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An association analysis of the HLA gene region in latent autoimmune diabetes in adults

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Abstract

Aims/hypothesis—Pathophysiological similarities between latent autoimmune diabetes in adults (LADA) and type 1 diabetes indicate an overlap in genetic susceptibility. *HLA-DRB1* and *HLA-DQB1* are major susceptibility genes for type 1 diabetes but studies of these genes in LADA have been limited. Our aim was to define patterns of *HLA*-encoded susceptibility/protection in a large, well characterised LADA cohort, and to establish association with disease and age at diagnosis.

Materials and methods—Patients with LADA (n=387, including 211 patients from the UK Prospective Diabetes Study) and non-diabetic control subjects (n=327) were of British/Irish European origin. The *HLA-DRB1* and *-DQB1* genes were genotyped by sequence-specific PCR.

Results—As in type 1 diabetes mellitus, *DRB1*0301_DQB1*0201* (odds ratio [OR]=3.08, 95% CI 2.32–4.12, p=1.2× 10^{-16}) and *DRB1*0401_DQB1*0302* (OR=2.57, 95% CI 1.80–3.73, p=4.5×10^{-8}) were the main susceptibility haplotypes in LADA, and *DRB1*1501_DQB1*0602* was protective (OR=0.21, 95% CI 0.13–0.34, p=4.2×10^{-13}). Differential susceptibility was conferred by DR4 subtypes: *DRB1*0401* was predisposing (OR=1.79, 95% CI 1.35–2.38, p=2.7×10^{-5}) whereas *DRB1*0403* was protective (OR=0.37, 95% CI 0.13–0.97, p=0.033). The highest-risk genotypes were *DRB1*0301/DRB1*0401* and *DQB1*0201/DQB1*0302* (OR=5.14, 95% CI 2.68–10.69, p=1.3×10^{-8}; and OR=6.88, 95% CI 3.54–14.68, p=1.2×10^{-11}, respectively). These genotypes and those containing *DRB1*0401* and *DQB1*0302* associated with a younger age at diagnosis in LADA, whereas genotypes containing *DRB1*1501* and *DQB1*0602* associated with an older age at diagnosis.

Conclusions/interpretation—Patterns of susceptibility at the *HLA-DRB1* and *HLA-DQB1* loci in LADA are similar to those reported for type 1 diabetes, supporting the hypothesis that autoimmune diabetes occurring in adults is an age-related extension of the pathophysiological process presenting as childhood-onset type 1 diabetes.

Keywords

Age of diagnosis; Genetic susceptibility; Protection; Type 1 diabetes

Introduction

Latent autoimmune diabetes in adults (LADA) and type 1 diabetes mellitus result from islet beta cell autoimmune destruction and are characterised by the presence of circulating islet autoantibodies. However, the later age of onset and the relatively less acute clinical onset of LADA can result in a clinical diagnosis of type 2 diabetes [1]. Differences in genetic susceptibility could contribute to the variation in both age and clinical severity at onset of autoimmune diabetes.

The HLA gene region is the major susceptibility locus in type 1 diabetes, accounting for 42% of the total familial risk; primary susceptibility is conferred by the *HLA-DRB1* and *HLA-DQB1* genes, and the highest risk is from *DRB1*04-DQB1*0302* and *DRB1*0301-*

*DQB1*0201* haplotypes, present in ~90% of type 1 diabetic patients [2]. In type 1 diabetes, the *DRB1*0301* and *DRB1*0401* alleles exhibit positive synergism such that the *DRB1*0401/DRB1*0301* genotype confers greater risk than either of the two alleles alone [3]. In addition, *DRB1*0301/DRB1*0401* and *DQB1*0201/DQB1*0302* genotypes occur more frequently in type 1 diabetic patients diagnosed at earlier ages [4]. Heterogeneity in disease risk conferred by the *DRB1*04-DQB1*0302* haplotype depends upon the allelic subtype of the DR4 antigen specificity present on it: *DRB1*0401, *0402* and **0405* associate with increased susceptibility, whereas **0403, *0406* and **0407* confer protection [5]. The *DRB1*1501-DQB1*0602* haplotype, which is negatively correlated with age at diagnosis, is considered to be protective against type 1 diabetes [6].

