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HLA-DQ relative risks for coeliac disease in European populations: a study of the European Genetics Cluster on Coeliac Disease

Key words:
coeliac disease; HLA heterodimer; MHC class II; relative risk

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Abstract: Coeliac disease is an enteropathy due to an intolerance to gluten. The association between HLA-DQ genes and CD is well established. The majority of patients carry the HLA-DQ heterodimer encoded by *DQA1*05/DQB1*02*, either in *cis* or in *trans*. The remaining patients carry either part of the DQ heterodimer or *DQA1*03-DQB1*0302*. The aim of the study was to estimate the risks associated with different DQ genotypes in European populations. HLA information was available for 470 trio families from four countries: France (117), Italy (128), and Norway and Sweden (225). Five *DQA1-DQB1* haplotypes were considered and control haplotype frequencies were estimated from the set of parental haplotypes not transmitted to the affected child. The possible genotypes were grouped into five genotype groups, based on the hierarchy of risk reported in the literature. A north–south gradient in the genotype group frequencies is observed in probands: homogeneity is strongly rejected between all country pairs. For each country, the relative risks associated with each genotype group were computed taking into account the control haplotype frequencies. Homogeneity of relative risks between countries was tested pairwise by maximum likelihood ratio statistics. The hypothesis of homogeneity of relative risks is rejected (P is approximately 10^{-6}) for all country pairs. In conclusion, the gradient in the genotype group frequencies in probands is not only due to differences in haplotype frequencies but also due to differences in genotype relative risks in the studied populations; the relative risks associated with each DQ genotype group are different between northern and southern European countries; neither are they ordered in the same way.

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Coeliac disease (CD) is a malabsorption disorder, characterized by a small bowel enteropathy mediated by intolerance to gluten (1). The pathogenic mechanism involves both genetic and environmental factors.

The involvement of human leukocyte antigen (HLA) genes in the susceptibility to CD is clearly established. Early studies reported association to the B8 allele in HLA class I (2). Later, association was shown to DR3, DR7 (3), and with DQ2 (4) alleles in the HLA class II complex. A significant step was achieved when it was shown that most CD patients (90–95%) expressed the heterodimer

*DQA1*05/DQB1*02* (5, 6). Among the *DQA1*05/DQB1*02* heterodimer carriers, the risk of CD has been shown to be increased in individuals homozygous for *DQB1*02* (7–9). Among the 10% of CD patients who do not carry the known high-risk heterodimer *DQA1*05/DQB1*02* (denoted DQ2 serologically), many of them carry the heterodimer *DQA1*03-DQB1*0302* (denoted DQ8 serologically) (10, 11).

A study of the European Genetic Cluster on Coeliac Disease showed that among 1007 unrelated European patients, 104 did not carry the heterodimer *DQA1*05/DQB1*02*. Among them, almost half (49 patients) carried the *DQA1*03-DQB1*0302* heterodimer. The remaining patients carried either *DQA1*05* or *DQB1*02* alone (12).

The aim of the present study was to further investigate the European Genetic Cluster data by estimating the risks associated with the different DQ genotypes in different European subpopulations.

Materials and methods

Family data

Trio families, one affected child and two parents, were recruited in four different European countries. A total of 470 European trio families were collected from Italy (128 families), France (117 families), and Norway and Sweden (225 families); data from Norway and Sweden were pooled, as they are expected to be genetically homogeneous and cited hereafter as Scandinavia. All patients fulfilled the revised European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria (13) for the diagnosis of CD.

HLA typing method

All family members (1410 individuals) were genotyped for HLA.

France

DRB1 and *DQB1* typings were performed by the reverse hybridization principle using the Murex and Innogenetics INNO LiPA *HLA-DQB1* and *DRB1* kits.

Italy

DRB1 and *DQB1* typing was performed with the Dynal AllSet+ SSP *DRB1* and *DQB1* low-resolution kits.

Scandinavia

DQA1 and *DQB1* genotyping was done by PCR-SSO.

In French and Italian populations, the *DQA1* alleles were inferred from *DRB1* and *DQB1* typing using the known linkage disequilibrium between alleles at these loci (14).

