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The relation between size at birth and risk of type 1 diabetes is not influenced by adjustment for the insulin gene (-23HphI) polymorphism or *HLA-DQ* genotype

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Abstract *Aims/hypothesis:* Associations have been described between higher birthweight and increased risk of type 1 diabetes, and of insulin (*INS*) and human leucocyte antigen (*HLA*) genotypes that protect against diabetes with larger size at birth. We studied simultaneously the effects of size at birth, *INS* and *HLA* genotypes on the risk of type 1

diabetes to test whether the relation between size at birth and risk of type 1 diabetes would be strengthened after adjustment for *INS* and *HLA* genotypes. *Subjects and methods:* We designed a population-based case-control study in Norway with 471 cases of childhood-onset type 1 diabetes and 1,369 control subjects who were genotyped for the *INS* -23HphI polymorphism (surrogate for *INS* variable number of tandem repeats) and *HLA-DQ* alleles associated with type 1 diabetes. Data on birthweight and other perinatal factors were obtained from the Medical Birth Registry of Norway by record linkage. *Results:* The data fitted a multiplicative model for the protective *INS* class III allele both within the *INS* locus and for the model with *INS*- and *HLA-DQ*-conferred risk of type 1 diabetes. We found no overall significant association between weight or head circumference at birth and the risk of type 1 diabetes, and adjustment for *INS* and *HLA* genotype did not influence this result. There was also no evidence for association of *INS* or *HLA* with size at birth among control subjects. *Conclusions/interpretation:* In contrast to suggestions from previous indirect studies, direct adjustment for *INS* and *HLA* genotypes did not lead to a stronger relation between birthweight and the risk of type 1 diabetes.

Members of Norwegian Childhood Diabetes Study Group, see Appendix

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Abbreviations ESM: Electronic supplementary material ·
INS: insulin gene · VNTR: variable number of tandem
repeats

Introduction

Type 1 diabetes is a result of immune-mediated destruction of the pancreatic beta cells, but the factors initiating the destructive process are largely unknown [1]. There is evidence for the involvement of both genetic and non-genetic factors in this development. The two quantitatively most important genetic susceptibility loci influencing the risk of type 1 diabetes are the *HLA* class II region and the

insulin gene (*INS*) [2]. Several *HLA-DQ* and *-DR* alleles and genotypes are associated with risk and protection to different degrees [3], and the *INS* variable number of tandem repeats (VNTR) class I or its surrogate marker, the -23HphI A allele, has consistently been found to confer increased risk of type 1 diabetes [4, 5]. Accumulating evidence suggests that environmental factors may play a role early in life [6] and that there is an effect of size at birth and other perinatal factors on the risk of type 1 diabetes, generally of relatively small magnitude [7–11]. Several large-scale studies have found a high birthweight to be associated with a modest but statistically significant increase in the risk of childhood-onset type 1 diabetes [8, 9, 11], although other, predominately smaller studies have not found a significant association [e.g. 7, 12]. The mechanism by which *INS* VNTR class III (or the linked -23HphI T) allele reduces the risk of type 1 diabetes has been hypothesised to be via increased thymic expression of insulin during fetal and/or postnatal life [4]. *INS* polymorphisms may also affect fetal growth via a variety of pathways, including differential expression of *IGF2*, although fetal pancreatic insulin expression is only moderately affected by allelic variation at the *INS* VNTR [4]. Some studies of children without diabetes have indicated that type 1 diabetes-protective alleles at the *INS* and *HLA* loci are associated with larger size at birth [13–16], suggesting that any positive association between size at birth and the risk of type 1 diabetes may be attenuated by allelic variation at these loci. If so, the association between size at birth and the risk of type 1 diabetes should be strengthened after statistical adjustment for variation at these loci.

We therefore aimed to assess directly whether the odds ratio for the relation between size at birth and type 1 diabetes would be strengthened after adjustment for the *INS* -23HphI polymorphism and *HLA-DQ* genotypes, regardless of whether an association existed before adjustment. Secondary objectives were to assess the joint effects of *HLA-DQ* and *INS* polymorphism on the risk of type 1 diabetes, associations of *INS* and *HLA* with size at birth in the general population, and the role of birth order in these relations.