Although the *HLA-DRB1* and *HLA-DQB1* genes are good candidate loci for LADA, HLA association studies in LADA have been hampered by small sample sizes and low genotyping resolution. Predisposing effects of *DRB1*0301* and *DRB1*0401* have been demonstrated, but results have been inconsistent [7–9] and a protective effect of *DQB1*0602* has not been confirmed throughout [8, 10]. The largest study, using UK Prospective Diabetes Study subjects (UKPDS), employed low-resolution typing restricted to detection of *HLA-DRB1* susceptibility variants DRB1*03 and DRB1*04 [7]. This demonstrated an increased frequency of the *DRB1*03/DRB1*04* heterozygote in LADA [7]. However, protective variants were not examined and *HLA-DQB1* allele analysis was restricted to determination of aspartate-57, a putative susceptibility determinant for type 1 diabetes [7].

This investigation extends the previous study [7] by using higher resolution typing and a larger LADA cohort. The aims were to (1) establish association patterns of HLA with disease and compare these with previously reported observations made in type 1 diabetes and (2) determine the relationship of *HLA-DRB1* and *HLA-DQB1* genotypes with age at diagnosis.

Subjects and methods

Subjects

LADA subjects (n=378) were from the UKPDS (n=211), the Warren 2 Repository (W2, n=130) [11] and the Exeter Young-Onset Type 2 Diabetes Study (YT2D, n=37) [12]. They were initially diagnosed with type 2 diabetes and were antibody-positive (for GAD and/or islet antigen 2A, IA-2A), with no requirement for insulin within 3 months after diagnosis. The control population comprised normoglycaemic, GADA/IA-2A-negative spouses/friends of probands recruited as part of the Diabetes in Families study (DIF, n=327). All subjects were unrelated and of British/Irish European origin (Table 1). Informed consent was obtained from all subjects, and all studies were carried out in accordance with the principles of the Declaration of Helsinki (1975, 1983, 2000).

Genotyping

The *HLA-DRB1* and *HLA-DQB1* genes were genotyped using sequence-specific PCR (PCR-SSP) [13]. Samples with inferred haplotypes that were uncommon or did not conform to known linkage disequilibrium patterns in UK Europids were regenotyped (n=27). Duplicate sample (n=15) genotyping concordance was 100% for both loci and success was >95%.

Statistical methods

Homogeneity (between LADA groups) and case–control association testing was performed using standard contingency table methods in StatXact 6 (Cytel Software, Cambridge, MA, USA). As appropriate, exact p values were calculated. Haplotype frequencies were

estimated using the expectation maximization algorithm implemented in HelixTree (Golden Helix, Bozeman, MT, USA). For diplotype analyses, the most probable haplotype pair was assigned to each individual and >97.8% of assigned haplotypes had posterior probabilities >0.999. Distributions of allele, genotype, haplotype and diplotype frequencies between cases and controls were assessed by $2\times n$ contingency tables (pooling categories with frequencies <1%). Where global tests of association indicated significant differences, variants with frequency >5% were tested for disease association by 2×2 contingency table analysis. Association of age at diagnosis with genotype was initially explored using recursive partitioning, as implemented in HelixTree. Linear regression modelling (SPSS, version 13.0; SPSS, Chicago, IL, USA) was subsequently performed for genotypes containing alleles associated with type 1 diabetes and/or shown to be associated with age at diagnosis. Power calculations (Quanto, version 1.0; http://hydra.usc.edu/gxe, last accessed in September 2006) indicated that our sample size provided >80% power to detect an odds ratio (OR) >1.85 for a minor allele frequency of 5% under the additive model. No corrections for multiple testing were applied and a p value of <0.05 was deemed significant.

