vs. L)	646	666	0.47	0.40	0.56	2.32E-17	270	425	0.28	0.23	0.35	1.25E-37
218a	R (vs. Q)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28

Tested by the chi-square test. The strongest associations in each population (bold).

Supplemental Table 7 Association of amino acid variants in *HLA-DQB1* with susceptibility to T1D.

<i>DQB1</i>	Amino acids	Swedish						Japanese					
		Case (2n = 1280)	Control (2n= 976)	OR	95% low	95% high	<i>P</i>	Case (2n= 1090)	Control (2n= 792)	OR	95% low	95% high	<i>P</i>
3β	S (vs. P)	1277	970	2.63	0.66	10.55	1.56E-01	937	565	2.46	1.95	3.10	6.05E-15
9β	FY (vs. L)	1277	970	2.63	0.66	10.55	1.56E-01	937	565	2.46	1.95	3.10	6.05E-15
	Y (vs. FL)	1215	791	4.37	3.25	5.88	2.41E-25	585	391	1.19	0.99	1.43	6.52E-02
	YL (vs. F)	1216	792	4.41	3.28	5.95	1.98E-25	661	537	0.73	0.60	0.89	1.43E-03
	G (vs. A)	1192	826	2.46	1.86	3.25	7.69E-11	919	512	2.94	2.36	3.66	5.79E-23
14β	M (vs. L)	1175	828	2.00	1.53	2.61	2.09E-07	955	605	2.19	1.71	2.79	1.72E-10
23β	R (vs. L)	1278	971	3.29	0.64	17.00	1.32E-01	692	615	0.50	0.41	0.62	4.51E-11
26β	L (vs. YG)	1037	644	2.20	1.81	2.67	4.78E-16	533	291	1.65	1.37	1.99	1.54E-07
	LG (vs. Y)	1192	826	2.46	1.86	3.25	7.69E-11	919	512	2.94	2.36	3.66	5.79E-23
	LY (vs. G)	1123	789	1.70	1.35	2.14	6.39E-06	627	490	0.83	0.69	1.01	5.81E-02
28β	T (vs. S)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
30β	YH (vs. S)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
	Y (vs. SH)	678	515	1.01	0.85	1.19	9.24E-01	868	563	1.59	1.29	1.97	1.80E-05
	YS (vs. H)	1077	684	2.26	1.85	2.78	1.31E-15	868	563	1.59	1.29	1.97	1.80E-05
37β	YD (vs. I)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
	YI (vs. D)	1277	970	2.63	0.66	10.55	1.56E-01	937	565	2.46	1.95	3.10	6.05E-15
	Y (vs. ID)	878	801	0.48	0.39	0.58	3.64E-13	937	565	2.46	1.95	3.10	6.05E-15
38β	A (vs. V)	775	658	0.74	0.62	0.88	7.82E-04	879	459	3.02	2.46	3.71	8.30E-27
45β	G (vs. E)	1193	827	2.47	1.87	3.27	7.41E-11	995	658	2.13	1.61	2.82	7.68E-08
46β	V (vs. E)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
47β	Y (vs. F)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
52β	P (vs. L)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
53β	L (vs. Q)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
55β	PR (vs. L)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
	P (vs. LR)	615	335	1.77	1.49	2.10	6.13E-11	440	243	1.53	1.26	1.86	1.60E-05
	LP (vs. R)	1014	504	3.57	2.97	4.29	1.61E-43	440	243	1.53	1.26	1.86	1.60E-05
56β	P (vs. L)	1226	932	1.07	0.71	1.61	7.38E-01	685	596	0.56	0.45	0.68	1.20E-08
57β	A (vs. DSV)	903	307	5.22	4.36	6.25	5.50E-76	113	73	1.14	0.84	1.55	4.09E-01
	AVS (vs. D)	1068	479	5.23	4.31	6.34	6.10E-68	248	184	0.97	0.78	1.21	8.07E-01
	ADS (vs. V)	1118	803	1.49	1.18	1.88	7.95E-04	880	612	1.23	0.98	1.54	6.74E-02
	ADV (vs. S)	1273	967	1.69	0.63	4.56	2.93E-01	1011	699	1.70	1.24	2.33	8.36E-04
	AD (vs. SV)	1113	799	1.48	1.17	1.86	8.66E-04	878	600	1.33	1.06	1.65	1.24E-02
	AS (vs. DV)	908	311	5.22	4.36	6.25	5.27E-76	115	85	0.98	0.73	1.32	8.99E-01
	AV (vs. DS)	1063	475	5.17	4.26	6.26	1.44E-67	246	172	1.05	0.84	1.31	6.61E-01
	E (vs. D)	826	762	0.51	0.42	0.62	2.94E-12	609	450	0.96	0.80	1.16	6.83E-01
	V (vs. I)	826	762	0.51	0.42	0.62	2.94E-12	609	450	0.96	0.80	1.16	6.83E-01
	R (vs. EG)	1078	563	3.91	3.22	4.77	1.14E-44	603	431	1.04	0.86	1.25	6.98E-01
71β	RG (vs. E)	1226	932	1.07	0.71	1.61	7.38E-01	685	596	0.56	0.45	0.68	1.20E-08
	RE (vs. G)	1130	602	4.68	3.78	5.80	1.03E-49	931	546	2.64	2.11	3.31	9.06E-18
	TDA (vs. K)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
	T (vs. ADK)	724	620	0.75	0.63	0.89	8.43E-04	627	490	0.83	0.69	1.01	5.81E-02
	KTA (vs. D)	1226	932	1.07	0.71	1.61	7.38E-01	685	596	0.56	0.45	0.68	1.20E-08
	KTD (vs. A)	1175	828	2.00	1.53	2.61	2.09E-07	955	605	2.19	1.71	2.79	1.72E-10