Subjects and methods

Study design

We designed a population-based case-control study in Norway, using cases of type 1 diabetes diagnosed before age 15 years between 1997 and 2000 and control children in the same age group randomly selected from the official population registry. All children were born between 1985–1999 and aged 1–15 years at the time of data collection [17]. Fifty-six per cent of controls and 73% of cases participated, with similar participation rates among regions, sexes and age groups [18]. DNA was collected using mailed mouth swabs and extracted as previously described [19]. Information on perinatal factors was obtained from the Medical

Birth Registry of Norway [20] by record linkage and additional data were collected using questionnaires mailed to the families [17]. Written informed consent was obtained from all participants, and the regional ethics committee and the Norwegian Data Inspectorate approved the study. After exclusion of children not born in Norway, twins, and children whose mother had diabetes during pregnancy, a total of 471 cases and 1,369 controls had complete data on *INS*, *HLA* and size at birth.

Genotyping

For both *HLA* and *INS* genotyping, cases and controls were genotyped at the same time, and laboratory personnel were blinded to the status (case or control) of the DNA samples. *HLA* genotyping was performed using sequence-specific PCR identifying *HLA-DQA1*02*, *DQA1*03*, *DQA1*05*, *HLA-DQB1*0201*, *DQB1*0201/0302*, *DQB1*0302/3*, *DQB1*0303*, *DQB1*0602*, *DQB1*0603/7* and *DQB1*0301/4*, as previously described [21, 22]. *DQA1-DQB1* haplotypes were determined based on known linkage equilibria. Samples identified as *DQA1*05-DQB1*0201/X* (*DQ2/X*) were typed for additional alleles to determine whether they were homozygous for *DQ2* using PCR and allele-specific lanthanide (III) chelate-labelled probes in streptavidin-coated microtitration wells according to the manufacturer's protocol (Perkin-Elmer Life Sciences, Turku, Finland). Individuals were categorised in four groups based on *HLA* type: (1) protective: at least one *HLA-DQB1*0602* allele; (2) high risk: *DQA1*03-DQB1*0302/DQA1*05-DQB1*0201* (*DQ8/DQ2*); (3) moderate risk: *DQ2/DQ2*, *DQ8/DQ8* or *DQ8/X*, where *X* represents alleles/haplotypes not defined above; and (4) all other genotypes (*X/X*, *DQ2/X*), which were regarded as a neutral reference category for the purpose of this study, although this latter category includes genotypes with some variation in risk.

The *INS* -23HphI polymorphism (surrogate for *INS* VNTR) was genotyped in two independent laboratories. One laboratory used a TaqMan assay (Applied Biosystems, Foster City, CA, USA), run on an ABI 7900 HT Fast Real-time PCR system (Applied Biosystems). The other laboratory used RFLP analysis as previously described [23], but using nested PCR. Discrepant results were re-run in both laboratories and resolved or excluded. Additional details on genotyping are available from the authors. We refer to the -23HphI A (risk) allele as (VNTR) class I and the T (protective) allele as class III [4].

Data analysis

We used logistic regression analysis to assess associations of size at birth, *INS* and *HLA* genotypes with type 1 diabetes, including likelihood ratio tests of multiplicative interactions, and we used ANOVA and linear regression to assess associations of *INS* and *HLA* genotypes with size at birth among control children. A two-sided *p* value less than

0.05 or a 95% CI excluding the null value (1.00 for the odds ratio) was taken as indicating statistical significance.

Power

Based on previous results [9], we assumed for the prestudy power analyses a logit-linear model for the risk of type 1 diabetes according to birthweight in four groups, and that the crude odds ratio for birth weight of 4,000 g or greater vs <2,500 g is 1.6. We hypothesised that the odds ratio would increase to 1.8 after adjustment for *INS* and *HLA* genotype. This scenario would provide 81% power to detect a significant association between birthweight and type 1 diabetes with 500 cases and 1,500 controls. Under a recessive model (*INS* class III or I/III vs I/I), the use of 1,500 control subjects provides 90% power to detect significant differences in birthweight and head circumference if the true difference is 89 g and 0.27 cm, respectively.

