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ORIGINAL ARTICLE

Increased HLA class II risk is associated with a more aggressive presentation of clinical type 1 diabetes

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Abstract

Aim: To determine the association of HLA class II risk with the demographic and clinical characteristics of type 1 diabetes at diagnosis.

Methods: We conducted a register-based retrospective cohort study of 4993 Finnish children (2169 girls) – diagnosed with type 1 diabetes under the age of 15 years in 2003–2016. The participants were divided into six risk groups based on their HLA DR/DQ genotype. Demographic characteristics, family history of type 1 diabetes and metabolic markers at the time of diagnosis were compared between the groups.

Results: In total, 4056/4993 children (81.2%) carried an HLA genotype associated with an increased risk of type 1 diabetes (risk groups 3–5), whereas 937/4993 children (18.8%) carried a HLA genotype conferring no or decreased disease risk. Children with higher HLA risk were younger at diagnosis ($p < 0.001$) and had a shorter duration of classical symptoms before diagnosis ($p = 0.016$). Subjects in the high-risk group were more likely to have a family member affected by type 1 diabetes when compared to those in the neutral risk group (11.5% vs. 8.8%, $p = 0.05$).

Conclusion: Children with stronger HLA disease susceptibility are younger at their disease manifestation and have a shorter period of symptoms before diagnosis, suggesting that the HLA class II genes are associated with a more aggressive disease presentation.

KEYWORDS
clinical characteristics, diagnosis, HLA class II, type 1 diabetes

1 | INTRODUCTION

The class II human leukocyte antigen (HLA) genes are considered the main genetic risk determinants of type 1 diabetes.[1] The HLA region on chromosome 6p21 is divided into two classes that affect independently the disease progression. The class I genes are believed to influence the rate of beta-cell destruction, whereas the class II genes are implied to affect the initiation of the autoimmune process.[2,3] The class II genotype comprising two haplotypes inherited from each parent determines the risk of type 1 diabetes. Based on the class II genotypes, individuals can be classified into six risk groups ranging from strongly decreased risk to high risk of developing type 1 diabetes.[3]

Abbreviations: DIPP, Diabetes Prediction and Prevention; DKA, diabetic ketoacidosis; FPDR, Finnish Paediatric Diabetes Register; HLA, human leukocyte antigen; IA-2A, islet antigen 2 autoantibodies.

A complete list of the investigators for the Finnish Pediatric Diabetes Register is found in the Appendix S1.

Previous studies have shown that the age of developing type 1 diabetes is partly determined genetically and that high-risk HLA class II genotypes seem to be associated with a younger age at the manifestation of the disease.[4–6] Risk for diabetic ketoacidosis (DKA) has been associated with a decreased HLA class II risk.[7] However, contrary findings have been reported as well.[8] Results from the Type 1 Diabetes Prediction and Prevention (DIPP) Study suggested that the high HLA class II risk may be associated with a more rapid progression to clinical disease.[9] However, most studies describing the association of HLA class II risk and clinical presentation at diagnosis have been limited in size and scope, mainly focusing on high- or low-risk genotypes.[6]

The aim of this study was to analyse, whether demographic characteristics or metabolic markers at diagnosis differ according to risk for type 1 diabetes, conferred by the HLA class II genotype. Secondary, we assessed whether patients with high-risk HLA genotypes were more likely to have affected first-degree relatives.

Key Notes

- HLA class II genes are considered the main genetic risk determinant for type 1 diabetes and have been associated to affect the initiation of disease process leading to overt type 1 diabetes.
- Children with stronger HLA class II disease susceptibility are younger at diagnosis and have a shorter period of symptoms before diagnosis.
- A higher HLA class II risk seems to lead up to a more aggressive disease manifestation.

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted a retrospective register-based cohort study of children diagnosed with type 1 diabetes between January 2003 and December 2016. The study protocol has been approved by the ethics committee of the hospital district of Helsinki and Uusimaa.

2.2 | Subjects

Since 2002 children and adolescents diagnosed with type 1 diabetes have been asked to participate in the Finnish Paediatric Diabetes Register (FPDR) in Finland. The coverage of the register is more than 90% of the children diagnosed thereafter.[10] Biological samples are collected from the children with newly diagnosed type 1 diabetes and their first-degree relatives are analysed for islet autoantibodies and HLA class II haplotypes. The sample repository covers approximately 72% of the participants in the register. The family and the care-giving nurse or doctor at the paediatric units answer a structured questionnaire including information on the family history of diabetes and the degree of metabolic decompensation at diagnosis. The parents or legal guardians of the children and their sibling under the age of 18 give written consent, and the children aged 10–17 years give informed assent.