Notation

Let α_5 represent the *DQA1*05* allele and α all other *DQA1* alleles, β_2 represent the *DQB1*02* allele, β_3 the *DQB1*0302* allele, and β all the other *DQB1* alleles. As β_3 is always found with the *DQA1*0301* allele, let $\alpha_3\beta_3$ denote the *DQA1*0301-DQB1*0302* haplotype. According to our notation, five *DQA1-DQB1* haplotypes are defined: $\alpha_5\beta_2$, $\alpha\beta_2$, $\alpha_5\beta$, $\alpha_3\beta_3$, and $\alpha\beta$. Other combinations of *DQA1* and *DQB1* alleles are not considered because they are never observed in the studied populations.

The usual corresponding DR alleles (from the well-established associations between *DRB1-DQA1-DQB1*) carried by these *DQA1-DQB1* haplotypes are DR3 by $\alpha_5\beta_2$, DR7 by $\alpha\beta_2$, DR5 by $\alpha_5\beta$, and DR4 by $\alpha_3\beta_3$.

It is known from the literature that, among the heterodimer carriers, individuals homozygous for *DQB1*02* are at higher risk (7, 8, 15). In addition, the risk is different when the heterodimer is present in *cis* or in *trans* (16, 17).

Based on these results, the $\alpha_5\beta_2$ heterodimer carriers can be split into three groups:

1. Group 1 (G_1): comprising two β_2 alleles (DR3DR3 and DR3DR7).
2. Group 2 (G_2): comprising one β_2 allele and one α_5 allele encoded in *trans* (DR5DR7).
3. Group 3 (G_3): comprising one β_2 allele and one α_5 allele encoded in *cis* (DR3DRX with X different from 3 and 7).

Besides, the non-$\alpha_5\beta_2$ carriers can be split into two genotype groups:

1. Group 4 (G_4): comprising two at-risk β alleles, β_2 or β_3 (DR4DR4, DR4DR7, and DR7DR7).
2. Group 5 (G_5): comprising only one at-risk allele α_5, β_2, or β_3 (all other possibilities).

Statistical methods

Control *DQA1-DQB1* haplotype frequencies were estimated from parental haplotypes that were not transmitted to the affected child. As shown by Thomson (18), these control haplotype frequencies are considered representative of the population from which the patients are derived, because the trio has only been ascertained for the presence of one affected child, whatever the parental and sib status for the disease. Such controls are usually referred to as Affected Family Based Controls.

Homogeneity between haplotype frequencies obtained for the different countries was tested by a Chi-square homogeneity test with four degrees of freedom.

For each population and given the haplotype frequencies estimated in this population, we calculated the relative risk (*RRi*) of each genotype group (G*i*) relative to the group with the maximum risk G_1. The probability to have genotype G*i* in the general population is based on control haplotype frequencies assuming Hardy–Weinberg equilibrium (*Appendix A*).

The confidence intervals of the relative risks have been estimated by a bootstrap procedure (*Appendix B*). For each population, 1000 bootstrap rounds of families and control alleles were carried out.

Pairwise maximum likelihood ratios were employed as a test of homogeneity of relative risks between pairs of countries (*Appendix C*). This test permits to see whether the difference between genotype frequencies in patients according to their population of origin can be explained by the difference between haplotype frequencies in these populations or whether the relative risks are significantly different from one country to another.

Results

Control *DQA1-DQB1* haplotype frequencies estimation

Control *DQA1-DQB1* haplotype frequencies for each country with the usual corresponding DR allele are reported (Table 1). The haplotype frequencies follow a strong north–south gradient. The $\alpha\beta_2$ and $\alpha_5\beta$ haplotypes are more frequent in southern Europe than in northern Europe and conversely for the $\alpha_3\beta_3$ haplotype. Homogeneity is rejected for all country pairs: $P = 0.015$ for France and Italy; P is approximately 0.001 for France and Scandinavia; and P is approximately 10^{-5} for Italy and Scandinavia. Even when corrected for multiple tests, all tests are significant at the 5% level. The distance between haplotype frequencies, as shown by the significance of the homogeneity tests, clearly increases with the geographic distance.