Results

Perinatal factors were not significantly associated with type 1 diabetes, but there was a slightly lower risk for children whose mothers were better educated, as previously reported [17] (Electronic supplementary material [ESM] Table 1). The well-established effect of *HLA* on the risk of type 1 diabetes was confirmed; the distribution among the 471 cases was 8, 83, 208 and 172 with protective, neutral, moderate-risk and high-risk genotypes, respectively, and

412, 619, 281 and 57, respectively, among the 1,369 controls (ESM Table 2). The effect of *HLA* was essentially similar after stratification by birth order, with no significant interaction (not shown).

The distribution of *INS* genotypes class III/III, I/III and I/I was 15, 120 and 336 among cases and 111, 527 and 731 among controls. The *INS* data fitted a multiplicative odds model (gene dose model) very well, with a nearly two-fold decrease in the risk of type 1 diabetes per protective class III allele (ESM Table 2). The odds ratio for the class I/I genotype vs I/III or III/III was 1.75 for first-born children and 2.55 for second- and later-born children, but the interaction between birth order and *INS* was not significant ($p=0.11$).

The odds ratio for *INS* class I/I vs I/III or III/III was very similar in all subgroups of *HLA*-associated risk, with no significant deviation from a multiplicative model for *INS*- and *HLA*-conferred risk (ESM Table 3).

Association between size at birth and type 1 diabetes after adjustment for *INS* and *HLA*

There was a tendency for those with the lowest birthweight to have a higher risk of type 1 diabetes, but there was no overall significant association between birthweight and the risk of type 1 diabetes, and this was essentially not influenced by adjustment for *INS*, *HLA* or other potential confounders (Table 1). No significant interaction between birthweight and *INS* ($p=0.83$), *HLA* ($p=0.62$) or birth order

Table 1 Association between size at birth and risk of type 1 diabetes after adjustment for *INS* and *HLA* genotype using logistic regression

Birthweight (g)	Cases (n=471)	Controls (n=1,369)	Odds ratio (95% CI)		
			Unadjusted	Adjusted for <i>INS</i> and <i>HLA</i> ^a	Additional adjustment ^b
<2,500	20 (4.2%)	22 (1.6%)	2.68 (1.42, 5.06)	2.46 (1.11, 5.45)	1.99 (0.82, 4.82)
2,500–2,999	39 (8.3%)	107 (7.8%)	1.07 (0.71, 1.63)	1.13 (0.68, 1.87)	0.99 (0.59, 1.68)
3,000–3,499	141 (29.9%)	416 (30.4%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3,500–3,999	168 (35.7%)	518 (37.8%)	0.96 (0.74, 1.24)	0.93 (0.68, 1.28)	0.91 (0.66, 1.26)
≥4,000	103 (21.9%)	306 (22.4%)	0.99 (0.74, 1.33)	0.91 (0.63, 1.30)	0.91 (0.63, 1.33)
Trend ^c			0.982 (0.962, 1.002)	0.979 (0.955, 1.004)	0.987 (0.960, 1.015)
Test for trend ^c			$p=0.10$	$p=0.08$	$p=0.36$
Head circumference (cm)					
<33	22 (4.7%)	38 (2.8%)	1.78 (1.03, 3.07)	1.99 (1.01, 3.93)	1.55 (0.73, 3.30)
33–34	118 (25.1%)	326 (23.8%)	1.11 (0.86, 1.44)	1.02 (0.75, 1.39)	0.96 (0.70, 1.33)
35–36	237 (50.3%)	729 (53.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
37–38	88 (18.7%)	261 (19.1%)	1.04 (0.78, 1.38)	1.03 (0.73, 1.45)	1.05 (0.73, 1.50)
≥39	6 (1.3%)	15 (1.1%)	1.23 (0.47, 3.21)	1.30 (0.41, 4.10)	1.34 (0.42, 4.34)
Trend ^c			0.943 (0.880, 1.010)	0.952 (0.875, 1.035)	0.980 (0.895, 1.073)
Test for trend ^c			$p=0.09$	$p=0.25$	$p=0.66$

