

ORIGINAL ARTICLE

Country-specific birth weight and length in type 1 diabetes high-risk HLA genotypes in combination with prenatal characteristics

Y Sterner^{1,10}, C Törn^{1,10}, H-S Lee², H Larsson¹, C Winkler³, W McLeod², K Lynch¹, O Simell⁴, A Ziegler³, D Schatz⁵, W Hagopian⁶, M Rewers⁷, J-X She⁸, JP Krischer², B Akolkar⁹ and Å Lernmark¹, for the TEDDY Study Group¹¹

¹Department of Clinical Sciences, Lund University/CRC, University Hospital MAS, Malmö, Sweden; ²Pediatric Epidemiology Center, Department of Pediatrics, University of South Florida, Tampa, FL, USA; ³Diabetes Research Institute, Munich, Germany; ⁴Department of Pediatrics, Turku University Central Hospital, University of Turku, Turku, Finland; ⁵Department of Pediatrics, University of Florida, Gainesville, FL, USA; ⁶Pacific Northwest Diabetes Research Institute, Seattle, WA, USA; ⁷Department of Pediatrics, University of Colorado at Denver and Health Sciences Center, Barbara Davis Center for Childhood Diabetes, Denver, CO, USA; ⁸Center for Biotechnology and Genomic Medicine, Medical College of Georgia, Augusta, GA, USA and ⁹National Institute of Diabetes and Digestive and Kidney Disorders, National Institutes of Health, Bethesda, MD, USA

Objective: To examine the relationship between high-risk human leukocyte antigen (HLA) genotypes for type 1 diabetes and birth size in combination with prenatal characteristics in different countries.

Study Design: Four high-risk HLA genotypes were enrolled in the Environmental determinants of Diabetes in the Young study newborn babies from the general population in Finland, Germany, Sweden and the United States. Stepwise regression analyses were used to adjust for country, parental physical characteristics and environmental factors during pregnancy.

Result: Regression analyses did not reveal differences in birth size between the four type 1 diabetes high-risk HLA genotypes. Compared with DQ 4/8 in each country, (1) DQ 2/2 children were heavier in the United States ($P = 0.028$) mostly explained however, by parental weight; (2) DQ 2/8 ($P = 0.023$) and DQ 8/8 ($P = 0.046$) children were longer in Sweden independent of parents height and as well as (3) in the United States for DQ 2/8 ($P = 0.023$), but again dependent on parental height.

Conclusion: Children born with type 1 diabetes high-risk HLA genotypes have comparable birth size. Longitudinal follow-up of these children should reveal whether birth size differences between countries contribute to the risk for islet autoimmunity and type 1 diabetes.

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Keywords: HLA-DQ; gene–environment interaction; parental height; parental weight

Introduction

Height and weight measures in the newborn are influenced by both genetic and environmental factors. The health and nutrition status of the mother are known to influence the birth size of the baby.¹ Women with increased blood glucose levels give birth to children with larger birth size.^{2,3} Retrospective epidemiological studies have indicated that young children diagnosed with type 1 diabetes were heavier or born large for gestational age.^{4–7} The impact of genetic factors on birth size is not fully understood.⁸ Some studies have indicated that the human leukocyte antigen (HLA) system on chromosome 6 may act on birth size.^{9–12} The HLA system contributes about 50% of the risk for sib-pairs to develop type 1 diabetes.^{13,14} The HLA genotypes conferring the highest risk in the general Caucasian population are limited to the DR3-DQA1*0501-DQB1*0201/DR4-DQA1*0301-DQB1*0302; DR4-DQA1*0301-DQB1*0302/DR4-DQA1*0301-DQB1*0302; DR8-DQA1*0401-DQB1*0402/DR4-DQA1*0301-DQB1*0302 and DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201 genotypes.¹⁵ Results have been conflicting concerning the possible impact of these HLA-DQ genotypes on birth weight in the general population. The type 1 diabetes high-risk HLA genotypes have shown an association with higher birth weight in the general population in Sweden¹² and Finland.¹¹ Nevertheless, the same genotypes have shown a relation to lower birth weight in Norway.¹⁶ To be a carrier of any of these four genotypes was the criteria for the enrollment of newborn babies into the Environmental determinants of Diabetes in the Young (TEDDY) study.^{17,18} Maternal smoking influences birth size, however it is less established that the resulting reduction in birth weight may also interact with the HLA-DQ type of the child.¹⁰ Maternal alcohol consumption was suggested to impair intrauterine growth but results have been

Correspondence: Professor Å Lernmark, Department of Clinical Sciences, Lund University/CRC, University Hospital MAS, Entrance 72 60:11, Skåne University Hospital SUS, Malmö, Sweden.

