

# Associations Between Human Leukocyte Antigen (HLA) Genotype and Acute Myocardial Infarction

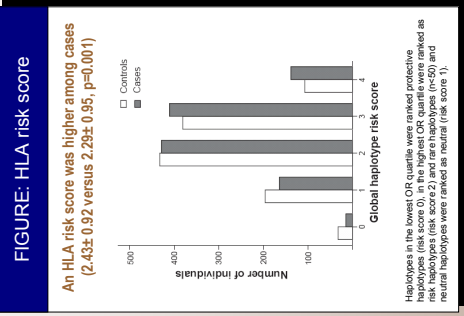
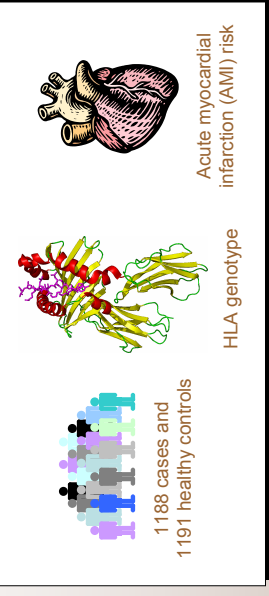
Harry Björkbacka<sup>1</sup>, Eva H. Lavant<sup>2,3</sup>, Gunilla Nordin Fredrikson<sup>1,3</sup>, Olle Melander<sup>1</sup>, Göran Berglund<sup>1</sup>, Joyce A. Carlson<sup>1,4</sup> and Jan Nilsson<sup>1</sup>

<sup>1</sup>Department of Clinical Sciences and <sup>2</sup>Department of Laboratory Medicine, Malmö University Hospital, Lund University, <sup>3</sup>Department of Biomedical Laboratory Science, Malmö University, <sup>4</sup>Department of Laboratory Medicine, Lund University Hospital, Lund University, Sweden

**Background**

HLAs are polymorphic molecules involved in antigen presentation. Associations between HLA of the DR-DQ type and autoimmune diseases, such as type 1 diabetes and rheumatoid arthritis, are well established. The possible association with cardiovascular disease has not been systematically investigated in large cohorts.

**The importance of HLA association studies is stressed by recent experimental findings of an involvement of autoimmunity in the atherosclerotic disease process**



**TABLE 4: Haplotype frequencies**

DRB1\*0701 | DQA\*0201 | DQB\*0202 was associated with reduced risk for AMI (OR 0.79; 95% CI 0.64-0.99)

DRB1\*0101 | DQA\*0101 | DQB\*0301 was associated with increased risk for AMI (OR 1.22; 95% CI 1.1-1.49)