^aAdjusted for *INS* and *HLA* risk genotypes

^bAdjusted for *INS* and *HLA* risk genotypes, plus gestational age, maternal age, birth order, maternal education and maternal smoking. Forty individuals were excluded because of missing data for at least one of the variables included as covariates (missing data: birth order, six cases, 11 controls; maternal education, seven cases, ten controls; maternal smoking during pregnancy, five cases, ten controls). Those with missing information for gestational age were included as a separate category

^cTrend in logit-linear risk model (logistic regression): odds ratio for type 1 diabetes per 100 g change in birthweight or per cm head circumference

($p=0.28$) was observed. Very similar patterns were found for head circumference at birth (Table 1).

Association of INS and HLA with size at birth among population-based control children

There were significant associations of sex, gestational age, birth order and maternal smoking during pregnancy with size at birth (ESM Table 4). There was no significant association of *INS* genotype with size at birth (Table 2). No association was seen in either category of birth order (not shown).

Children carrying the type 1 diabetes-protective allele *HLA-DQB1*0602* tended to be larger at birth, but the overall ANOVA test was not significant (Table 2), and this suggestive association was attenuated after adjustment for covariates (not shown). Inspired by a recent report [16], we also investigated *HLA-DQB1*0603*. The 170 control children carrying at least one *HLA-DQB1*0603* allele had a mean birthweight of 3,594 g compared with 3,621 g for non-carriers ($p=0.52$).

Discussion

We present for the first time a simultaneous analysis of the effect of size at birth and genetic factors on the risk of type 1 diabetes in a well-powered study. We were thus able to test directly whether the association between size at birth and type 1 diabetes is enhanced after adjustment for *INS* and *HLA* genotypes. Although previous indirect studies have provided circumstantial evidence for such enhancement [13–16], our direct test in the present report showed that this was not the case. The controls in the present study included only individuals who were not part of our pilot

study [15], and thus provide an independent study of controls. Of the 471 cases, 175 (37%) were also part of our previous cohort study based on linkage of registries without information on molecular genetic markers [9], whereas the rest of the cases in the present study had not been analysed previously.

Strengths of the present study include: (1) the inclusion of children drawn from registries with nearly complete population coverage; (2) linkage of registries via unique personal identification numbers; (3) the inclusion of a large number of type 1 diabetes cases; and (4) adjustment for a number of relevant covariates.

Among the study's limitations were: (1) we did not know the parental origin of the *INS* and *HLA* alleles; (2) we did not have postnatal growth data; and (3) participation was incomplete—a problem inherent in most clinical research. Although the response in our study was in line with that in many other studies in which biological specimens were collected [24], there is room for potential bias. The distribution of birthweight among the controls in the present study was shifted towards higher birthweights compared to the distribution of birthweights reported to The Medical Birth Registry of Norway [20] between 1985 and 1998 in which the mother did not have diabetes registered before or during pregnancy (e.g. 1.6% of participating controls had a birthweight <2,500 g compared with 4.5% for all births in The Medical Birth Registry). Our controls also had mothers who were slightly older when giving birth compared with the background population. This may have been due to selection of participating controls whose mothers were more highly educated than average. Regarding maternal education, Vangen et al. [25] linked data from Statistics Norway on maternal education to The Medical Birth Registry of Norway for all births during 1986–1998, and found that 30.5% of women had more than 12 years of education, 59.8% had 10–12 years of education, 8.4% had less than 10 years, and 1.3%

Table 2 Associations of *HLA* and *INS* polymorphisms with birthweight and head circumference at birth in 1,369 singleton control children born in Norway to mothers who did not have diabetes during pregnancy