Results

Allele frequency distributions between the UKPDS, W2 and YT2D LADA groups did not significantly differ at *HLA-DRB1* and *HLA-DQB1* (p=0.20 and 0.81, respectively). Accordingly, genotyping data of the three patient groups were combined, forming a single group (‘LADA’), and compared with control subjects.

The overall distribution of allele frequencies at *HLA-DRB1* and *HLA-DQB1* differed significantly between LADA and control subjects (both p<0.0001). Analysis of individual alleles showed predisposing effects of *DRB1*0301* (OR=3.08, 95% CI 2.32–4.11), *DRB1*0401* (OR=1.79, 95% CI 1.35–2.38), *DQB1*0201* (OR=3.19, 95% CI 2.40–4.26) and *DQB1*0302* (OR=2.38, 95% CI 1.77–3.25) (Table 2). Protection was conferred by *DRB1*0403(06/07)* (OR=0.37, 95% CI 0.13–0.97), *DRB1*1101(04)* (OR = 0.25, 95% CI 0.12–0.48), *DRB1*1501-06* (OR = 0.20, 95% CI 0.13–0.32), *DQB1*0301* (OR=0.51, 95% CI 0.37–0.69), *DQB1*0303* (OR=0.29, 95% CI 0.14–0.57) and *DQB1*0602* (OR=0.21, 95% CI 0.13–0.34) (Table 2).

The distribution of *HLA-DRB1* and *HLA-DQB1* genotypes differed significantly between LADA and control subjects (p<0.0001; see Electronic supplementary material [ESM] Tables 1 and 2, respectively). Specifically, increased susceptibility to LADA was conferred by genotypes, *DRB1*0301/DRB1*0401* (OR=5.14, 95% CI 2.68–10.69), *DRB1*0301/DRB1*0301* (OR=4.51, 95% CI 1.93–12.23), *DRB1*0301/DRB1*0701* (OR=2.38, 95% CI 1.13–5.38), *DQB1*0201/DQB1*0302* (OR=6.88, 95% CI 3.54–14.68), *DQB1*0201/DQB1*0201* (OR=5.11, 95% CI 2.21–13.77), *DQB1*0201/DQB1*0202* (OR= 2.47, 95% CI 1.04–6.51), *DQB1*0201/DQB1*0501* (OR=2.84, 95% CI 1.07–8.79) and *DQB1*0302/DQB1*0302* (OR=2.84, 95% CI 1.07–8.79) (Table 3). Additionally, protective effects of *DRB1*0701/DRB1*1501-06* (OR=0.05, 95% CI 0.001–0.31) and *DQB1*0301/DQB1*0602* (OR=0.11, 95% CI 0.02–0.38) were observed (Table 3). The highest point estimate for genotypic risk at *HLA-DRB1* was seen in the *DRB1*0301/DRB1*0401* heterozygotes, though this was not significantly greater than the estimate for either homozygote group (data not shown).

DRB1_DQB1 haplotype distribution was different between LADA and control subjects (p<0.0001; ESM Table 3). Haplotypes *DRB1*0301_DQB1*0201* and *DRB1*0401_DQB1*0302* were predisposing (OR=3.08, 95% CI 2.32–4.12; and OR=2.57, 95% CI 1.80–3.73, respectively) whereas *DRB1*1101(04)_DQB1*0301* and

*DRB1*1501-06_DQB1*0602* (OR=0.25, 95% CI 0.12–0.48; and OR=0.21, 95% CI 0.13–0.34, respectively) conferred protection against LADA (Table 4).

Similarly, *DRB1_DQB1* diplotype frequencies differed significantly between LADA and control subjects ($p<0.0001$; ESM Table 4), with *DRB1*0301_DQB1*0201-DRB1*0401_DQB1*0302* and *DRB1*0301_DQB1*0201-DRB1*0301_DQB1*0201* occurring more frequently in LADA compared with control subjects (OR=8.70, 95% CI 3.67–25.13, $p=8.1\times10^{-10}$ and OR=4.51, 95% CI 1.93–12.23, $p=7.6\times10^{-5}$, respectively). A nominally significant predisposing effect of *DRB1*0301_DQB1*0201-DRB1*0701_DQB1*0202* was also observed (OR=2.46, 95% CI 1.04–6.49, $p=0.048$).