Haplotype	No. of controls (%)	No. of cases (%)	OR (95% CI)
<b>Protective haplotypes*</b>			
DRB1*0701   DQA*0201   DQB*0202	185 (55.4%)	149 (44.6%)	0.79 (0.64-0.99)†
DRB1*0301   DQA*0301   DQB*0402	100 (55.2%)	81 (44.8%)	0.81 (0.61-1.09)
DRB1*0701   DQA*0201   DQB*0303	76 (55.1%)	62 (44.9%)	0.81 (0.58-1.14)
DRB1*16   DQA*0102   DQB*0902	28 (65%)	22 (44%)	0.70 (0.45-1.30)
<b>Risk haplotypes*</b>			
DRB1*0101   DQA*0101   DQB*0501	194 (44.3%)	201 (55.7%)	1.25 (1.01-1.55)†
DRB1*0301   DQA*0301   DQB*0303	25 (40.3%)	37 (69.7%)	1.49 (0.89-2.49)
DRB1*0301   DQA*0301   DQB*0201	289 (48.1%)	312 (61.9%)	1.1 (0.92-1.3)
DRB1*0401   DQA0201   DQB*0301   DQB*0302	218 (48%)	236 (52%)	1.1 (0.9-1.33)
<b>Neutral haplotypes*</b>			
DRB1*11   DQA*0102   DQA*0301   DQB*0301	222 (85.5%)	240 (51.5%)	1.09 (0.9-1.33)
DRB1*0402   DQA*0301   DQB*0302	29 (59.8%)	14 (41.2%)	0.7 (0.35-1.39)
DRB1*0403   DQA*0301   DQB*0301	0 (0%)	2 (100%)	5.02 (0.24-104.6)
DRB1*0408   DQA*0301   DQB*0301	2 (100%)	0 (0%)	0.2 (0.01-4.18)
DRB1*0409   DQA*0301   DQB*0301	1 (50%)	1 (50%)	1 (0.06-16.05)
DRB1*0409   DQA*0301   DQB*0302	6 (62.7%)	3 (33.3%)	0.5 (0.19-1.32)†
DRB1*0409   DQA*0301   DQB*0303	19 (65.9%)	15 (44.1%)	0.79 (0.44-1.56)
DRB1*11   DQA*0101   DQB*0503	38 (53.5%)	33 (46.5%)	0.87 (0.54-1.39)
DRB1*0408   DQA*0301   DQB*0302	84 (62.2%)	77 (47.8%)	0.92 (0.67-1.26)
DRB1*0408   DQA*0301   DQB*0304	2 (33.3%)	1 (33.3%)	2.01 (0.37-10.97)
DRB1*0407   DQA*0301   DQB*0302	4 (66.7%)	2 (33.3%)	0.5 (0.09-2.74)
DRB1*0303   DQA*0301   DQB*0301	8 (60%)	8 (60%)	1 (0.39-2.68)
DRB1*0303   DQA*0301   DQB*0501	9 (47.4%)	3 (15.8%)	0.31 (0.12-0.81)
DRB1*1301   DQA*0101   DQB*0306	1 (25%)	3 (75%)	3 (0.31-28.97)
DRB1*0408   DQA*0301   DQB*0302	134 (69.8%)	142 (68.8%)	1.02 (0.88-1.16)
DRB1*0401   DQA*0104   DQB*0301	17 (51.5%)	17 (51.5%)	1.02 (0.38-1.3)
DRB1*0407   DQA*0301   DQB*0301	1 (25%)	2 (50%)	0.94 (0.08-1.07)
DRB1*0409   DQA*0301   DQB*0301	9 (47.4%)	10 (52.6%)	1.05 (0.67-1.65)
DRB1*0406   DQA*0301   DQB*0301	8 (60%)	8 (60%)	1 (0.39-2.68)
DRB1*1001	17 (51.5%)	16 (48.5%)	0.94 (0.48-1.87)
Total	2298 (48.3%)	2314 (48.5%)	

OR = Odds ratio; 95% CI = 95% confidence interval  
 † p = 0.045 (χ<sup>2</sup> test); p = 0.049 (Fisher's exact test)  
 \* Haplotypes in the lowest OR quartile were ranked protective haplotypes (risk score 0)  
 † Haplotypes in the highest OR quartile were ranked as risk haplotypes (risk score 2)  
 ‡ Haplotypes (n=50) and haplotypes not included in a and b were ranked as neutral (risk score 1)

**TABLE 1: DRB1 allele frequencies**

DRB1\*0701 was associated with reduced risk for AMI (OR 0.78; 95% CI 0.65-0.95)

DRB1\*0101 was associated with increased risk for AMI (OR 1.24; 95% CI 1.1-1.24)

Allele	No. of controls (%)	No. of cases (%)	OR (95% CI)
DRB1*0701	281 (65.3%)	211 (44.7%)	0.78 (0.65-0.95)†
DRB1*0101	164 (44.9%)	124 (14.54)†	1.24 (1.1-1.49)†
DRB1*0301	100 (55.2%)	81 (44.8%)	0.8 (0.59-1.08)
DRB1*0201	25 (40.3%)	37 (69.7%)	1.48 (0.92-2.49)
DRB1*0401	20 (68.8%)	14 (41.2%)	0.69 (0.35-1.38)
DRB1*11   DQA*0102   DQB*0902	222 (48.1%)	240 (51.5%)	1.06 (0.9-1.26)
DRB1*0301	289 (48.1%)	312 (61.9%)	1.06 (0.91-1.26)
DRB1*16	28 (65%)	22 (44%)	0.7 (0.45-1.07)
DRB1*0401	352 (48.6%)	372 (51.4%)	1.06 (0.91-1.24)
DRB1*0406	3 (37.5%)	5 (62.5%)	1.67 (0.47-6.01)
DRB1*0407	86 (62.8%)	77 (47.2%)	0.89 (0.65-1.22)
DRB1*0408	23 (56.1%)	18 (43.9%)	0.79 (0.45-1.38)
DRB1*14	38 (53.5%)	33 (46.5%)	0.87 (0.54-1.39)
DRB1*0403	7 (68.3%)	5 (41.7%)	0.72 (0.23-2.26)
DRB1*1301   DQA*0101   DQB*0306	642 (49.8%)	648 (50.2%)	1.02 (0.88-1.16)
DRB1*0102	9 (47.4%)	10 (52.6%)	1.1 (0.46-2.72)
DRB1*0406	8 (60%)	8 (60%)	1 (0.06-15.97)
DRB1*0303	1 (25%)	3 (75%)	3 (0.31-28.97)
DRB1*1001	17 (51.5%)	16 (48.5%)	0.94 (0.48-1.87)
Total	2298 (48.3%)	2314 (48.5%)	