During the study time, there were 6913 children and adolescents of age under 15 years registered in the FPDR. We excluded children diagnosed during the first 6 months of their lives potentially suffering for monogenic diabetes. Only children with blood sample taken for the HLA genotyping were included in the study. If there were more than one child with type 1 diabetes in a family, we included only the first child diagnosed as the index case. One case of maturity-onset diabetes of the young was diagnosed after the manifestation of diabetes, and this patient was excluded from the study subjects.

2.3 | HLA risk classification and genotyping

Each of the participants who had been analysed for their HLA genotypes in the FPDR has been categorised into one of six risk groups based on the summary effect of their HLA-DR/DQ haplotypes: strongly decreased risk (0), decreased risk (1), neutral (2), slightly increased risk (3), moderately increased risk (4) and high risk (5). HLA class II -based risk categorisation is presented in Appendix S1, Tables S1 and S2. Due to the low prevalence of the strongly decreased risk genotypes ($N = 40$), we decided to combine the groups of strongly and slightly decreased risk (0 and 1). Thus, we used five groups in the analyses and named the combined group as the decreased risk group (1, $N = 142$). The HLA genotyping was performed with a PCR-based lanthanide-labelled hybridization method and time-resolved fluorometry detection.[3]

2.4 | Metabolic markers at diagnosis

Blood samples were drawn as soon as possible after the diagnosis at the paediatric units treating the child. The samples were analysed for blood pH, plasma glucose, HbA_{1C} and beta-hydroxybutyrate concentrations. Ketoacidosis was determined as blood pH <7.30 and severe ketoacidosis as pH <7.10. Information on weight loss, the level of consciousness, puberty status and the duration of the type 1 diabetes -related symptoms were provided by the treating doctor/nurse at the time of diagnosis.

2.5 | Statistics

The data was analysed with the IBM SPSS Statistics 24.0 and R 3.4.0 package. The Kruskal–Wallis test was used to compare the non-parametric values between all the five risk groups and if significances were found the Mann–Whitney U test was used for paired analyses. Categorical variables were analysed using cross-tabulation and the chi-square test with continuity correction when comparing two groups (2×2 table). Adjustment for sex and age was performed

TABLE 1 Demographic characteristics and metabolic markers at diagnosis of type 1 diabetes according to HLA risk group

	n	High risk (5), *N* = 1068 (21.4%)	Moderately increased risk (4), *N* = 1854 (37.1%)	Slightly increased risk (3), *N* = 1134 (22.7%)	Neutral (2), *N* = 795 (15.9%)	Decreased risk (1), *N* = 142 (2.8%)	Unadjusted *p* value*	Adjusted *p* value[a,*]
Female, %	4993	44.5	43.6	44.7	39.2	46.5	0.113	
Age at diagnosis, years	4993	7.57 (0.65–14.96)	7.88 (0.53–14.98)	8.38 (0.63–14.99)	8.69 (0.52–14.99)	9.40 (0.59–14.89)	<0.001 5 vs. 4 $p = 0.038$ 5 vs. 3 $p = 0.002$ 5 vs. 2 $p < 0.001$ 5 vs. 1 $p < 0.001$ 4 vs. 2 $p = 0.004$ 4 vs. 1 $p = 0.001$ 3 vs. 1 $p = 0.008$	
Pubertal, %	4993	13.7 (11.3–16.0)	16.7 (14.8–18.6)	19.4 (16.8–22.1)	18.7 (15.6–21.9)	23.1 (15.0–31.2)	0.008 5 vs. 3 $p = 0.008$ 5 vs. 2 $p = 0.013$ 5 vs. 1 $p = 0.016$	0.310
Impaired consciousness, %	4784	4.8 (3.5–6.1)	5.5 (4.4–6.5)	5.7 (4.3–7.1)	5.7 (4.1–7.4)	5.8 (1.9–9.8)	0.911	0.423
Weight loss, %	4610	4.7 (0.0–40.0)	5.1 (0.0–32.3)	5.3 (0.0–33.2)	5.9 (0.0–26.5)	5.2 (0.0–24.4)	0.002 5 vs. 2 $p = 0.002$ 4 vs. 2 $p = 0.002$ 3 vs. 2 $p = 0.004$	0.036 3 vs. 2 $p = 0.049$
Plasma glucose, mmol/L	4869	23.6 (3.6–81.0)	23.8 (3.2–97.6)	23.4 (4.4–95.6)	24.6 (4.3–74.2)	24.1 (7.6–62.8)	0.102	0.115
pH	4817	7.38 (6.79–7.54)	7.38 (6.72–7.57)	7.38 (6.82–7.53)	7.38 (6.80–7.54)	7.37 (6.96–7.53)	0.090	0.644
DKA, %	4817	15.8 (13.6–18.0)	17.7 (15.9–19.5)	19.1 (16.8–21.4)	19.6 (16.8–22.4)	19.1 (12.5–25.7)	0.214	0.086
Severe DKA, %	4817	3.7 (2.6–4.9)	4.4 (3.4–5.3)	5.0 (3.7–6.3)	5.6 (4.0–7.2)	5.9 (1.9–9.8)	0.331	0.076
Plasma β- hydroxybutyrate, mmol/L	4384	1.60 (0.00–18.0)	1.70 (0.00–27.0)	1.65 (0.00–17.0)	2.05 (0.00–17.4)	2.0 (0.0–13.0)	0.005 5 vs. 3 $p = 0.019$ 5 vs. 2 $p = 0.005$ 5 vs. 1 $p = 0.035$ 4 vs. 2 $p = 0.027$	0.244
HbA_{1C}, mmol/mol	841	84.7 (39.0–154.0)	89.0 (38.0–176.0)	93.0 (36.0–189.0)	98.0 (44.0–168.0)	98.5 (50.0–156.0)	<0.001 5 vs. 3 $p = 0.002$ 5 vs. 2 $p < 0.001$ 5 vs. 1 $p = 0.037$ 4 vs. 3 $p = 0.032$ 4 vs. 2 $p < 0.001$	0.097
HbA_{1C}, %	841	9.9 (5.7–16.2)	10.3 (5.6–18.3)	10.7 (5.4–19.4)	11.1 (6.2–17.5)	11.2 (6.7–16.4)	<0.001 5 vs. 3 $p = 0.002$ 5 vs. 2 $p < 0.001$ 5 vs. 1 $p = 0.039$ 4 vs. 3 $p = 0.031$ 4 vs. 2 $p < 0.001$	0.111

