CLINICAL INVESTIGATIONS

HLA class II alleles and haplotypes in Lithuanian children with type 1 diabetes and healthy children (HLA and type 1 diabetes)

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Key words: *type 1 diabetes mellitus; children; human leukocytes antigens; alleles; case-control study.*

Summary. *Objective. Type 1 diabetes mellitus is a slowly progressive autoimmune disease. The genetic background of type 1 diabetes mellitus is polygenic with the major disease locus located in the human leukocytes antigen (HLA) region. High risk and protective alleles, haplotypes, and genotypes have been determined in Lithuanian children with type 1 diabetes mellitus and healthy children.*

Material and methods. In this case-control study, 124 children with diabetes (55 males and 69 females; mean age, 9.2±3.9 years) were tested for HLA class II and compared with 78 healthy controls (43 males and 35 females; mean age, 10.8±3.4 years; range, 0–15 years). HLA DRB1, DQA1, and DQB1 alleles were genotyped using a polymerase chain reaction.

Results. T1D risk-associated haplotypes (DR4)-DQA1*0301-DQB1*0302, (DR3)-DQA1*0501-DQB1*0201, and (DR1)-DQA1*0101-04-DQB1*0501 were more prevalent among children with diabetes than controls (50.0%, 41.1%, and 37.9% vs. 10.3%, 5.1%, and 24.4%, P<0.001). The haplotypes (DR4)-DQA1*0301-DQB1*0302 and (DR3)-DQA1*0501-DQB1*0201 increased T1D risk by 8.75 and 12.93 times, respectively (P<0.001). Protective haplotypes (DR2)-DQA1*0102-B1*0602, (DR11/12/13)-DQA1*05-DQB1*0301, and (DR13)-DQA1*0103-DQB1*0603 were significantly more prevalent among controls than children with diabetes (25.6%, 33.3%, 19.2% vs. 0%, 3.2%, 0%; P<0.001). These frequencies are quite similar to those from neighbor countries with varying incidence of type 1 diabetes mellitus.

Conclusions. HLA class II haplotypes associated with type 1 diabetes mellitus positively or negatively were the same in Lithuanian children as in other European Caucasian populations. Differences in incidence and clinical manifestations of type 1 diabetes might be due to different environmental factors and/or lifestyle.

Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease caused by the selective destruction of the insulin-producing pancreatic beta cells (1). The initiation of this process may sometimes occur early in life. Genetic predisposition is an important part of the etiology. The genetic background of T1D is polygenic (2). The human leukocytes antigen (HLA) region on the short arm of chromosome 6p21.3 contains genes that encode for class I, class II, and class III antigens.

Associations have been first established between T1D and HLA class I HLA-B8 and HLA-B15 genes, but the strongest genetic associations with T1D so far identified are the associations with HLA class II genes (3). HLA genes are thought to contribute to as much as 50% of the genetic risk for T1D. Several HLA genotypes have been associated with susceptibility and/or protection for T1D (4–7). High-risk alleles, haplotypes, and genotypes as well as protective alleles, haplotypes, and genotypes have been identified.

Among Caucasians, T1D is positively associated with DR3-DQ2 and DR4-DQ8 haplotypes and negatively associated with DR2-DQ6 (6, 8–10). Recent studies from different European countries have confirmed that the HLA DR3-DQ2/DR4-DQ8 genotype is associated with the highest diabetes risk (8, 9, 11). DQ8(DQA1*0301-DQB1*0302) (74%) and DQ2(DQA1*0501-DQB1*0201) (52%) or both are found in 89% of the Caucasian patients with T1D before the age of 15 years (12). It is possible that different genetic background may contribute to both different incidence and clinical manifestation of the disease. As an example DR3- and DR4-containing haplotypes are not associated with T1D in Southeast Asian communities, including Japan and Korea (13, 14), where the incidence is much lower and clinical manifestation tends to differ (15–17). There is a big difference in the incidence of T1D between Lithuania and closely situated countries such as Nordic countries (17). In the previous study, we have also shown that clinical manifestations and prevalence of antibodies differ comparing Lithuania and Sweden (18). Thus, we found it important to determine the frequency of HLA class II alleles and haplotypes in Lithuanian children with diabetes and healthy children and compare these results with the figures seen in neighbor countries.