Genotype frequencies of probands

From the 470 probands, only two (one Italian and one French) do not belong to any of the five DQ genotype groups defined above and were therefore excluded from the analysis. The clinical diagnosis of these two probands is being re-checked.

The frequency of each genotype group for probands is summarized in Table 2. As expected, the majority of probands carry the $\alpha_5\beta_2$ heterodimer (groups 1, 2, and 3): 86, 87, and 92% for Italy, France, and Scandinavia, respectively. The proportion of group 3 probands increases from south–north: from 24% in Italy to 54% in Scandinavia. The gradient is reversed for group 2 (i.e., $\alpha_5\beta/\alpha\beta_2$): from 37% in Italy to 4% in Scandinavia. Homogeneity is rejected between all country pairs: P is approximately 0.001 for France and Italy ($\chi^2_{4df} = 19.0$), P is approximately 10^{-6} for France and Scandinavia ($\chi^2_{4df} = 30.6$), and P is approximately 10^{-15} for Italy and Scandinavia ($\chi^2_{4df} = 74.5$). After correcting for multiple tests, all tests remain significant at the 1% level.

The question is to determine whether the differences in genotype frequencies are only due to the gradient in the DQ haplotype frequencies or whether the genotype relative risks are different from one country to another.

Relative risk of genotype groups

Table 3 summarizes the relative risks and confidence intervals for each genotype group relative to the greater at-risk group (G_1) for each country.

In all populations, we observe, among the $\alpha_5\beta_2$ heterodimer carriers, a dose effect for β_2: the risk is higher for group 1 (two doses) than that for groups 2 and 3 (one dose). In addition, there is a position effect in Italy and France with a higher risk for group 2 (*trans*) than that for group 3 (*cis*); the estimated relative risk for group 2 is three times the one for group 3. Such a difference is not observed in Scandinavia.

Control haplotype frequencies in each country

Notation	DQA1-DQB1 haplotypes	DR alleles	Italy	France	Scandinavia
$\alpha_5\beta_2$	DQA1*05-DQB1*02	DR3	0.09	0.13	0.11
$\alpha\beta_2$	DQA1*02-DQB1*02	DR7	0.15	0.10	0.06
$\alpha_5\beta$	DQA1*05-DQB1*03	DR5	0.26	0.17	0.10
$\alpha_3\beta_3$	DQA1*0301-DQB1*0302	DR4	0.02	0.06	0.15
$\alpha\beta$	Other	Other	0.48	0.54	0.58
Number of haplotypes			254	232	450

Table 1

Proportion of probands in each genotype group

Genotype group	Italy	France	Scandinavia
G_1	0.26	0.47	0.33
G_2	0.37	0.15	0.04
G_3	0.24	0.26	0.54
G_4	0.06	0.04	0.04
G_5	0.08	0.09	0.04
Number of probands	127	116	225

Table 2

For all country pairs, the hypothesis of homogeneity of relative risks is rejected (P is approximately 10^{-6}): $\chi^2_{4df} = 29.4$ for France and Italy; $\chi^2_{4df} = 30.3$ for France and Scandinavia; and $\chi^2_{4df} = 23.9$ for Italy and Scandinavia. This means that the differences in haplotype frequencies do not explain the difference in DQ genotype frequencies between countries.

Discussion

The involvement of the *DQA1*0501-DQB1*0201* and *DQA1*0301-DQB1*0302* heterodimers in the susceptibility to CD has been reported in many studies (11). In a recent article (9), the effect of the *DQA1-DQB1* genotype on the magnitude of gluten-specific T-cell responses, implicated in CD was studied. Our results are in agreement with their conclusions: greater risk for *DQA1*05-DQB1*02/DQA1*05-DQB1*02* and *DQA1*05-DQB1*02/DQA1*0201-DQB1*02* individuals, medium risk for *DQA1*05-DQB1*02/non-DQ2* individuals, and lower risk for *non-DQ2/non-DQ2* individuals.