Diagnostic criteria for LADA have been proposed, including age at diagnosis >30 years and no clinical requirement for insulin within 6 months after diagnosis [14]. Using these criteria, we repeated the analyses, excluding 50 non-compliant cases. The effect sizes (odd ratios) were comparable (data not shown) with those described above.

Within the LADA group, the *DRB1*0301/*0401* genotype associated with a younger age of diagnosis (mean age±SD in carriers vs non-carriers, 42.1±10.3 vs 46.6±10.2 years, $p=0.0016$), as did possession of the *DRB1*0401* allele (43.8±9.8 vs 47.4±10.5 years, $p=0.00075$). Similarly, an earlier age of diagnosis was associated with the *DQB1*0201/DQB1*0302* genotype (42.8±9.8 vs 46.5± 10.3 years, $p=0.0051$) and with possession of the *DQB1*0302* allele (44.3±9.8 vs 46.9± 10.5 years, $p=0.018$). Conversely, patients carrying *DRB1*1501-06* were older at diagnosis than those not carrying this allele (50.3±10.7 vs 45.6±10.2 years, $p=0.030$), as were carriers of *DQB1*0602* (50.3±10.7 vs 45.5±10.2 years, $p=0.029$).

Discussion

The major LADA susceptibility determinants at the two loci were *DRB1*0301, DRB1*0401, DQB1*0201* and *DQB1*0302*. This confirms previously reported genotype associations of *DRB1*0301/DRB1*0401*, *DRB1*0301/DRB1*0301*, *DQB1*0201/DQB1*0201*, *DQB1*0201/DQB1*0302* and *DQB1*0302/DQB1*0302* in LADA [7, 8]. This is the first report to demonstrate that DR4 antigen specificity subtypes confer differential risk of LADA: *DRB1*0401* conferred susceptibility to LADA, whereas *DRB1*0403(06/07)* had a protective effect. The synergistic effects of the *DRB1*0301* and *DRB1*0401* alleles reported in type 1 diabetes [3] were not statistically significant in LADA, although the greatest point estimate for genotypic risk at *HLA-DRB1* was observed for *DRB1*0301/DRB1*0401* heterozygotes, which conferred an approximately 5-fold risk of disease (OR=5.14, 95% CI 2.68–10.69, $p=1.3\times10^{-8}$).

The major protective alleles in our LADA cohort were *DRB1*1501-06* and *DQB1*0602*, as seen in Swedish patients [10] though not in Finns [8]. *DRB1*1101(04), DQB1*0301* and *DQB1*0303* were also protective, as seen in type 1 diabetes [2]. However, we found that *DRB1_DQB1* haplotypes/diplotypes were very strongly associated with LADA and, in some cases, could account for the genotype/allele effects, e.g. protection conferred by *DRB1*1101(04)_DQB1*0301*. The age-related associations observed in this study are similar to those reported in type 1 diabetes and LADA [4, 6, 7].

We conclude that the architecture of HLA-conferred susceptibility to LADA is similar to that observed in type 1 diabetes, although individual effect sizes may differ. Susceptibility conferred by the insulin gene region is indistinguishable from that observed in type 1 diabetes [15]. Thus, similarities in genetic predisposition conferred by the two major type 1 diabetes susceptibility loci suggest that adult-onset autoimmune diabetes is an age-related extension of the pathophysiological process presenting as type 1 diabetes in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DIF	Diabetes in Families study
HLA	human leucocyte antigen
OR	odds ratio
UKPDS	UK Prospective Diabetes Study
W2	Warren 2 Repository
YT2D	Exeter Young-Onset Type 2 Diabetes Study