E-mail: ake.lernmark@med.lu.se

¹⁰These authors contributed equally to this work.

¹¹The TEDDY study group is listed in the Supplementary Appendix.

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conflicting.¹⁹ Furthermore, parental height is related to the birth length of the baby.^{1,8} Taken together, it is necessary to adjust for a wide range of confounders across different populations to examine plausible effects of HLA on birth size of newborn babies in the general population. The aim of this study was, therefore, to examine the relationship between birth size and type 1 diabetes high-risk HLA genotypes in combination with prenatal characteristics in the four different countries of the multinational TEDDY study.^{17,18}

Materials and methods

Subjects

Children from the general population were recruited into the TEDDY study and defined as eligible based on whether they had any one of the four following high risk genotypes for type 1 diabetes; DR3-DQA1*0501-DQB1*0201/DR4-DQA1*0301-DQB1*0302 (DQ2/DQ8 or A in TEDDY); DR4-DQA1*0301-DQB1*0302/DR4-DQA1*0301-DQB1*0302 (DQ8/DQ8 or B in TEDDY); DR8-DQA1*0401-DQB1*0402/DR4-DQA1*0301-DQB1*0302 (DQ4/DQ8 or C in TEDDY) or DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201 (DQ2/DQ2 or D in TEDDY; Table 1). The genotype DQ4/DQ8 is associated with the lowest risk for type 1 diabetes among these four high risk genotypes.^{15,20} Therefore, this genotype was selected as the reference genotype in the multiple regression models and the risk estimates of the other three genotypes were based on comparison with this specific genotype. Since 1 September 2004 until 31 December 2010, about 350 000 newborn children were screened for high risk genotypes for type 1 diabetes in Finland, Germany, Sweden and the United States. Of these, a total of 8013 newborns were enrolled into the follow-up study. The blood samples were obtained in the maternity clinics either as cord blood or dry blood spots on day 3 to 4. If the child was eligible for the TEDDY study based on the HLA genotype, the family was contacted by a TEDDY nurse and invited to participate in a 15-year-follow-up study.^{17,18} For our analysis, we included only children born as singletons, as twins and triplets are known to have lower birth weight. Children who were first-degree relatives to a subject with type 1 diabetes were excluded in this report. Focusing on babies whose birth weight ranged from 2 to 6 kg and birth length from 40 to 60 cm, a total of 5461 children were included in the analyses. However, paternal height was only available from 1495 children.

The TEDDY study has been approved by Ethical Review Committees (Finland, Germany, Sweden) and Institutional Review Boards (US) and all participating families signed an informed consent.

Birth data

Birth weight (g) and birth length (cm) were obtained according to standard procedures in respective country and recorded on study forms from hospital records or forwarded by parents. Coordinated data on prenatal factors, such as country, gestational age,

Table 1 HLA eligibility for FDR and the GP infants^a

Code	Haplotype genotypes	Abbreviation	GP
A	DR4-DQA1*030X-DQB1*0302/DR3-DQA1*0501-DQB1*0201	DQ 2/8	Y
B	DR4-DQA1*030X-DQB1*0302/DR4-DQA1*030X-DQB1*0302	DQ 8/8	Y
C	DR4-DQA1*030X-DQB1*0302/DR8-DQA1*0401-DQB1*0402	DQ 4/8	Y
D	DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201	DQ 2/2	Y

Abbreviations: FDR, first degree relative; GP, general population; HLA, human leukocyte antigen; N, not eligible for the Environmental determinants of Diabetes in the Young inclusion; Y, eligible.

^aDR4 subtyping was used to exclude GP infants with DRB1*0403. DQB1*0304 in place of DQB1*0302 qualifies subjects for the Environmental determinants of Diabetes in the Young inclusion. Subtyping was not required to distinguish DQB1*020X and DQA1*030X subtypes.

gestational diabetes, type 1 or type 2 in first-degree relatives, gestational length (weeks), maternal smoking, maternal alcohol consumption, delivery complication, maternal age when baby was born, height and weight at end of pregnancy, were recorded on the first clinical visit at 3 months of age. Paternal height was recorded at the 9-month visit.

