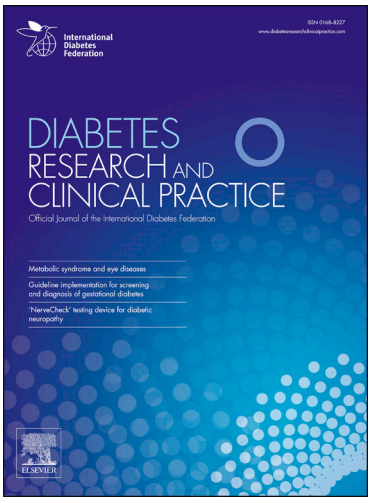
Journal Pre-proofs



Finnish children carrying the high-risk HLA genotype have a 45-fold increased risk of type 1 diabetes compared to peers with neutral or protective genotypes

Antti-Mathias Taka, Anna But, Johanna Lempainen, Tommi Vatanen, Taina Härkönen, Jorma Ilonen, Mikael Knip

PII: S0168-8227(23)00021-9
DOI: https://doi.org/10.1016/j.diabres.2023.110256
Reference: DIAB 110256

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 6 September 2022
Revised Date: 28 December 2022
Accepted Date: 6 January 2023

Please cite this article as: A-M. Taka, A. But, J. Lempainen, T. Vatanen, T. Härkönen, J. Ilonen, M. Knip, Finnish children carrying the high-risk HLA genotype have a 45-fold increased risk of type 1 diabetes compared to peers with neutral or protective genotypes, *Diabetes Research and Clinical Practice* (2023), doi: https://doi.org/10.1016/j.diabres.2023.110256

Finnish children carrying the high-risk HLA genotype have a 40-fold increased risk of type 1 diabetes compared to peers with neutral or protective genotypes

Antti-Mathias Taka[1,2], Anna But[3], Johanna Lempainen[4,5,6], Tommi Vatanen[2,7,8],Taina Härkönen[1,2], Jorma Ilonen[4] and Mikael Knip[1,2,9]

[1]Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[2]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[3]Biostatistics consulting, Department of Public Health, University Hospital, University of Helsinki Helsinki, Finland

[4]Immunogenetics Laboratory, Institute of Biomedicine, University of Turku, Turku, Finland

[5]Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland

[6]Clinical Microbiology, Turku University Hospital, Turku, Finland

[7]Broad Institute of MIT and Harvard, Cambridge, MA, USA

[8]Liggins Institute, University of Auckland, Auckland, New Zealand

[9]Tampere Center for Child Health Research, Tampere University Hospital, Tampere, Finland

Keywords Type 1 diabetes ● Incidence ● HLA genotype ● Genetic risk

The association between HLA genotypes and type 1 diabetes is well known. We set out to examine incidence rates and ratios of type 1 diabetes depending on the risk afflicted by HLA genotype. Children with the high-risk genotype have a 45-fold disease risk compared to peers with neutral or protective genotypes.

1. Introduction

Type 1 diabetes is the third most common autoimmune disease in Finland where its incidence is highest in the world. The incidence rate of type 1 diabetes grew for decades until peaking at 64.2/100 000 in 2005 after which the incidence rates have remained quite stable. (1) The disease is associated by genetic predisposition, primarily by the HLA class II genotype accounting for about 50% of the genetic disease susceptibility. DRB1*04:01/02/04/05-DQA1*03-DQB1*03:02 (DR4-DQ8) and DRB1*03:01-DQA1*05-DQB1*02 (DR3-DQ2) are the haplotypes that inflict the strongest predisposition to type 1 diabetes. Because of their synergistic effects, a genotype formed by these two haplotypes confers the highest disease risk. Some haplotypes act neutrally and others such as DRB1*15-DQA1*01-DQB1*06 (DR15-DQ6) confer protection from the disease. (2) The disease process may be triggered by an environmental factor such as an enterovirus infection, decreased microbial exposure early in life and/or vitamin D deficiency (3). The dramatic rise in type 1 diabetes incidence after World War II emphasizes the role of environmental elements. Indeed several studies show that high-risk HLA genotypes have become less frequent among subjects with newly diagnosed type 1 diabetes over time when comparing recently diagnosed patients to those presenting with type 1 diabetes 30 to 80 years ago (4,5). As far as we are aware the rate of type 1 diabetes has not previously been related to the HLA-conferred disease risk. Here we set out to estimate the disease incidence in relation to different HLA class II risk genotypes among Finnish children under the age of 15 years diagnosed over a period of 16 years