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Table 1

Clinical characteristics of study subjects

Sample (*n*)	Study (*n*)	Ascertainment criteria	Age at onset (years) mean±SD (range),	Duration of diabetes (years), mean±SD	BMI (kg/m^2), mean±SD	Male (%)
LADA (378)	UKPDS (211)	Newly diagnosed type 2 diabetes: not insulin-requiring within 3 months of diagnosis. Ketonuria <3 mmol/l	46.3±10.6 (25–65)	Studied at diagnosis	25.1±4.8[a]	52
	W2 (130)	Clinical diagnosis of type 2 diabetes: not insulin requiring within 12 months of diagnosis	47.4±10.0 (26–68)	8.9±6.7[b]	28.6±5.3[b]	57
	YT2D (37)	Clinical diagnosis of type 2 diabetes: not insulin-requiring within 3 months of diagnosis	38.4±5.4 (29–45)	11.9±7.7[b]	27.5±5.8[b]	43
Control subjects	DIF (327)	Spouses/friends of probands collected in the DIF study. Normoglycaemic	55.3±19.8[b] (20–91)	N/A	25.4±4.0[b]	46

Antibody positivity was defined as a titre >97.5th percentile compared with control samples (UKPDS, YT2D and DIF samples measured in the laboratory of P. J. Bingley, University of Bristol) or >10 U (corresponding to ~8 SD above the mean of 88 normal control subjects) for the W2 samples measured in the laboratory of G. F. Bottazzo (Royal London Hospital). All LADA patients were GADA-positive with the exception of two YT2D patients who were positive for IA-2A only. Control subjects were negative for GADA and IA-2A at sample collection.

[a] At diagnosis

[b] At time of sample collection

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Table 2

HLA-DRB1 and *HLA-DQB1* allele frequencies and associated OR and *p* values

	LADA (*n*=756)[a,b]	Control subjects (*n*=654)[a]	OR (95% CI)	*p* value
DRB1 allele				
**0101*	53 (0.070)	64 (0.098)	0.70 (0.47–1.03)	0.066
**0103*	4 (0.005)	3 (0.005)		ND
**0301*	236 (0.312)	84 (0.128)	3.08 (2.32–4.11)	9.1×10^{-17}
**0302*	0	1 (0.002)		ND
**0401*	178 (0.235)	96 (0.147)	1.79 (1.35–2.38)	2.7×10^{-5}
**0402*	4 (0.005)	2 (0.003)		ND
**0403(06/07)*	7 (0.009)	16 (0.024)	0.37 (0.13–0.97)	0.033
**0404*	34 (0.045)	22 (0.034)		ND
**0405*	8 (0.011)	3 (0.005)		ND
**0701*	100 (0.132)	94 (0.144)	0.91 (0.66–1.25)	0.54
**0801*	16 (0.021)	22 (0.034)		ND
**0901(02)*	6 (0.008)	9 (0.014)		ND
**1001*	1 (0.001)	1 (0.002)		ND
**1101(04)*	13 (0.017)	43 (0.066)	0.25 (0.12–0.48)	3.4×10^{-6}
**1102(03)*	15 (0.020)	7 (0.011)		ND
**1201*	3 (0.004)	10 (0.015)		ND
**1301*	20 (0.026)	27 (0.041)		ND
**1302*	22 (0.029)	30 (0.046)		ND
**1303*	1 (0.001)	1 (0.002)		ND
**1401*	5 (0.007)	12 (0.018)		ND
**1501-06*	26 (0.034)	97 (0.148)	0.20 (0.13–0.32)	2.1×10^{-14}
**1601*	4 (0.005)	10 (0.015)		ND
DQB1 allele				
**0201*	239 (0.317)	83 (0.127)	3.19 (2.40–4.26)	7.1×10^{-18}
**0202*	82 (0.109)	66 (0.101)	1.09 (0.76–1.56)	0.66
**0301*	82 (0.109)	127 (0.194)	0.51 (0.37–0.69)	8.3×10^{-6}
**0302*	178 (0.236)	75 (0.115)	2.38 (1.77–3.25)	2.5×10^{-9}