HLA typing

HLA genotypes were analyzed using either a genotyping system with an asymmetric polymerase chain reaction and subsequent hybridization of allele-specific probes for HLA-DQA1, DQB1 and DRB1 as described²¹ using DELFIA reagents (Perkin-Elmer, Waltham, MA, USA) or in a dot blot hybridization assay as detailed elsewhere.²² The different analytical methods used by the TEDDY centers provided accurate results for the genetic risk assessment.²³

Statistical analyses

Birth weight and birth length were reported as mean \pm standard deviation, together with the lower and upper quartiles overall and by country. Univariate analysis was carried out to explore whether potential confounders such as demographic or prenatal characteristics differed by either HLA types or birth size (that is, birth weight and birth length). For HLA types, Pearson's χ^2 -test was used for categorized data and analysis of variance for continuous data. For birth weight or birth length, two sample *t*-test or analysis of variance was used for categorical data and simple regression for continuous data.

Factors that showed a statistical significance in univariate analysis were considered for multiple regression analysis to investigate the relationship between birth size and HLA types. In this study, birth weight and birth length were examined with HLA genotypes, respectively, implementing the following four different models: model (1) unadjusted, model (2) adjusted for country, sex and gestational length (weeks), model (3) additionally adjusted for maternal smoking, maternal alcohol consumption, delivery complication, maternal age at delivery, height and weight at end of pregnancy, and model (4) additionally adjusted for

paternal height. Furthermore, we investigated whether parental physical characteristics differed by HLA types in the newborns. Regression parameter estimates and standard errors were summarized for each model separately.

All statistical analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC, USA). P -values <0.05 were considered significant.

Results

Birth size, HLA type and demographic characteristics as univariate parameters

Germany, Sweden and the United States showed similar frequencies of the four genotypes, the most frequent genotype being DQ 2/8 (40 to 46%), followed by DQ 2/2 (22 to 25%), DQ 8/8 (18 to 22%) and finally DQ 4/8 (11 to 16%; Supplementary Table 3-1). The genotype DQ 4/8 was more frequent in Finland (34%), which contributed to a significant difference in HLA genotypes between countries ($P < 0.0001$). Babies carrying the DQ 4/8 genotype tended to be smaller at birth in all countries except in Germany where the babies carrying this genotype seemed to be largest (Supplementary Table 2). There was no difference between gender or gestational length with respect to HLA genotypes (Supplementary Table 3-1).

Prenatal factors and birth length and weight

Children from the United States and Sweden were similar in birth length, but a lower birth weight on average was observed in the children from United States compared with children from Swedish. Swedish children were heaviest (Supplementary Table 3-2). Boys were both heavier ($P < 0.0001$) and longer ($P < 0.0001$) at birth. Children exposed to maternal smoking had an average birth weight reduction of 100 g compared with children not exposed to smoking. Maternal alcohol consumption did not seem to influence birth weight, but babies born to mothers with moderate alcohol consumption (one to two drinks per month) were longest at birth. Any delivery complication was associated to an average birth weight reduction of 80 g (Supplementary Table 3-2). Gestational length was strongly correlated to birth weight ($P < 0.0001$) and more so to birth length ($P < 0.0001$). As expected, parental height and weight were significantly associated with height and weight of the baby.

Multiple regression models

We examined if there was an effect of HLA genotype with respect to birth size using multiple regression models. The comparison was reported as overall and each genotype effect was compared with the DQ 4/8 genotype.

Birth weight

Overall, the unadjusted and the three different types of adjusted models failed to detect a difference between HLA genotypes and birth weight. However, in the United States, model 2 showed that

children carrying the DQ 2/2 genotype were heavier than those carrying DQ 4/8 if their gender and gestational length were same ($P = 0.028$; Supplementary Table 4-2). This trend disappeared in models 3 and 4 when we additionally adjusted for parental physical characteristics.

Birth length

Overall, birth length differed by HLA type in model 1, implying that children with the genotype DQ 4/8 were shorter than those with the other genotypes ($P = 0.009$; Supplementary Table 4-1), but the trend disappeared in adjusted models. In the United States, models 1 ($P = 0.029$) and 2 ($P = 0.023$) indicated that children with the genotype DQ 2/8 were longer than those with DQ 4/8 (Supplementary Table 4-2). However, this finding disappeared in models adjusted for parental physical characteristics. On the other hand, Swedish children with the genotypes DQ 2/8 ($P = 0.023$) and DQ 8/8 ($P = 0.046$) were significantly longer at birth than the DQ 4/8 children after adjusting for parental physical characteristics (model 4; Supplementary Table 4-2).