Material and methods

This study was a part of the case-control study mainly aimed at studying environmental factors important for the development of T1D. All 286 newly diagnosed T1D children during the period of August 1, 1996, and August 1, 2000, and 813 age- and sex-matched double randomly selected healthy controls participated in that study (18). Blood samples were obtained from children with diabetes as well as control children and stored at –20°C.

HLA was determined in 124 Lithuanian children with diabetes (55 males and 69 females; mean age, 9.2±3.9 years) and compared with 78 Lithuanian controls (43 males and 35 females; mean age, 10.8±3.4 years). In both groups, the age varied between 0 and 15 years.

DNA was extracted from blood leukocytes by standard phenol-chloroform method (19). DNA was dissolved in sterile double distilled water. HLA DRB1, DQA1, and DQB1 alleles for diabetic children were genotyped using a polymerase chain reaction (PCR) with amplification of the second exon of the genes as described earlier (19). An amplified product was manually dot blotted onto nylon membranes. Synthetic sequence-specific oligonucleotide (SSO) probes were

3´-end-labeled with αP32-dCTP and used for hybridization followed by stringency washes and autoradiography (20). Laboratory analysis was carried out at the Department of Molecular Immunogenetics, Karolinska Institute, Stockholm, Sweden.

HLA DRB1, DQA1, and DQB1 alleles for control children were genotyped using the PCR with sequence specific primers (SSP-PCR) supplied by Protrans and following manufacture's recommendations (PRO-TRANS Medizinische Diagnostische Produkte GmbH, Germany). The amplified products were determined by means of agarose gel electrophoresis. Laboratory analysis was carried out at the Laboratory of Immunology and Genetics, Hospital of Kaunas University of Medicine, Kaunas, Lithuania.

The study was approved by the Research Ethics Committee of Kaunas University of Medicine, Lithuania.

Statistical analysis. Comparison of means between groups of cases and controls were performed by the Student's *t* test or Mann-Whitney *U* test (nonparametric values). Proportions were compared using chi-square or Fisher's exact test. Differences were considered significant at $P<0.05$. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical package SPSS 13.0 for Windows release was used for the data analysis.

Results

Among HLA-DRB1 alleles tested, DRB1*04 was found to be the most frequent allele among T1D patients (50.8% compared to 14.1% of the control children; OR=6.29, $P<0.001$), followed by DRB1*03 (42.7% and 5.1%, respectively; OR=13.81 $P<0.001$) and DRB1*01 (37.9% and 24.4%, respectively; OR=1.9, $P=0.046$), whereas DRB1*13, DRB1*15, and DRB1*11 alleles were found to be more frequent among control children (30.8%, 30.8%, and 23.1, respectively; $P<0.001$) (Table 1).

DQA1*0301 was found most frequently in the group of T1D children (53.2% compared to 11.5% of the control children; OR=8.72, $P<0.001$), followed by DQA1*0501 (43.5% and 10.3%, respectively; OR=6.75, $P<0.001$) and DQA1*0101 (37.1% and 16.7%, respectively; OR=2.95, $P=0.002$). DQA1*0102, DQA1*0103 and DQA1*0505 alleles were most frequent in the control children (39.7%, 23.1%, and 23.1%, respectively; $P<0.001$) (Table 2).

Among DQB1 alleles tested, DQB1*0201 was found to be the most frequent in T1D patients (56.5% compared to 5.1% of the control children, OR=23.98, $P<0.001$), followed by DQB1*0302 (50.0% and 10.3%, respectively; OR=8.75, $P<0.001$) and

Table 1. Distribution of DRB1 alleles among children with type 1 diabetes (T1D) and control children

Alleles (serology)	T1D n=124 n (%)	Control n=78 n (%)	OR (95% CI)	*P*
DRB1*01 (DR1)	47 (37.9)	19 (24.4)	1.90 (1.01–3.57)	0.046
DRB1*03 (DR3)	53 (42.7)	4 (5.1)	13.81 (4.75–40.15)	<0.001
DRB1*04 (DR4)	63 (50.8)	11 (14.1)	6.29 (3.04–13.03)	<0.001
DRB1*07 (DR7)	28 (22.6)	15 (19.2)	1.23 (0.61–2.47)	0.571
DRB1*08 (DR8)	14 (11.3)	7 (9.0)	1.29 (0.50–3.36)	0.600
DRB1*09 (DR9)	5 (4.0)	1 (1.3)	3.24 (0.37–28.23)	0.409
DRB1*11 (DR11)	4 (3.2)	18 (23.1)	0.11 (0.04–0.34)	<0.001
DRB1*12 (DR12)	0 (0)	4 (5.1)	–	0.021
DRB1*13 (DR13)	0 (0)	24 (30.8)	–	<0.001
(DR11/12/13)	4 (3.2)	41 (52.6)	0.03 (0.01–0.09)	<0.001
DRB1*14 (DR14)	9 (7.3)	6 (7.7)	0.94 (0.32–2.75)	0.909
DRB1*15 (DR2)	0 (0)	24 (30.8)	–	<0.001
DRB1*16 (DR2)	0 (0)	7 (9.0)	–	0.001

OR, odds ratio; CI, confidence interval.