Note: *N* = 4993. Median (min-max). %, (95% CI). *n* refers to number of individuals with data recorder.

[a]Adjusted for age and sex.

*Each significant *p* value of the comparisons between two groups described separately.

with logistic/ordinal/multinomial regression for dichotomous/ordinal/categorical variables and quantile regression in R (package quantreg) for nonparametric variables. A p value of <0.05 was considered to indicate statistical significance.

3 | RESULTS

After exclusions a total of 4993 children were included in the study. The majority of the subjects were male (N = 2824, 56.6%), but no difference was observed in the frequency of females and males between the risk groups (p = 0.113). The classification of the study subjects into the five HLA risk groups is presented in Table 1. The moderately increased risk group (4) was the largest (N = 1854, 37.1%), whereas the decreased risk group (1) was the smallest (N = 142, 2.8%).

3.1 | Age at diagnosis

The median age at diagnosis was 8.14 years (minimum 0.52, maximum 14.99). The HLA risk was inversely associated with age at diagnosis with a median age of 7.57 in the highest HLA risk group compared to 9.40 years in the decreased risk group (p < 0.001) (Table 1). All the following analyses were then adjusted for age at diagnosis and sex.

3.2 | Metabolic markers at diagnosis

As presented in Table 1, the relative weight loss was the highest in the neutral risk group and higher especially when compared to the slightly increased risk group (p = 0.049). The frequency of children presenting with DKA or severe DKA were lower in the highest HLA risk groups, but the differences were not statistically significant (DKA adjusted p = 0.086 and severe DKA adjusted p = 0.076). Plasma beta-hydroxybutyrate (p = 0.005) and HbA_{1c} (p < 0.001) concentrations differed, although age and sex adjustment removed the significance (p = 0.244 and p = 0.097, respectively). The duration of symptoms before diagnosis varied according to HLA risk (adjusted p = 0.016) (Figure 1). After adjusting for age and sex, the neutral and the slightly increased risk groups had a longer duration of symptoms before diagnosis than the moderately increased risk group (4 vs. 3 p = 0.006, 4 vs. 2 p = 0.016).

3.3 | Familial type 1 diabetes

In total, 519 of the 4993 index cases (10.4%) had a family member diagnosed with type 1 diabetes at the time of diagnosis (Table 2). After age and sex adjustment, the frequency of affected first-degree relative was highest amongst children with the highest HLA associated risk (p = 0.012). Children in the neutral risk group were less likely to have a first-degree relative with type 1 diabetes compared to the high-risk group (p = 0.05). We also compared the proportion of affected fathers versus affected mothers between risk groups, but no difference was seen (p = 0.406).