OR = Odds ratio; 95% CI = 95% confidence interval  
 † p = 0.045 (χ<sup>2</sup> test); p = 0.048 (Fisher's exact test)

**Conclusions**

Weak associations were found between the HLA haplotypes and risk for development of acute myocardial infarction (AMI)

**The HLA-DRB1\*0101-DQA\*0101-DQB\*0301 haplotype was found to be associated with increased risk for AMI (OR 1.24; 95% CI 1.003-1.541)**

The DRB1\*0701-DQA\*0201-DQB\*0202 haplotype conferred protection (OR 0.79; 95% CI 0.635-0.994)

**An HLA risk score taking each individual's both haplotypes into account was higher among cases (2.43±0.92 versus 2.29±0.95, p=0.001)**

**TABLE 2: DQB allele frequencies**

DQB\*0202 was associated with reduced risk for AMI (OR 0.79; 95% CI 0.64-0.99)

DQB\*0501 was associated with increased risk for AMI (OR 1.22; 95% CI 1.1-1.49)

Allele	No. of controls (%)	No. of cases (%)	OR (95% CI)
DQB*0202	185 (55.4%)	149 (44.6%)	0.79 (0.64-0.99)†
DQB*0501	190 (45.6%)	227 (64.4%)	1.22 (1.1-1.49)†
DQB*0402	101 (55.5%)	81 (44.5%)	0.8 (0.59-1.07)
DQB*0304	3 (30%)	7 (70%)	2.34 (0.61-9.08)
DQB*0201	250 (42.2%)	312 (51.5%)	1.09 (0.92-1.29)
DQB*0502	28 (56%)	22 (44%)	0.79 (0.45-1.38)
DQB*0301	386 (48.9%)	403 (51.1%)	1.06 (0.91-1.23)
DQB*0503	38 (53.5%)	33 (46.5%)	0.87 (0.54-1.39)
DQB*06	642 (49.8%)	648 (50.2%)	1.02 (0.88-1.16)
DQB*0303	101 (50.5%)	99 (49.5%)	0.98 (0.74-1.3)
DQB*0302	332 (50.1%)	332 (49.9%)	1 (0.86-1.16)
DQB*0305	0 (0%)	1 (100%)	3.01 (0.12-73.36)
DQB*05	1 (100%)	0 (0%)	0.33 (0.01-9.21)
Total	2292 (50.1%)	2376 (49.9%)	

OR = Odds ratio; 95% CI = 95% confidence interval  
 † p = 0.045 (χ<sup>2</sup> test); p = 0.049 (Fisher's exact test)  
 \* p = 0.054 (χ<sup>2</sup> test); p = 0.061 (Fisher's exact test)

**TABLE 3: DQA allele frequencies**

DQA\*0201 was associated with reduced risk for AMI (OR 0.78; 95% CI 0.65-0.95)