Table 2. Distribution of DQA1 alleles among children with type 1 diabetes (T1D) and control children

Alleles (serology)	T1D n=124 n (%)	Control n=78 n (%)	OR (95% CI)	*P*
DQA1*0101	46 (37.1)	13 (16.7)	2.95 (1.47-5.93)	0.002
DQA1*0102	0 (0)	31 (39.7)	–	<0.001
DQA1*0103	9 (7.3)	18 (23.1)	0.26 (0.11–0.62)	0.001
DQA1*0104	0 (0)	11 (14.1)	–	0.001
DQA1*0106	0 (0)	5 (6.4)	–	0.008
DQA1*0201	29 (23.4)	16 (20.5)	1.18 (0.59–2.36)	0.633
DQA1*0301	66 (53.2)	9 (11.5)	8.72 (4.00–19.01)	<0.001
DQA1*0302	0 (0)	2 (2.6)	–	0.148
DQA1*0401	13 (10.5)	6 (7.7)	1.41 (0.51–3.87)	0.508
DQA1*05	55 (44.4)	30 (38.5)	1.28 (0.72–2.27)	0.41
DQA1*0501	54 (43.5)	8 (10.3)	6.75 (2.99–15.22)	<0.001
DQA1*0502	1 (0.8)	0 (0)	–	1.000
DQA1*0505	0 (0)	18 (23.1)	–	<0.001
DQA1*0601	6 (4.8)	0 (0)	–	0.084

OR, odds ratio; CI, confidence interval.

DQB1*0501 (38.7% and 24.4%, respectively; OR=1.96, *P*=0.035). DQB1*0301, DQB1*0602, and DQB1*0603 alleles were found to be most frequent in the control children (34.6%, 28.2%, and 19.2%, respectively; *P*<0.001) (Table 3).

The distribution of HLA (DR)-DQA1-DQB1 haplotypes among Lithuanian children with T1D and nondiabetic control children (Table 4) matched closely with the Caucasoid individuals in other European countries.

For analysis, the children were divided into three groups according to their age: 0–4, 5–9, and 10–15 years old. There were no differences in the frequency of risk and protective haplotypes related to age and sex (data not shown).

T1D-risk related haplotypes (DR3)-DQA1*0501- DQB1*0201 and/or (DR4)–DQA1*0301-DQB1*0302 were present in 79% (98/124) of children with diabetes as compared to 15.4% (12/78) of controls (*P*<0.001). The presence of a single risk haplotype increased the risk of T1D by 20.7 times (95% CI, 9.77–43.97).

Protective haplotypes (DR2)-DQA1*0102-B1* 0602, (DR11/12/13)-DQA1*05-DQB1*0301, and (DR13)-DQA1*0103-DQB1*0603 were significantly more prevalent among controls in comparison with T1D children (25.6%, 33.3%, 19.2% and 0%, 3.2%, 0%, respectively; *P*<0.001). At least one of these protective haplotypes was present in 3.2% of children with diabetes compared with 69.2% of the controls (*P*<0.001). The presence of a single protective haplotype decreased the risk of T1D by 67.7 times (95% CI, 22.22–200.0).

Table 3. Distribution of DQB1 alleles among children with type 1 diabetes (T1D) and control children