4 | DISCUSSION

In the current study of Finnish children with newly diagnosed type 1 diabetes, we observed the affected children to be younger at diagnosis in parallel with the increasing HLA class II risk. There was no difference in the levels of plasme glucose or pH between the groups. The higher levels of beta-hydroxybutyrate and HbA1c seemed to be associated with decreasing HLA risk. However, it may be explained by differences between the groups in age at diagnosis and sex since the result became non-significant after adjustment for age and sex. The duration of diabetes-related symptoms before diagnosis was

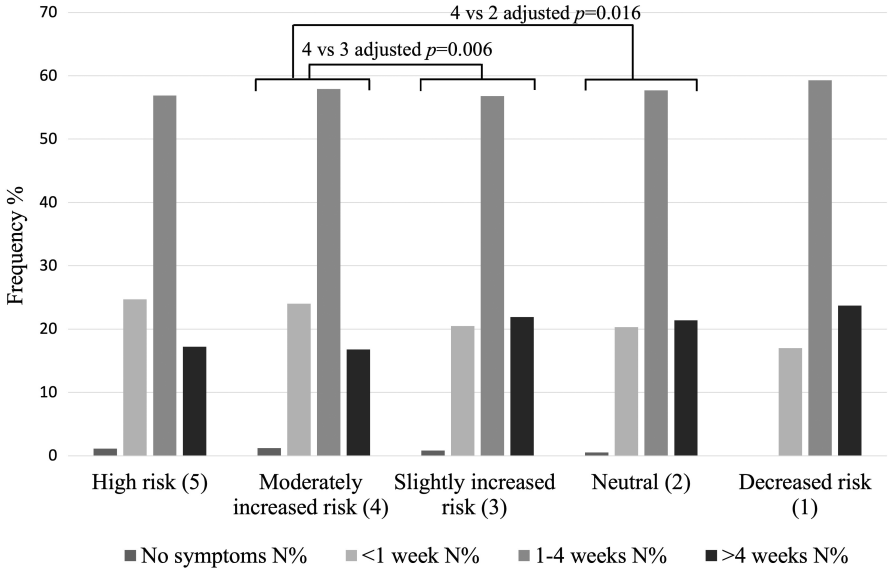

FIGURE 1 Duration of the symptomatic period preceding the diagnosis of type 1 diabetes in relation to HLA-conferred risk for type 1 diabetes.

TABLE 2 Presence of familial type 1 diabetes (T1D) between the five HLA risk groups

	High risk (5)	Moderately increased risk (4)	Slightly increased risk (3)	Neutral (2)	Decreased risk (1)	*p* value*	Adjusted *p* value[a,*]
N = 4993	1068	1854	1134	795	142		
Familial T1D, %	11.5 (9.6–13.4)	11.3 (9.8–12.7)	9.3 (7.7–11.0)	8.8 (6.8–10.8)	7.7 (3.3–12.1)	0.110	0.012 5 vs. 2 $p = 0.05$
Multiple T1D, %	0.7 (0.2–1.3)	0.8 (0.4–1.1)	0.4 (0.1–0.8)	0.4 (0.0–0.8)	0.7 (0.0–2.1)	0.699	0.222
Father T1D, %	5.5 (4.2–6.9)	6.3 (5.2–7.4)	5.5 (4.1–6.8)	3.9 (2.6–5.2)	3.5 (0.5–6.6)	0.118	0.062
Mother T1D, %	3.4 (2.3–4.5)	3.3 (2.5–4.1)	2.6 (1.6–3.5)	2.5 (1.4–3.6)	2.1 (0.0–4.5)	0.585	0.204
Sibling T1D, %	3.2 (2.1–4.2)	2.3 (1.6–2.9)	1.7 (0.9–2.4)	2.5 (1.4–3.6)	2.8 (0.1–5.5)	0.225	0.167
Brother T1D, %	1.8 (1.0–2.6)	1.3 (0.8–1.8)	0.9 (0.3–1.4)	1.6 (0.8–2.5)	2.8 (0.1–5.5)	0.211	0.845
Sister T1D, %	1.5 (0.8–2.2)	1.1 (0.6–1.5)	0.8 (0.3–1.3)	1.0 (0.3–1.7)	0.0 (0.0–0.0)	0.371	0.052

Note: %, (95% CI). *n* refers to number of individuals with data recorder.

[a]Adjusted for age and sex.

*Each significant *p* value of the comparisons between two groups described separately.

shorter in the children with a higher HLA class II risk compared to those in the lower risk groups.