Influence from parental physical characteristics

The relationship between parental physical characteristics and HLA genotypes in the children was further investigated. In the United States, mothers to children with the genotype DQ 2/2 were heavier compared with mothers to the DQ 4/8 children ($P = 0.009$; Table 2a). Moreover, mothers of children who carried the genotype DQ 2/8 ($P = 0.040$) or DQ 2/2 ($P = 0.001$) were taller than those with DQ 4/8 (Table 2b). Overall, fathers of children that carried the genotype DQ 2/2 were also taller than those with DQ 4/8 ($P = 0.003$; Table 2b). When separated for the participating countries, this finding was significant only in the United States ($P = 0.015$). However, in Sweden, maternal weight at the end of pregnancy was lower in mothers to babies carrying the genotype DQ 2/8 than those with DQ 4/8 ($P = 0.041$; Table 2a).

Discussion

The major most important finding in this study was that newborns with the four type 1 diabetes high-risk HLA genotypes did not differ in birth size following the stepwise regression analysis. This is important as these children with type 1 diabetes high-risk HLA genotypes will be followed for 15 years for the development of islet autoimmunity and type 1 diabetes.^{17,18} It is an advantage that the children enrolled in the TEDDY study would be comparable at baseline with respect to birth size. Several epidemiological studies^{4,5} including meta-analyses²⁴ have suggest that children developing type 1 diabetes were born large for gestational age. This relationship has not been understood. One possible explanation was that children were born large for gestational age because of gestational infections.²⁵ An alternative explanation was that HLA genotypes conferring risk of type 1 diabetes were strongly associated

Table 2a Mother height and weight at the end of pregnancy with TEDDY HLA types

TEDDY HLA genotype	Height (cm)					Weight at the end of pregnancy (kg)				
	n	PE	s.e.	Pr> t	Pr>F	n	PE	s.e.	Pr> t	Pr>F
<i>Overall</i>										
AvsC		0.680	0.264	0.010**			1.130	0.578	0.051*	
BvsC	5328	0.446	0.302	0.140	0.001**	5255	0.853	0.662	0.198	<0.0001**
DvsC		1.140	0.298	0.000**			3.145	0.652	<0.0001**	
<i>United States</i>										
AvsC		1.056	0.514	0.040**			1.644	1.134	0.148	
BvsC	2023	1.059	0.576	0.066*	0.012**	2007	0.844	1.274	0.508	0.042**
DvsC		1.846	0.558	0.001**			3.246	1.234	0.009**	
<i>Finland</i>										
AvsC		-0.018	0.435	0.967			0.148	0.892	0.869	
BvsC	1128	0.064	0.544	0.906	0.999	1122	-0.297	1.116	0.790	0.544
DvsC		0.017	0.555	0.975			1.452	1.138	0.202	
<i>Germany</i>										
AvsC		0.904	1.252	0.471			4.153	2.979	0.164	
BvsC	275	0.943	1.420	0.507	0.131	274	5.397	3.376	0.111	0.216
DvsC		2.700	1.346	0.046**			6.576	3.201	0.041**	
<i>Sweden</i>										
AvsC		0.273	0.445	0.539			-2.026	0.990	0.041**	
BvsC	1902	-0.372	0.492	0.450	0.228	1852	-2.033	1.093	0.063*	0.017**
DvsC		0.440	0.493	0.372			0.150	1.098	0.892	

Abbreviations: HLA, human leukocyte antigen; PE, multiple regression parameter estimate; Pr>|t|, *P*-value for parameter estimate; Pr>F, *P*-value for analysis of covariance; TEDDY, the Environmental determinants of Diabetes in the Young. Additionally adjusted for parental physical characteristics; ***P*<0.05; **P*<0.1.

with an increased birth weight¹² alone, or in combination with possible gestational infection.²⁶ Furthermore, we can not exclude that the present newborns carrying the four type 1 diabetes high-risk HLA genotypes had increased birth weight and length compared with newborns with low-risk HLA genotypes. The fact that parental weight and height most likely explained some of the differences in birth weight (Finland and United States) and length (United States but not Sweden) underscore the possible importance of country-specific environmental determinants of birth sizes. The dissimilar country-specific sub-structure of the four HLA genotypes will be taken into account as the TEDDY children are followed prospectively for the development of islet autoimmunity and type 1 diabetes.^{17,18}