Alleles (serology)	T1D n=124 n (%)	Control n=78 n (%)	OR (95% CI)	P
DQB1*0201	70 (56.5)	4 (5.1)	23.98 (8.25–69.70)	<0.001
DQB1*0202	1 (0.8)	11 (14.1)	0.05 (0.01–0.39)	<0.001
DQB1*0203	0 (0)	1 (1.3)	–	0.386
DQB1*0301	14 (11.3)	27 (34.6)	0.24 (0.11–0.62)	<0.001
DQB1*0302	62 (50.0)	8 (10.3)	8.75 (3.89–19.70)	<0.001
DQB1*0303	7 (5.6)	6 (7.7)	0.72 (0.23–2.22)	0.564
DQB1*0305	0 (0)	2 (2.6)	–	0.148
DQB1*0402	9 (7.3)	5 (6.4)	1.14 (0.37–3.54)	0.817
DQB1*0501	48 (38.7)	19 (24.4)	1.96 (1.04–3.69)	0.035
DQB1*0502	1 (0.8)	7 (9.0)	0.08 (0.01–0.68)	0.006
DQB1*0503	9 (7.3)	5 (6.4)	1.14 (0.37–3.54)	0.817
DQB1*0601	0 (0)	3 (3.8)	–	0.056
DQB1*0602	0 (0)	22 (28.2)	–	<0.001
DQB1*0603	0 (0)	15 (19.2)	–	<0.001
DQB1*0604	0 (0)	6 (7.7)	–	0.003

OR, odds ratio; CI, confidence interval.

Table 4. Distribution of HLA (DR)-DQA1-DQB1 haplotypes among children with type 1 diabetes (T1D) and control children

Haplotypes	T1D n=124 n (%)	Control n=78 n (%)	OR (95% CI)	P
(DR1)-DQA1*0101-04-DQB1*0501	47 (37.9)	19 (24.4)	1.90 (1.01–3.57)	0.046
(DR2(DR15))-DQA1*0102-DQB1*0602	0 (0)	20 (25.6)	–	<0.001
(DR3)-DQA1*0501-DQB1*0201	51 (41.1)	4 (5.1)	12.93 (4.44–37.60)	<0.001
(DR4)-DQA1*0301-DQB1*0301	6 (4.8)	2 (2.6)	1.93 (0.38–9.82)	0.713
(DR4)-DQA1*0301-DQB1*0302	62 (50.0)	8 (10.3)	8.75 (3.89–19.70)	<0.001
(DR7)-DQA1*0201-DQB1*0303	5 (4.0)	4 (5.1)	0.78 (0.20–2.99)	0.736
(DR11)-DQA1*0501-DQB1*0301	3 (2.4)	0 (0)	–	0.285
(DR11)-DQA1*0505-DQB1*0301	0 (0)	17 (21.8)	–	<0.001
(DR11/12/13)-DQA1*05-DQB1*0301	4 (3.2)	26 (33.3)	0.07 (0.02–0.29)	<0.001
(DR13)-DQA1*0102-DQB1*0602	0 (0)	5 (6.4)	–	0.008
(DR13)-DQA1*0103-DQB1*0603	0 (0)	15 (19.2)	–	<0.001
(DR14)-DQA1*0101-DQB1*0503	2 (1.6)	0 (0)	–	0.524
(DR14)-DQB1*0503	9 (7.3)	5 (6.4)	1.14 (0.37–3.54)	0.817

OR, odds ratio; CI, confidence interval.

Discussion

There is a great difference in the incidence of T1D between different countries, even neighboring countries such as Lithuania from the Baltic states and Sweden from the Nordic countries. Furthermore, the clinical manifestations seem to differ too (18). One explanation for this could that there is a different genetic background in the populations and/or different genetic traits among those who get T1D. In the present study, alleles DRB1*04, DRB1*03, DRB1*01, DQA1*0101, DQA1*0301, DQA1*0501, DQB1*0201, DQB1*0302, DQB1*0501 and haplotypes (DR3)-DQA1*0501-DQB1*0201, (DR4)-DQA1*0301-DQB1*0302, (DR1)-DQA1*0101-04-DQB1*0501 were found significantly more frequently among children with diabetes than among control children in Lithuania. These alleles and haplotypes conferred the highest risk of the disease. Similar data were obtained in neighboring countries with rather low incidence of T1D – Estonia, Latvia, Poland, Russia (10, 12, 21–23) – as well as in other countries in Europe – Sweden, Finland, France, Greece (9, 24–26), some of them having much higher incidence and somewhat different clinical manifestations. In some studies, (DR1)- DQA1*0101-04-DQB1*0501 has been found to be protective (22, 25). We could not confirm these findings possibility due to a small sample size in our study.

A majority of studies have found that diabetic children have diabetes risk alleles and haplotypes (23,

27) more often than adult diabetic patients (21, 26). In our study, we found no such differences, but we studied a narrow age range and relatively small number of patients.

