HHEX-IDE Polymorphism Is Associated with Low Birth Weight in Offspring with a Family History of Type 1 Diabetes

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Context: The fetal insulin hypothesis proposes that common genetic variants that reduce insulin secretion also reduce birth weight, and an association of low birth weight and the type 2 diabetes risk alleles at the *HHEX-IDE* and *CDKAL1* loci were recently reported.

Objective: Here, we examined the relationship between type 2 diabetes risk alleles and birth weight in a diabetic environment presented in children of mothers with type 1 diabetes.

Research Design and Methods: Birth weight and genotyping of single nucleotide polymorphisms (SNPs) at the *CDKAL1*, *HHEX-IDE*, and *SLC30A8* loci was obtained and analyzed in 729 singleton full-term children of mothers with type 1 diabetes born in Germany.

Results: The fetal risk alleles of *HHEX-IDE* SNP rs5015480 and SNP rs10882102 were associated with reduced birth weight: 81g (95% confidence interval, 20–140 g; $P = 0.009$) and 85 g (95% confidence interval, 25–145 g; $P = 0.005$) lower birth weight per risk allele, respectively. The association remained significant after adjusting for maternal pregnancy-glycosylated hemoglobin. Fetal genotypes at the *CDKAL1* and *SLC30A8* loci were not associated with birth weight in this cohort.

Conclusions: The association of low birth weight and type 2 diabetes risk alleles of the *HHEX-IDE* locus is confirmed in children of mothers with type 1 diabetes. **(*J Clin Endocrinol Metab* 94: 4113–4115, 2009)**

Type 2 diabetes is associated with polymorphisms at several genes and with reduced birth weight (1, 2). Linking these findings, birth weight was recently reported to be lower in neonates carrying the type 2 diabetes risk alleles at the *HHEX-IDE* and *CDKAL1* loci (3). The genetic effect on birth weight is suggested to be mediated via reduced fetal insulin secretion, a notion that is consistent with the fetal insulin hypothesis (4). An interesting model that would corroborate the findings and hypothesis is one in which the fetus is exposed to increased β-cell stimulation. Children of mothers with type 1 diabetes are exposed to hyperglycemia during fetal life and, as a consequence, have increased insulin concentrations and higher birth weight (5, 6). We therefore examined birth weight in relation to the type 2 diabetes risk alleles at the *CDKAL1*, *HHEX-IDE*, and *SLC30A8* loci in children born to mothers with type 1 diabetes to determine whether the previously reported

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Abbreviations: CI, Confidence interval; HbA1c, glycosylated hemoglobin; SNP, single-nucleotide polymorphism.

TABLE 1. Birth weight in relation to fetal genotype in children of mothers with type 1 diabetes

	Fetal genotype (no. of type 2 diabetes risk alleles)			
Locus (SNP)	**0**	**1**	**2**	***P***
HHEX-IDE (rs5015480)	3689 (3583–3794)	3603 (3543–3663)	3525 (3455–3595)	0.009
n	113	348	260	
HHEX-IDE (rs10882102)	3686 (3582–3789)	3600 (3540–3659)	3515 (3445–3584)	0.005
n	116	354	259	
SLC30A8 (rs3802177)	3563 (3423–3702)	3548 (3482–3614)	3633 (3573–3693)	0.10
n	66	294	358	
CDKAL1 (rs4712526)	3641 (3508–3774)	3533 (3470–3596)	3632 (3570–3695)	0.31
n	72	319	331	

Data are expressed as mean birth weight in grams (95% CI).

gene-birth weight interactions can be replicated in a cohort exposed to hyperglycemia.

Subjects and Methods

Children of mothers with type 1 diabetes were recruited in Germany between 1989 and 2004 in the context of two prospective birth cohort studies, BABYDIAB and BABYDIET (7, 8). A total of 729 children (377 female) were available for genotyping. Birth weight and gestational age were obtained from hospital records. Subjects included in the study were singleton birth and were born at a gestational age of 37 wk or later. For 557 children, maternal glycosylated hemoglobin (HbA1c) during the last trimenon of pregnancy was recorded. Written informed consent was obtained from all families participating in the study. The study was approved by the ethics committee (Bayerische Landesärztekammer Nr. 95357, and Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilian-Universität Nr. 329/00).

The genotyping of the *CDKAL1* single nucleotide polymorphism (SNP) rs4712526, *HHEX-IDE* SNP rs10882102, *HHEX-IDE* SNP rs5015480, and *SLC30A8* SNP rs3802177 was performed with the MassARRAY system using the iPLEX chemistry (Sequenom, San Diego, CA). The allele-dependent primer extension products were loaded onto one 384-element chip using a nanoliter pipetting system (SpectroCHIP, SpectroPOINT Spotter; Sequenom), and the samples were analyzed by matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (Bruker Daltonik, Leipzig, Germany). The resulting mass spectra were analyzed for peak identification via the SpectroTYPER RT 3.4 software (Sequenom). To control for reproducibility, 16.3% of samples were genotyped in duplicate with a discordance rate less than 0.5%. The *HHEX-IDE* SNP rs10882102 and *HHEX-IDE* SNP rs5015480 are in strong linkage. All SNPs were tested for deviation from Hardy-Weinberg equilibrium by means of χ^2 or Fisher's exact test.

The association between birth weight and fetal genotype for each SNP was examined using linear regression, with genotypes coded as 0, 1, or 2 risk alleles, and with sex and gestational age as covariates. The distribution of birth weight was near normal, and data were not transformed for analysis. The statistical analysis was performed using the Statistical Package for Social Science (SPSS 16.0; SPSS, Chicago, IL).

Results

The type 2 diabetes risk alleles of *HHEX-IDE* SNPs rs5015480 and rs10882102 were associated with reduced birth weight in children born to mothers with type 1 diabetes (Table 1). Per risk allele, the birth weight was lower by 81 g [95% confidence interval (CI), 20–140 g] for SNP rs5015480 and by 85 g (95% CI, 25–145 g) for SNP rs10882102 ($P = 0.009$ and $P = 0.005$, respectively, adjusted for gestational age and gender). The association remained significant after adjusting for maternal pregnancy-HbA1c in the subset of children (n = 557) where maternal HbA1c was available. Fetal genotypes at the *CDKAL1* and *SLC30A8* loci were not associated with birth weight in our cohort.

Discussion

Our results strongly support the findings of Freathy *et al.* (3) that fetal inheritance of alleles of certain genes conferring increased risk for type 2 diabetes is associated with reduced birth weight. Novel and potentially interesting in our study is that the association between *HHEX-IDE* SNPs rs5015480 and rs10882102 and birth weight is also present in children exposed to increased and often varied glycemia during fetal growth, and who also have a genetic predisposition to type 1 diabetes. The effect in this cohort appears strong with more than 80-g differences observed between infants carrying zero or at least one risk allele. Thus, the data provide further evidence that the type 2 genetic susceptibility conferred by the *HHEX*-IDE gene is related to insulin secretion capacity and that the association of low birth weight with type 2 diabetes is secondary to gene-insulin secretion interactions. We did not confirm the association with *CDKAL1*. This may be due to limited effects on insulin secretion in response to hyperglycemia or simply due to limited power given the smaller cohort size compared with the report in the general population. We also did not observe synergistic effects between the *HHEX-IDE* and *CDKAL1* genotypes on birth weight

(data not shown). As observed in the general population, there was no association between the *SLC30A8* SNP alleles and birth weight. We suggest that fetal hyperglycemia could be a useful model to identify gene effects on insulin secretion, and we conclude that the relationship between *HHEX-IDE* and birth weight could be reproduced in this model.

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