Data on the participants in this study was derived from the Finnish Pediatric Diabetes Register (FPDR) initiated in 2002. The register covers more than 90% of all newly diagnosed pediatric patients with type 1 diabetes. Our study comprised 7894 children under the age of 15 years diagnosed with type 1 diabetes between 2003 and 2018. Annual population sizes for each age group were derived from the civil registry. Data on the HLA class II genotype was available for 6085 participants (77.1%). Those lacking HLA genotype data were excluded from our analysis. Ilonen et al. established in 2016 a HLA risk classification that categorized patients into six risk groups (strong protection, slight protection, neutral, slightly increased risk, moderately increased risk, high risk) based on the disease risk afflicted by each HLA class II genotype (Supplementary tables 1 and 2) (6). Because of the small sample sizes among patients with protective and neutral genotypes, we combined them into one group: “protective/neutral”. We then calculated incidence rates per 100 000 for each HLA risk class among newly diagnosed T1D patients during the time period from 2003 to 2018 taking into account the size of each risk group in the entire population as previously reported by Ilonen et al. and shown in Table 1 (6). The data was assessed in the total series as well as based on sex and three age groups (<5 years, 5-9 and 10-14 years). R studio was used to calculate confidence intervals for incidence rate ratios.

The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

3. Results

The overall incidence of type 1 diabetes among 0-14-year-old children diagnosed between 2003 and 2018 was 42.4 per 100 000. It was considerably higher among boys than girls (47.0 vs 37.7, ratio 1.25, 95% CI 1.19-1.31). When the overall incidence is calculated taking into account the availability of HLA data (77.1%) and the coverage of the FPDR (91.7%) (7) the rate turns out to be 59.5, which is close to the rate of 62.5 reported earlier for the time period 2006-2011 (1). Incidence rates were highest among the 5-9-year-olds and lowest in the youngest age group with the

exception of the high risk group where the incidence rates were virtually equal among the oldest participants when compared to the youngest (429.7 vs 429.8) but considerably higher among 5-9-year-olds (514.9). The differences between 5-9 and 10-14-year-old participants were less conspicuous when looking at the incidence rates in risk groups other than the high-risk one. The incidence rate in the high-risk genotype was markedly lower (324.6) among girls in the oldest age-group than in the middle age group (462.3).

There were notable differences in the incidence rates for each risk genotype. The ratio between the rate in those carrying the high-risk genotype and those with the protective/neutral genotypes was 45.8 in the whole study population, being highest among girls under the age of 5 years (Table 1). The lowest ratio was seen among boys aged 10-14 years. Comparing incidences of other risk genotypes to the group with protective or neutral genotypes the ratio was 7.1 in those with slightly increased risk and 21.1 in those carrying moderately increased risk. The corresponding ratios were highest in the youngest age-group; 8.5 and 26.5, respectively.

The incidence rates among boys were higher than among girls in each risk group. However, incidence rate ratios when other risk groups were compared to the protective/neutral risk group were higher among girls. The incidence rate ratios for boys in each risk group were as follows: slightly increased risk 6.6, moderately increased risk 19.8 and high risk 43.4. The corresponding ratios for girls were: 7.9, 23.1 and 49.3. As among all the participants, the incidence rates were lowest among the youngest female participants and highest among 5 to 9-year-old girls with the exception of the high risk group where the oldest age group had the lowest incidence rate. Incidence rates were lowest among the youngest male patients in all of the risk groups. Between participants carrying protective, neutral or slightly increased risk the incidence rates were highest among the oldest male patients whereas genotypes afflicting higher risk were most common among 5 to 9-year-olds.

Table 1. Proportion of risk groups in the Finnish population and among patients with type 1 diabetes as well as sex- and age specific incidence rates (/100 000) of type 1 diabetes during the time period 2003-2018 in Finnish children under the age of 15 years in relation to their HLA-conferred disease risk.