Here, we estimated the relative risks of at-risk DQ genotypes in four European countries. We show that the relative risks differ between European countries, even when taking into account the strong variation of DQ haplotype frequencies in those countries. An important feature only observed in southern (France and Italy) populations is the higher risk for group 2 individuals (DR5/DR7), carrying the heterodimer in *trans*, than that for group 3 individuals (DR3/DRX), carrying the heterodimer in *cis*. Similar findings have previously been observed in the Tunisian population (16), in another French sample (19), and in two other independent Italian samples (17).

The observed data could be explained by the involvement of another HLA factor subdividing the *DQA1-DQB1* haplotypes in different at-risk subhaplotypes, some being more at risk than the others. In that case, the difference observed between north and south could be explained by different proportions of these subhaplotypes, according to the geographic area. The hypothesis of two *DRB1*03-DQA1*05-DQB1*02* haplotypes with different risks has already been argued in several studies. The underlying idea is that at least another *HLA* gene, additional to *DQA1* and *DQB1*, is involved in the disease susceptibility. In 1979, Demarchi et al. (20) showed that B8-DR3 and B18-DR3 haplotypes differed in risk for CD. These two haplotypes have a very different relative frequency in northern and southern countries. To demonstrate the presence of a HLA risk factor additional to DQ, studies have been set up considering *DRB1*03-DQA1*05-DQB1*02* haplotypes transmitted and non-transmitted to the affected offspring in families selected for having at least one *DRB1*03*-positive parent. Using such a strategy, several studies have reported different frequencies between cases and controls of DP (21), tumour necrosis factor (TNF) (22, 23), MHC class I related gene (MICA) (24, 25) alleles, and of microsatellites in HLA (26, 27).

These literature results are good arguments in favor of the hypothesis of different proportions of *DRB1*03-DQA1*05-DQB1*02* subhaplotypes according to the geographic area. It means that it would be possible to refine our HLA risk estimates by getting some homogenous typing of non-class II genes in our four patient samples.

Genotype group risks relatively to the greater at-risk genotype group risk G1 (95% confidence intervals in brackets)

DQ genotypes	Corresponding DR genotype*	Genotype group	Italy	France	Scandinavia
$\alpha_5\beta_{2/}\alpha_5\beta_2$	DR3/DR3	G_1	1	1	1
$\alpha_5\beta_{2/}\alpha\beta_2$	DR3/DR7	G_1	1	1	1
$\alpha_5\beta_{/}\alpha\beta_2$	DR5/DR7	G_2	0.68 [0.31, 1]	0.28 [0.11, 0.61]	0.23 [0.16, 0.33]
$\alpha_5\beta_{2/}\alpha_5\beta$,$\alpha_5\beta_{2/}\alpha_3\beta_3$, $\alpha_5\beta_{2/}\alpha\beta$	DR3/DRX	G_3	0.23 [0.12, 0.38]	0.09 [0.05, 0.15]	0.23 [0.16, 0.33]
$\alpha\beta_{2/}\alpha\beta_2$	DR7/DR7	G_4	0.27 [0.08, 0.65]	0.10 [0.02, 0.28]	0.08 [0.03, 0.16]
$\alpha\beta_{2/}\alpha_3\beta_3$	DR7/DR4	G_4	0.27 [0.08, 0.65]	0.10 [0.02, 0.28]	0.08 [0.03, 0.16]
$\alpha_3\beta_{3/}\alpha_3\beta_3$	DR4/DR4	G_4	0.27 [0.08, 0.65]	0.10 [0.02, 0.28]	0.08 [0.03, 0.16]
Others	Others	G_5	0.02 [0.01, 0.05]	0.01 [0.00, 0.03]	0.01 0.00, 0.02]

*Based on the known linkage disequilibrium between alleles at these loci.
X = different from 3 and 7.