	KT (vs. AD)	1123	789	1.70	1.35	2.14	6.39E-06	627	490	0.83	0.69	1.01	5.81E-02
	TA (vs. KD)	827	763	0.51	0.42	0.62	2.58E-12	685	596	0.56	0.45	0.68	1.20E-08
	TD (vs. KA)	776	659	0.74	0.62	0.88	7.45E-04	955	605	2.19	1.71	2.79	1.72E-10
74β	ES (vs. A)	879	802	0.48	0.39	0.58	3.10E-13	1013	711	1.50	1.08	2.08	1.46E-02
	E (vs. AS)	724	620	0.75	0.63	0.89	8.43E-04	627	490	0.83	0.69	1.01	5.81E-02
	AE (vs. S)	1123	789	1.70	1.35	2.14	6.39E-06	627	490	0.83	0.69	1.01	5.81E-02
75β	L (vs. V)	724	620	0.75	0.63	0.89	8.43E-04	627	490	0.83	0.69	1.01	5.81E-02
77β	T (vs. R)	776	659	0.74	0.62	0.88	7.45E-04	955	605	2.19	1.71	2.79	1.72E-10
84β	Q (vs. E)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
85β	L (vs. V)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
86β	E (vs. AG)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	EG (vs. A)	1129	601	4.67	3.77	5.77	1.13E-49	855	400	3.57	2.92	4.36	6.42E-37
	AE (vs. G)	1215	913	1.29	0.90	1.84	1.61E-01	926	669	1.04	0.81	1.34	7.73E-01
87β	L (vs. YF)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	LF (vs. Y)	1112	770	1.77	1.42	2.21	4.40E-07	868	563	1.59	1.29	1.97	1.80E-05
	LY (vs. F)	1232	744	8.00	5.79	11.06	2.56E-46	913	506	2.92	2.35	3.62	4.97E-23
89β	T (vs. G)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
90β	T (vs. I)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
116β	V (vs. I)	1175	828	2.00	1.53	2.61	2.09E-07	955	605	2.19	1.71	2.79	1.72E-10
125β	AG (vs. S)	1175	828	2.00	1.53	2.61	2.09E-07	955	605	2.19	1.71	2.79	1.72E-10
	A (vs. SG)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
	AS (vs. G)	1169	686	4.45	3.51	5.65	2.30E-38	826	464	2.21	1.81	2.70	2.18E-15
126β	Q (vs. H)	1273	967	1.69	0.63	4.56	2.93E-01	1011	699	1.70	1.24	2.33	8.36E-04
130β	R (vs. Q)	1215	913	1.29	0.90	1.84	1.61E-01	926	669	1.04	0.81	1.34	7.73E-01
140β	T (vs. A)	667	374	1.75	1.48	2.07	7.55E-11	768	358	2.89	2.39	3.50	2.62E-28
167β	R (vs. H)	1192	826	2.46	1.86	3.25	7.69E-11	919	512	2.94	2.36	3.66	5.79E-23
182β	N (vs. S)	667	374	1.75	1.48	2.07	7.55E-11	768	358	2.89	2.39	3.50	2.62E-28
185β	I (vs. T)	582	230	2.70	2.25	3.25	6.71E-27	750	305	3.52	2.91	4.27	4.63E-39
197β	S (vs. N)	1277	970	2.63	0.66	10.55	1.56E-01	937	565	2.46	1.95	3.10	6.05E-15
203β	I (vs. V)	1067	544	3.98	3.28	4.83	6.39E-47	844	504	1.96	1.60	2.40	5.61E-11
220β	H (vs. R)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
221β	H (vs. Q)	1066	543	3.97	3.27	4.82	6.45E-47	768	358	2.89	2.39	3.50	2.62E-28
224β	Q (vs. R)	1175	828	2.00	1.53	2.61	2.09E-07	955	605	2.19	1.71	2.79	1.72E-10

Tested by the chi-square test. The strongest association in the Swedish population (bold).