<i>HLA</i> or <i>INS</i> genotype ^a	Birthweight (g) ^b	Test of difference ^c	Head circumference at birth (cm) ^b	Test of difference ^c
<i>INS</i> class I/I ($n=731$)	3,604 (499)	$p=0.56$	35.30 (1.451)	$p=0.70$
<i>INS</i> class I/III ($n=527$)	3,632 (508)		35.38 (1.538)	
<i>INS</i> class III/III ($n=111$)	3,637 (434)		35.33 (1.435)	
Coefficient for trend ^d	21.5	$p=0.31$	0.04	$p=0.53$
Adjusted coefficient, trend ^d	11.9	$p=0.55$	0.007	$p=0.91$
<i>HLA DQB1*0602</i> ($n=412$)	3,659 (488)	$p=0.15$	35.45 (1.404)	$p=0.12$
<i>HLA X/X, DQ2/X</i> ($n=619$)	3,586 (515)		35.28 (1.542)	
<i>HLA DQ2/2, 8/X, 8/8</i> ($n=281$)	3,625 (470)		35.25 (1.444)	
<i>DQ8/2</i> ($n=57$)	3,615 (497)		35.58 (1.535)	

^aRisk categories defined a priori: protective = at least one *HLA-DQB1*0602* allele; *DQ8* = *DQA1*03-DQB1*0302*; *DQ2* = *DQA1*05-DQB1*0201*

^b*X*, alleles/haplotypes not defined above

INS was genotyped at the -23HphI polymorphism, where the A allele corresponds to the class I VNTR (risk) allele and the HphI T allele corresponds to VNTR class III

^cData are mean (SD)

^dOverall one-way ANOVA test

^eCoefficient for trend based on linear regression (additive model), expressing increase in gram birthweight or centimeter head circumference per increase in class III allele. Test was the Wald test from the linear regression model. Adjusted coefficient is the same coefficient in the model also including sex, gestational age, birth order and maternal smoking during pregnancy

had missing information. Corresponding results from our participating control children [18] were 37.1% (>12 years), 54.3% (10–12 years), 7.3% (<10 years) and 1.4% (missing information). Despite slightly different calendar years and inclusion criteria, the above data indicate selection of children with higher birthweight and older and more highly educated mothers among our controls. Whether similar selection among our cases with type 1 diabetes occurred is unknown, but we can speculate that any such selection may have been weaker among case children, in whom there was a higher proportion of responses. If so, this may partly explain the lack of association of maternal age and birthweight with the risk of type 1 diabetes in the present study in contrast to our earlier reports [9, 10], in addition to the smaller sample size in the present study. On the other hand, there is little reason to suspect that the effect of molecular genetic markers on size at birth or on the relation between size at birth and type 1 diabetes should be influenced by any such potential bias, because it is hard to imagine that *INS* or *HLA* genotype should be strongly associated with behaviour directing participation in the study.

In relation to our secondary objectives, we note that the initial report of an association between the *INS* polymorphism and size at birth among children from the general population [13] has not been supported by recent reports [26–28]. A new study from the UK has indicated that the association between *INS* and size at birth primarily concerns head circumference, and was stronger for second and later children than for first-born children, presumably because first-born children experience more environmental restrictions on fetal growth than later-born children [14]. In our study, we found no indication of association between *INS* and size at birth in any group of birth order. In a previous study [15], we found a tendency for the *HLA-DQB1*0602* allele, which is strongly protective against type 1 diabetes, to be associated with higher birthweight. We found a similar indication in the present data set, but this was not a significant or robust finding. A very large study from Sweden reported that *HLA-DQB1*0603* (protective against type 1 diabetes) and the high-risk *DQ2/DQ8* genotype were associated with higher birthweight for gestational age [16], but we were unable to confirm this in our study. Consistent with other recent results [5], the protective class III alleles seemed to display a multiplicative allele dose effect, in contrast to the previous notion of a dominantly protective effect against type 1 diabetes [4].

From the present results it seems that, at least in our population, possible effects of *INS* and *HLA* on birthweight [13, 15, 16] and of birthweight on the risk of type 1 diabetes [9, 11] are of too small a magnitude to allow clear findings of confounding or interacting effects on the risk of type 1 diabetes unless sample sizes are exceedingly large.

We conclude that, in contrast to indications from previous indirect studies, the relation between size at birth and type 1 diabetes was not influenced by adjustment for *INS* and *HLA*.

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Duality of interest The authors declare that they have no duality of interest.

Appendix

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