HLA (DR3)-DQA1*0501-DQB1*0201/(DR4)-DQA1*0301-DQB1*0302 genotype is found in 20–30% of patients with T1D and in almost 50% of patients diagnosed in childhood (8, 11, 28). In the present study, (DR3)-DQA1*0501-DQB1*0201/(DR4)-DQA1*0301-DQB1*0302 genotype was found only in 12.1% of T1D children (*P*=0.001).

Haplotypes (DR2)-DQA1*0102-B1*0602, (DR11/12/13)-DQA1*05-DQB1*0301 as well as (DR13)-DQA1*0103-DQB1*0603 were found frequently among control children in our study. These alleles and haplotypes are protective and are associated with reduced risk for T1D in most populations (12, 24, 25, 29).

We found no differences in the frequency of risk and protective haplotypes comparing males and females.

Conclusions

HLA class II haplotypes associated with type 1 diabetes mellitus positively or negatively were the same in Lithuanian children as in other European Caucasian populations, including the neighboring Nordic countries. Differences in incidence and clinical manifestations of type 1 diabetes might be due to different environmental factors and/or lifestyle.

HLA antros klasės alelių ir haplotipų paplitimas tarp sergančiųjų 1 tipo cukriniu diabetu ir sveikų Lietuvos vaikų

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Raktažodžiai: 1 tipo cukrinis diabetas, vaikai, žmogaus leukocitų antigenai (ŽLA), alelės, atvejo ir kontrolės tyrimas.

Santrauka. *Įvadas.* 1 tipo cukrinis diabetas yra lėtai progresuojanti autoimuninė liga. Genetinė 1 tipo cukrinio diabeto kilmė yra poligeninė. Dauguma genų, lemiančių cukrinio diabeto pasireiškimą, priklauso žmogaus leukocitų antigenams (ŽLA). Šio tyrimo metu nustatėme antros klasės ŽLA alelių bei haplotipų, teigiamai ir neigiamai susijusių su 1 tipo CD pasireiškimu, paplitimą tarp sergančiųjų CD ir sveikų Lietuvos vaikų.

Tyrimo medžiaga ir metodai. Atliktas atvejo ir kontrolės tyrimas, antros klasės ŽLA buvo ištirta 124 vaikams (55 berniukams ir 69 mergaitėms, amžiaus vidurkis – 9,2±3,9 metų), sergantiems 1 tipo cukriniu diabetu, ir 78 sveikiems kontrolinės grupės vaikams (43 berniukams ir 35 mergaitėms, amžiaus vidurkis – 10,8±3,4 metų), vaikų amžiaus ribos – nuo 0 iki 15 metų. ŽLA DRB1, DQA1 ir DQB1 aleliai nustatyti atliekant polimerazės grandininę reakciją.

Rezultatai. Haplotipai susiję su vaikų 1 tipo cukrinio diabeto pasireiškimu, t. y. rizikos haplotipai (DR4)–DQA1*0301–DQB1*0302, (DR3)–DQA1*0501–DQB1*0201 ir (DR1)–DQA1*0101–04–DQB1*0501 dažniau nustatyti cukriniu diabetu sergantiems vaikams, atitinkamai – 50,0, 41,1 ir 37,9 proc. nei kontrolinės grupės vaikams, atitinkamai – 10,3, 5,1 ir 24,4 proc., p<0,001. Haplotipai (DR4)–DQA1*0301–DQB1*0302 ir (DR3)–DQA1*0501–DQB1*0201 didino susirgimo 1 tipo CD riziką, atitinkamai – 8,75 ir 12,93 kartų (p<0,001). Neigiamai susijusių su cukriniu diabetu, t. y. apsauginių haplotipų paplitimas (DR2)–DQA1*0102–B1*0602, (DR11/12/13)–DQA1*05–DQB1*0301 ir (DR13)–DQA1*0103–DQB1*0603 buvo patikimai didesnis tarp kontrolinės grupės vaikų, atitinkamai – 25,6, 33,3, 19,2 proc. nei cukriniu diabetu segančių vaikų grupėje, atitinkamai, – 0, 3,2, 0 proc., p<0,001.

Išvados. ŽLA antros klasės haplotipai teigiamai arba neigiamai susiję su 1 tipo cukriniu diabetu Lietuvoje yra tokie patys kaip ir kitose kaukazoidų populiacijose Europoje. Skirtingas pirminis sergamumas bei klinikinis cukrinio diabeto pasireiškimas įvairiose šalyse gali būti dėl aplinkos veiksnių ir (ar) gyvenimo būdo.

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