Allele	No. of controls (%)	No. of cases (%)	OR (95% CI)
DQA*0201	281 (65.3%)	211 (44.7%)	0.78 (0.65-0.95)†
DQA*0101	164 (44.9%)	124 (14.54)†	1.24 (1.1-1.49)†
DQA*0301	100 (55.2%)	81 (44.8%)	0.8 (0.59-1.08)
DQA*0401	25 (40.3%)	37 (69.7%)	1.48 (0.92-2.49)
DQA*0102	20 (68.8%)	14 (41.2%)	0.69 (0.35-1.38)
DQA*0301	222 (48.1%)	240 (51.5%)	1.06 (0.9-1.26)
DQA*0303	289 (48.1%)	312 (61.9%)	1.06 (0.91-1.26)
DQA*16	28 (65%)	22 (44%)	0.7 (0.45-1.07)
DQA*0401	352 (48.6%)	372 (51.4%)	1.06 (0.91-1.24)
DQA*0406	3 (37.5%)	5 (62.5%)	1.67 (0.47-6.01)
DQA*0407	86 (62.8%)	77 (47.2%)	0.89 (0.65-1.22)
DQA*0408	23 (56.1%)	18 (43.9%)	0.79 (0.45-1.38)
DQA*14	38 (53.5%)	33 (46.5%)	0.87 (0.54-1.39)
DQA*0403	7 (68.3%)	5 (41.7%)	0.72 (0.23-2.26)
DQA*1301   DQA*0101   DQB*0306	642 (49.8%)	648 (50.2%)	1.02 (0.88-1.16)
DQA*0102	9 (47.4%)	10 (52.6%)	1.1 (0.46-2.72)
DQA*0406	8 (60%)	8 (60%)	1 (0.06-15.97)
DQA*0303	1 (25%)	3 (75%)	3 (0.31-28.97)
DQA*1001	17 (51.5%)	16 (48.5%)	0.94 (0.48-1.87)
Total	2298 (48.3%)	2314 (48.5%)	

OR = Odds ratio; 95% CI = 95% confidence interval  
 † p = 0.045 (χ<sup>2</sup> test); p = 0.048 (Fisher's exact test)

**Methods**

Baseline clinical characteristics:

	Cases (n=1188)	Controls (n=1191)	P
Age (years)	62.7 (6.5)	62.7 (6.5)	n.s.
Gender (% male)	76	76	n.s.
Systolic blood pressure (mmHg)	150.21	148.20	<0.02
Diastolic blood pressure (mmHg)	89.10	88.10	n.s.
Body mass index (kg/m <sup>2</sup> )	26.9 (3.9)	26.1 (3.5)	<0.001
Current smokers (%)	34	24	<0.001
Lipid-lowering treatment (%)	19	3	<0.001
Treatment for diabetes (%)	7	2	<0.001

Values are mean±standard deviation

DNA had been extracted from granulocyte suspension or buffy coats using QIAamp mini kits (Qiagen) and genotyped for HLA-DRB1\*0101 and -DQB1\*0202 by PCR-SSP method optimized for capillary electrophoresis on Applied Biosystems 3730 DNA Analyzer. Acute myocardial infarction (AMI) cases are matched pairs recruited from the Swedish Myocardial Infarction Register. A total of 1244 AMI cases were identified and matched for age, sex and time of baseline investigation with 1244 controls who were free from AMI during follow-up. DNA for genetic analyses were obtained from 1188 AMI cases and 1191 controls. The studies were approved by the Lund University ethics committee.

**TABLE 4: Haplotype frequencies**

DRB1\*0701 | DQA\*0201 | DQB\*0202 was associated with reduced risk for AMI (OR 0.79; 95% CI 0.64-0.99)

DRB1\*0101 | DQA\*0101 | DQB\*0301 was associated with increased risk for AMI (OR 1.22; 95% CI 1.1-1.49)