The second major finding was that Swedish DQ 2/8 and DQ 8/8 children were longer than the DQ 4/8 children used as a reference group. This observation, which was independent of parental weight and height, was a confirmation of the observation that DQ2/8 was associated with an increase relative birth weight¹² and length.²⁶ It is noted that the Swedish population frequency of DQ4/8 (1.4%) is

half of that of DQ2/8 (3.5%). However, among children developing type 1 diabetes before 18 years of age, the DQ2/8 (30%) is more common than the DQ4/8 (5%) genotype.²⁷ Finnish babies more often carried the DQ 4/8 genotype, whereas DQ2/8 children were less frequent compared with the other countries. The shorter Finnish babies compared with the other countries could indicate either a lesser exposure or a different reaction to gestational infections.⁹ HLA DQ-DR seems to contribute less to the risk of type 1 diabetes compared with 20 years ago since the frequency of the high risk genotypes in type 1 diabetes patients has decreased over time^{20,28-30} at the same time as the incidence of type 1 diabetes has increased.²⁴

Our observations support the view that environmental factors in pregnancy as well as in early childhood may contribute to type 1 diabetes risk. For example, in young children an increased growth, independent of HLA types, was observed before the diagnosis of type 1 diabetes.³¹ Several factors could either support or dismiss the accelerator hypothesis,³² such as feeding behaviors in early childhood³³ or postnatal exposure to viruses that might alter the

Table 2b Father height with TEDDY HLA types

TEDDY HLA genotype	Father height (cm)				
	n	PE	s.e.	Pr> t	Pr>F
<i>Overall</i>					
AvsC		0.864	0.537	0.108	
BvsC	1495	0.292	0.614	0.634	0.015**
DvsC		1.771	0.602	0.003**	
<i>United States</i>					
AvsC		1.438	1.045	0.170	
BvsC	513	0.705	1.158	0.543	0.073*
DvsC		2.740	1.127	0.015**	
<i>Finland</i>					
AvsC		-0.501	1.196	0.676	
BvsC	235	-1.095	1.439	0.448	0.588
DvsC		1.204	1.535	0.434	
<i>Germany</i>					
AvsC		-0.664	2.233	0.767	
BvsC	87	1.314	2.645	0.621	0.764
DvsC		0.952	2.456	0.699	
<i>Sweden</i>					
AvsC		0.906	0.806	0.261	
BvsC	660	0.307	0.911	0.736	0.448
DvsC		1.252	0.896	0.163	

Abbreviations: HLA, human leukocyte antigen; PE, multiple regression parameter estimate; Pr>|t|, *P*-value for parameter estimate; Pr>F, *P*-value for analysis of covariance; TEDDY, the Environmental determinants of Diabetes in the Young. Additionally adjusted for parental physical characteristics; ***P*<0.05; **P*<0.1.

insulin response.³⁴ The finding that maternal smoking in all countries conferred a weight reduction is in accordance with results from previous studies.^{10,35}

An association between increased birth weight and later development of type 1 diabetes seems to be well established.^{6,36} A relationship between increased birth size and HLA high risk genotypes for type 1 diabetes has also been reported.¹² The strength of this study is the number of type 1 diabetes high risk participants and coordinated data in different countries. One limitation with our study is that we do not have data on low risk genotype children from the general population. However, most prediction studies of type 1 diabetes focus on subjects carrying any of the high-risk genotypes. In addition, we have not studied other genetic factors besides HLA that might influence intrauterine growth such as variants of melanocortin 4 receptor regulating energy homeostasis,³⁷ variants of the insulin gene,^{38–41} variants of ADCY5, one of the enzymes synthesizing cyclic adenosine monophosphate or CCN1 thought to be involved in pre-mRNA splicing and RNA processing.⁸

In conclusion, different factors influence birth size in different countries. In the United States, birth size was mostly because of the parental height and maternal weight at delivery. In Sweden, HLA genotype seemed to influence birth length. The variability in birth size between countries in children selected to have the same type 1 diabetes high risk HLA genotypes suggest that environmental factors, non-HLA genetic variants, or both may be related to the subsequent risk of islet autoimmunity and type 1 diabetes in these children.

Conflict of interest

The authors declare no conflict of interest.

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