Table 3

Members of the European Genetics Cluster on Coeliac Disease

Participants in the European Genetics Cluster on Coeliac Disease (project partner group leaders are italicized): Finland – P. Holopainen, K. Karell, *J. Partanen* (Department of Tissue Typing, Finnish Red Cross Blood Transfusion Service, Helsinki), P. Collin, K. Mustalahti, M. Mäki (Institute of Medical Technology and Department of Pediatrics, University of Tampere, Tampere). France – *F. Clerget-Darpoux*, M-C. Babron, P Margaritte-Jeannin (INSERM U535, Villejuif), F. Clot (INSERM U535 Villejuif, Fondation Jean Dausset – CEPH, Paris), J-P. Hugot (Fondation Jean Dausset – CEPH, Paris; Hôpital Robert Debré, Paris). Italy – S. D'Alfonso, E. Bolognesi, M. Giordano, M. Mellai, P. Momigliano-Richiardi [Department Medical Sciences, Eastern Piedmont University and I.R.C.A.D. (Interdisciplinary Research Center on Autoimmune Diseases), Novara], I. Coto, *L. Greco*, S. Percopo (Department of Paediatrics, University Federico II, Naples). R. Tosi [Istituto Biologia Cellulare, CNR, Monterotondo (Rome)]. Norway – A.S. Louka, *L.M. Sollid*, B. Talseth (Institute of Immunology, Rikshospitalet University Hospital, Oslo), J. Ek (Buskerud Hospital Trust, Drammen). Sweden – *H. Ascher*, A.H. Gudjónsdóttir, B. Kristiansson (Department of Paediatrics, Göteborg University, The Queen Silvia Children's Hospital, Göteborg), S. Adamovic, T. Martinsson, L. Samuelsson, Å. Torinsson Naluai, J. Wahlström (Department of Clinical Genetics, Göteborg University, Sahlgrenska University Hospital/Östra, Göteborg), S. Nilsson, Olle Nerman (Department of Mathematics, Chalmers University of Technology, Göteborg). United Kingdom – *P.J. Ciclitira*, J. Fraser, A. King, S.J. Moodie (Gastroenterology Unit, GKT, The Rayne Institute, St Thomas's Hospital, London).

*Appendix A

The risk Pi for an individual of genotype Gi to be affected can be computed using Bayes'theorem:

$P\text{i} = P(\text{affected}/\text{G}i) = [P(\text{G}i/\text{affected}) \times P(\text{affected})]/P(\text{G}i)$.

where P(Gi/affected) is the proportion of each genotype group in probands, P(Gi) the probability to have genotype Gi in the general population, based on control haplotype frequencies assuming Hardy–Weinberg equilibrium. P(affected) is the probability to be affected in the general population.

Let Pmax (corresponding to group G_1 in our data) be the maximum risk among all risk Pi (obtained for each Gi). For each Gi, the relative risk RRi, $RRi = Pi/P\text{max}$, is independent from P(affected).

*Appendix B

The relative risk confidence intervals have been calculated with a bootstrap procedure.

In each bootstrap round, a new family sample is constructed by drawing with replacement from the observed family dataset. Similarly, new control haplotype frequency estimates are obtained by resampling from the observed control haplotype pool.

The relative risks associated to each genotype groups are then calculated as outlined in *Appendix A*. Repeating this procedure 1000 times provides the distribution and 95% confidence interval of the relative risks in each population.

This bootstrapping procedure offers the advantage of taking into account the dependence between the relative risks.

*Appendix C

Let Lj be the likelihood of the parameters RRi_j (relative risk to be affected for an individual with genotype Gi in population j). Let Gi_j be the probability to have genotype Gi in population j and Ni_j, the number of probands with genotype Gi among the N_j probands in population j. Then, Lj can be written as:

$$L_j = \prod_i (RRi_j \times Gi_j \times N_j)^{Ni_j}$$

Considering two countries A and B, under the constraint of equality of relative risk of genotype Gi, $RRi_{AB} = RRi_A = RRi_B$, the likelihood L_{AB} can be expressed as

$$L_{AB} = \prod_i (RRi_{AB} \times Gi_A \times N_A)^{Ni_A} \times \prod_i (RRi_{AB} \times Gi_B \times N_B)^{Ni_B}$$

Under equality of the relative risks RRi_A and RRi_B the quantity

$$Q = -2[\ln L_{AB} - (\ln L_A + \ln L_B)]$$

follows a chi-square with $i-1$ degrees of freedom, since all Gi groups but one (with $RR_1 = 1$) have been considered.

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