Haplotype	No. of controls (%)	No. of cases (%)	OR (95% CI)
<b>Protective haplotypes*</b>			
DRB1*0701   DQA*0201   DQB*0202	185 (55.4%)	149 (44.6%)	0.79 (0.64-0.99)†
DRB1*0301   DQA*0301   DQB*0402	100 (55.2%)	81 (44.8%)	0.81 (0.61-1.09)
DRB1*0701   DQA*0201   DQB*0303	76 (55.1%)	62 (44.9%)	0.81 (0.58-1.14)
DRB1*16   DQA*0102   DQB*0902	28 (65%)	22 (44%)	0.70 (0.45-1.30)
<b>Risk haplotypes*</b>			
DRB1*0101   DQA*0101   DQB*0501	194 (44.3%)	201 (55.7%)	1.25 (1.01-1.55)†
DRB1*0301   DQA*0301   DQB*0303	25 (40.3%)	37 (69.7%)	1.49 (0.89-2.49)
DRB1*0301   DQA*0301   DQB*0201	289 (48.1%)	312 (61.9%)	1.1 (0.92-1.3)
DRB1*0401   DQA0201   DQB*0301   DQB*0302	218 (48%)	236 (52%)	1.1 (0.9-1.33)
<b>Neutral haplotypes*</b>			
DRB1*11   DQA*0102   DQA*0301   DQB*0301	222 (85.5%)	240 (51.5%)	1.09 (0.9-1.33)
DRB1*0402   DQA*0301   DQB*0302	29 (59.8%)	14 (41.2%)	0.7 (0.35-1.39)
DRB1*0403   DQA*0301   DQB*0301	0 (0%)	2 (100%)	5.02 (0.24-104.6)
DRB1*0408   DQA*0301   DQB*0301	2 (100%)	0 (0%)	0.2 (0.01-4.18)
DRB1*0409   DQA*0301   DQB*0301	1 (50%)	1 (50%)	1 (0.06-16.05)
DRB1*0409   DQA*0301   DQB*0302	6 (62.7%)	3 (33.3%)	0.5 (0.19-1.32)†
DRB1*0409   DQA*0301   DQB*0303	19 (65.9%)	15 (44.1%)	0.79 (0.44-1.56)
DRB1*11   DQA*0101   DQB*0503	38 (53.5%)	33 (46.5%)	0.87 (0.54-1.39)
DRB1*0408   DQA*0301   DQB*0302	84 (62.2%)	77 (47.8%)	0.92 (0.67-1.26)
DRB1*0408   DQA*0301   DQB*0304	2 (33.3%)	1 (33.3%)	2.01 (0.37-10.97)
DRB1*0407   DQA*0301   DQB*0302	4 (66.7%)	2 (33.3%)	0.5 (0.09-2.74)
DRB1*0303   DQA*0301   DQB*0301	8 (60%)	8 (60%)	1 (0.39-2.68)
DRB1*0303   DQA*0301   DQB*0501	9 (47.4%)	3 (15.8%)	0.31 (0.12-0.81)
DRB1*1301   DQA*0101   DQB*0306	1 (25%)	3 (75%)	3 (0.31-28.97)
DRB1*0408   DQA*0301   DQB*0302	134 (69.8%)	142 (68.8%)	1.02 (0.88-1.16)
DRB1*0401   DQA*0104   DQB*0301	17 (51.5%)	17 (51.5%)	1.02 (0.38-1.3)
DRB1*0407   DQA*0301   DQB*0301	1 (25%)	2 (50%)	0.94 (0.08-1.07)
DRB1*0409   DQA*0301   DQB*0301	9 (47.4%)	10 (52.6%)	1.05 (0.67-1.65)
DRB1*0406   DQA*0301   DQB*0301	8 (60%)	8 (60%)	1 (0.39-2.68)
DRB1*1001	17 (51.5%)	16 (48.5%)	0.94 (0.48-1.87)
Total	2298 (48.3%)	2314 (48.5%)	

OR = Odds ratio; 95% CI = 95% confidence interval  
 † p = 0.045 (χ<sup>2</sup> test); p = 0.049 (Fisher's exact test)  
 \* Haplotypes in the lowest OR quartile were ranked protective haplotypes (risk score 0)  
 † Haplotypes in the highest OR quartile were ranked as risk haplotypes (risk score 2)  
 ‡ Haplotypes (n=50) and haplotypes not included in a and b were ranked as neutral (risk score 1)

**Acknowledgement**

This study was supported by grants from the Swedish Medical Research Council, the Swedish Heart Lung Foundation, the Swedish Foundation for the Care of Inhabited, The Magnus Bergvall Foundation, the Knut and Alice Wallenberg Foundation, the Royal Physiographic Society, The Swedish Society of Medicine, The Las Hierta Memorial Foundation, The Thelma Ziegler Foundation, the Malmö University Hospital, the Albert Pahlsson Foundation and the Lundström Foundation. EL and JC were supported by the Type 1 Diabetes Genetics Consortium (T1DC) sponsored by NIDDK, NIAID, NHERF, NICHD and JDRF, supported by 101 DK062418.