Evidence of class II HLA genes affecting the age at diagnosis of type 1 diabetes was presented already in the 1990s.[4] Since then, strong HLA risk susceptibility has been seen more often in patients diagnosed at a younger age.[5,11,12] It has been shown that higher HLA risk is associated with increased rate of beta-cell destruction in the pancreas, which may explain faster progression of the disease process and earlier diagnosis.[9]

In an FPDR-based study, Taka et al. showed that the autoantibodies related to type 1 diabetes disease progression were more often positive and showed higher levels amongst patients with high HLA class II risk. Particularly, the islet antigen 2 autoantibodies (IA-2A) levels were higher amongst the children with stronger HLA class II susceptibility, which have been associated with a faster beta-cell destruction.[13,14] Similar to our study, they observed that higher HLA risk categories were associated with a younger age at diagnosis and with a shorter duration of symptoms pre-diagnosis. In their study, they used the same HLA risk classification as in the current study but compared two HLA risk groups by combining the risk groups 4–5 to a single high-risk group and groups 1–3 to a lower risk group. As in our study, they also found the HbA1c levels to be higher in the lower risk groups. However, after adjustment for age and sex, the differences in our study were not any longer significant, although the difference in the length of the symptoms before diagnosis remained. As HbA1c levels were available only for one-fith of the participants, our study may have been underpowered in this respect. Indeed, a non-significant trend towards increasing HbA1c with decreasing HLA-risk could be discerned even after adjustements.

There is conspicuous geographical variation in the frequency of DKA at diagnosis, which can be explained by the awareness of the disease and healthcare provision in the country.[15] The high incidence of type 1 diabetes in Finland makes health care professionals and the public more aware of the classic symptoms of type 1 diabetes. Therefore, the diagnosis is made in most cases before DKA emerges.[16,17] Finnish population-based studies have reported a higher incidence of DKA and severe DKA in children carrying a decreased HLA associated risk.[6,7] In contrast, the frequency of DKA was higher in children with high HLA risk in a study performed in Verona Italy.[8] In the present study, DKA and severe DKA were less often seen at diagnosis in children in the higher HLA risk groups, though this difference remained statistically non-significant. We assume that due to the high prevalence of type 1 diabetes in Finland, cases with a more aggressive disease progression are also more rapidly recognised. Additionally, younger age at diagnosis and having a family member diagnosed with type 1 diabetes, which both are linked to a stronger HLA class II susceptibility, seems to decrease the risk to DKA.[6,7,18]

The HLA class I genotype seems to have an impact in the progression to clinical disease as previously suggested.[2,9] A Finnish study combining information on two large prospective follow-up studies found that screening for the HLA genetic risk at birth without any subsequent follow-up did not reduce the risk of DKA at diagnosis even though children with high genetic risk were identified and the parents were notified.[17] In the current study, our results indicate that age and sex explain the higher levels of beta-hydroxybutyrate and HbA1c at diagnosis, rather than HLA risk class being an independent predictor. Accordingly, the clinical utility of the HLA class II determination seems to be limited.

After adjusting for age and sex, we observed familial type 1 diabetes to be more common in the children with stronger HLA susceptibility. Similarly, the genotypes associated with increased HLA risk have been reported more frequently in patients with a positive family history for type 1 diabetes in previous studies.[10,18,19] Fathers are known to transmit the disease to their children more often than mothers.[20] In line with these findings, we observed that children in all the five HLA-risk groups studied had more affected fathers than mothers.

Our nationwide data collection and large sample size constitute strengths of this study. We only included the children in the FPDR whose HLA genotype had been defined, which maybe a limitation. The excluded children might have impacted the results since they

had a more severe metabolic decompensation and were younger at diagnosis.[21] However, the exclusion was necessary since the focus in our study was on the role of HLA susceptibility.

In conclusion, the children with increased HLA risk seem to have a more aggressive disease course. They were younger at diagnosis than the patients with neutral or decreased HLA risk and had a shorter period of symptoms before diagnosis. Prospective studies are needed to better understand the underlying mechanisms of the association between the HLA class II genetics and the autoimmune process leading to type 1 diabetes.

AUTHOR CONTRIBUTIONS

VK analysed the data and wrote the first version of the manuscript. MT collected the data, reviewed the manuscript and contributed to the discussion. KL reviewed the manuscript and contributed to the discussion. TH was responsible for the autoantibody analyses, reviewed the manuscript and contributed to the discussion. JI was in charge of the HLA genotyping, reviewed the manuscript and contributed to the discussion. MK planned the study, reviewed the manuscript and contributed to the discussion. MK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

DATA AVAILABILITY STATEMENT

The data generated and analysed are available on reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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