	Protective/ Neutral	Slightly increased risk	Moderately increased risk	High risk	All risk groups	Ratio, high risk/protective and neutral risk (95% CI)
Proportion in the general population, %	76.90	13.64	7.42	2.04		0.026 (0.025-0.027)
Proportion among patients with T1D, %	18.13	22.93	36.93	22.02		1.21 (1.19-1.24)
Girls						
0-4	5.99	50.17	172.62	436.49		72.8 (57.7-92.5)
5-9	10.42	76.06	221.28	462.32		44.3 (36.5-53.9)
10-14	8.29	69.00	176.80	324.60		39.2 (31.4-48.9)
0-14	8.25	65.23	190.24	406.77	37.66	49.3 (43.6-55.8)
Boys						
0-4	7.25	62.41	178.01	423.43		58.4 (47.0-72.7)
5-9	13.02	82.12	265.98	565.18		43.4 (36.6-51.6)
10-14	14.59	86.38	248.14	530.57		36.4 (30.8-43.0)
0-14	11.68	77.16	231.25	507.21	47.01	43.4 (39.1-48.2)
All						
0-4	6.63	56.42	175.38	429.81		64.8 (55.3-76.1)
5-9	11.75	79.16	244.12	514.88		43.8 (38.5-49.8)
10-14	11.51	77.87	213.22	429.74		37.3 (32.7-42.7)
0-14	10.00	71.32	211.19	458.08	42.44	45.8 (42.3-49.6)

4. Discussion

We set out to assess the magnitude of differences between incidence rates among patients with type 1 diabetes carrying various HLA class II risk genotypes. These differences were notable, the incidence of patients carrying high risk genotypes was more than 45 times higher than in those with protective or neutral genotypes (Table 1). The incidence ratios, when higher risk groups were compared to protective/neutral, were highest among the youngest age group emphasizing the importance of genetic predisposition among patients diagnosed early in life. Also, the relative effects of HLA genotypes were larger among girls.

The current observations as well as earlier Finnish data (1) differ from findings from the 1990'ies (8) considering incidences in different age groups as we detected the highest incidence rates among 5 to 9-year-olds. In addition, our results emphasize the effect of gender on the incidence of T1D, the disease rate being higher among boys in every risk group and the total incidence was

results verify the crucial impact of the HLA genotype on the individual risk of type 1 diabetes.

Funding

This work was supported by Helsinki University Hospital Research Funds, Finska Läkaresällskapet, Lastentautien tutkimussäätiö and Medicinska understödsföreningen Liv och Hälsa.

Authors' relationships and activities

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement

ATM analysed the data and wrote the first draft of the manuscript. MK is the PI for the FPDR and together with TH in charge of the sample handling. JI and JL are responsible for the HLA typing of the participants. AB and TV have given advice for the statistical analyses and carried out a part of them. All authors critically revised the manuscript for important intellectual content and have approved the final version of the manuscript.

Journal Pre-proofs

References

1. Harjutsalo V, Sund R, Knip M, Groop P-H (2013) Incidence of type 1 diabetes in Finland. JAMA 310(4):427–428. https://doi.org/10.1001/jama.2013.8399

2. Noble JA, Valdes AM (2011) Genetics of the HLA region in the prediction of type 1 diabetes. Curr Diab Rep 11(6):533–542. https://doi.org/10.1007/s11982-011-0223-x

3. Knip M, Simell O (2012). Environmental triggers of type 1 diabetes. Cold Spring Harb Perspect Med 2(7):a007690. https://doi.org/doi:10.1101/cshperspect.a007690.

4. Hermann R, Knip M, Veijola R, et al (2003) Temporal changes in the frequencies of HLA genotypes in patients with type 1 diabetes – indication of an increased environmental pressure? Diabetologia 46 (3): 420-425. https://doi.org:10.1007/s00125-003-1045-4

5. Vehik K, Hamman RF, Lezotte D, et al (2008) Trends in high-risk HLA susceptibility genes among Colorado youth with type 1 diabetes. Diabetes Care 3(7):1392–1396. https;//doi.org/ 10.2337/dc07-2210

6. Ilonen J, Kiviniemi M, Lempainen J, et al (2016). Genetic susceptibility to type 1 diabetes in childhood – estimation of HLA class II associated disease risk and class II effect in various phases of islet autoimmunity. Pediatr Diabetes 17, Suppl 22:8–16. https://doi.org:10.1111/ pedi.12327

7. Hekkala A, Reunanen A, Koski M, Knip M, Veijola R (2010). Age-related differences in the frequency of ketoacidosis at diagnosis of type 1diabetes in children and adolescents. Diabetes Care 33(7):1500-1502. https://doi.org: 10.2337/dc09-2344

8. DIAMOND Project Group (2006) Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med 2006 23(8):857–866. https://doi.org 10.1111/j.1464-5491.2006.01925.x