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	LADA (n=756)[a,b]	Control subjects (n=654)[a]	OR (95% CI)	p value
**0303*	13 (0.017)	37 (0.057)	0.29 (0.14–0.57)	7.2×10^{-5}
**0401*	1 (0.001)	0		ND
**0402*	16 (0.021)	21 (0.032)		ND
**0501*	59 (0.078)	68 (0.104)	0.73 (0.50–1.07)	0.094
**0502*	3 (0.004)	10 (0.015)		ND
**0503*	4 (0.005)	12 (0.018)		ND
**0504*	1 (0.001)	0		ND
**0601*	0	4 (0.006)		ND
**0602*	25 (0.033)	91 (0.139)	0.21 (0.13–0.34)	2.5×10^{-13}
**0603*	15 (0.020)	30 (0.046)		ND
**0604*	36 (0.048)	30 (0.046)		ND

All OR were calculated under the multiplicative model and are presented as LADA vs control subjects. Genotyping was checked by two independent researchers.

ND denotes an association not determined because frequencies were <5% in both LADA and control groups.

[a] Data are given as number of chromosomes (frequency).

[b] LADA n=754 for *DQB1* allele.

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Table 3

Association of *HLA-DRB1* and -*DQB1* genotypes (frequencies >5% in either cases or controls) with LADA

	LADA[a]	Control subjects[a]	OR (95% CI)	*p* value
DRB1 genotype				
**0301/*0401*	62 (0.164)	12 (0.037)	5.14 (2.68–10.69)	1.3×10^{-8}
**0301/*0301*	34 (0.090)	7 (0.021)	4.51 (1.93–12.23)	7.6×10^{-5}
**0301/*0701*	29 (0.077)	11 (0.034)	2.38 (1.13–5.38)	0.014
**0401/*0701*	22 (0.058)	14 (0.043)	1.38 (0.66–2.97)	0.39
**0701/*1501-06*	1 (0.003)	17 (0.052)	0.05 (0.001–0.31)	2.9×10^{-5}
DQB1 genotype				
**0201/*0302*	73 (0.194)	11 (0.034)	6.88 (3.54–14.68)	1.2×10^{-11}
**0201/*0201*	38 (0.101)	7 (0.021)	5.11 (2.21–13.77)	9.4×10^{-6}
**0201/*0202*	22 (0.058)	8 (0.024)	2.47 (1.04–6.51)	0.038
**0201/*0501*	19 (0.050)	6 (0.018)	2.84 (1.07–8.79)	0.024
**0302/*0302*	19 (0.050)	6 (0.018)	2.84 (1.07–8.79)	0.024
**0201/*0301*	17 (0.045)	17 (0.052)	0.86 (0.41–1.83)	0.73
**0301/*0602*	3 (0.008)	22 (0.067)	0.11 (0.02–0.38)	1.7×10^{-5}

All OR were calculated as presence of the genotype in question vs all other genotypes and are presented as LADA compared with control subjects.

[a]Data are given as number of individuals (frequency).

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Table 4

Association of *HLA-DRB1_DQB1* haplotypes (frequencies >5% in either cases or controls) with LADA

Haplotype	LADA[a]	Control subjects[a]	OR (95% CI)	*p* value
**0301_*0201*	234 (0.310)	83 (0.127)	3.08 (2.32–4.12)	1.2×10^{-16}
**0401_*0302*	128 (0.169)	48 (0.073)	2.57 (1.80–3.73)	4.5×10^{-8}
**0701_*0202*	81 (0.107)	64 (0.098)	1.11 (0.77–1.59)	0.60
**0101_*0501*	52 (0.069)	64 (0.098)	0.68 (0.46–1.02)	0.052
**0401_*0301*	49 (0.065)	47 (0.072)	0.90 (0.58–1.39)	0.60
**1501-06_*0602*	25 (0.033)	90 (0.138)	0.21 (0.13–0.34)	4.2×10^{-13}
**1101(04)_*0301*	13 (0.017)	43 (0.066)	0.25 (0.12–0.48)	3.4×10^{-6}

All OR are calculated under the multiplicative model and are presented as LADA vs control subjects

[a]Data are given as number of chromosomes (frequency)