BMI at Age 8 Years Is Influenced by the Type 2 Diabetes Susceptibility Genes *HHEX-IDE* and *CDKAL1*

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OBJECTIVE—To determine whether *HHEX-IDE* and *CDKAL1* genes, which are associated with birth weight and susceptibility to type 2 diabetes, continue to influence growth during childhood.

RESEARCH DESIGN AND METHODS—BMI, weight, and height at age 8 years expressed as age- and sex-corrected standard deviation scores (SDS) against national reference data and single-nucleotide polymorphism genotyping of *HHEX-IDE* and *CDKAL1* loci were analyzed in 646 prospectively followed children in the German BABYDIAB cohort. All children were singleton full-term births; 386 had mothers with type 1 diabetes, and 260 had fathers with type 1 diabetes and a nondiabetic mother.

RESULTS—Type 2 diabetes risk alleles at the *HHEX-IDE* locus were associated with reduced BMI-SDS at age 8 years (0.17 SDS per allele; $P = 0.004$). After stratification for birth weight, both *HHEX-IDE* and *CDKAL1* risk alleles were associated with reduced BMI-SDS (0.45 SDS, $P = 0.0002$; 0.52 SDS, $P = 0.0001$) and weight-SDS (0.22 SDS, $P = 0.04$; 0.56 SDS, $P = 0.0002$) in children born large for gestational age (>90th percentile) but not children born small or appropriate for gestational age. Within children born large for gestational age, BMI and weight decreased with each additional type 2 diabetes risk allele (~ -2 kg per allele; >8 kg overall). Findings were consistent in children of mothers with type 1 diabetes ($P < 0.0001$) and children of nondiabetic mothers ($P = 0.008$).

CONCLUSIONS—The type 2 diabetes susceptibility alleles at *HHEX-IDE* and *CDKAL1* loci are associated with low BMI at age 8 years in children who were born large for gestational age. ***Diabetes*** **59:2063–2067, 2010**

Genome-wide association studies have recently identified common, novel type 2 diabetes susceptibility loci that are likely to predispose one to diabetes via impaired pancreatic β-cell function, impaired insulin secretion, and/or insulin sensitivity (1–3). Some effects occur during fetal growth. For example, the presence of type 2 diabetes risk alleles at the *HHEX-IDE* and *CDKAL1* loci are associated with reduced birth weight, consistent with reduced insulin responses during fetal development (4). This was also observed for the *HHEX-IDE* locus in our studies of children born to mothers with type 1 diabetes where the fetus is exposed to high and variable glucose concentrations (5). It is unknown whether the gene effects during fetal life persist and whether they are acting in a similar manner after birth. Here we partially address this by determining whether the type 2 diabetes risk alleles at the *HHEX-IDE* and *CDKAL1* loci are associated with growth during childhood in a cohort of children whose mothers or fathers had type 1 diabetes.

RESEARCH DESIGN AND METHODS

Children of parents with type 1 diabetes were recruited in Germany between 1989 and 2000 in the context of the BABYDIAB study (6). Relevant to the current study, birth as well as weight and height data during follow-up were collected from pediatric records that were completed by trained staff at delivery and by pediatricians at visits to the clinic after birth. Children from singleton full-term (≥37 weeks gestational age) births who had a pediatric visit as part of the study between the age of 7.5 and 8.5 years were included in the current analysis. Of these 731 children, genetic data, weight, and height were available from 646 children. This included 386 children who had a mother with type 1 diabetes and 260 children who had a father with type 1 diabetes and a nondiabetic mother. None of the children had a mother with known gestational diabetes. Children who had developed type 1 diabetes prior to age 8 years were not included, because they were lost to follow-up at the onset of their diabetes. All families gave written informed consent to participate in the BABYDIAB study. The study was approved by the ethical committee of Bavaria, Germany (Bayerische Landesärztekammer Nr. 95357).

All children were genotyped for the *CDKAL1* SNP rs4712526 and *HHEX-IDE* SNP rs5015480, rs10882102, and as a control for a type 2 diabetes susceptibility gene that is not associated with fetal growth, also the *SLC30A8* SNP rs3802177. Genotyping was performed with the MassARRAY system using the iPLEX chemistry (Sequenom, San Diego, CA) as previously described (5). To control for reproducibility, 16.3% of samples were genotyped in duplicate with discordance rate <0.5%. All SNPs were shown to be in Hardy-Weinberg equilibrium by means of Fisher exact test.

Homeostasis model assessment of insulin resistance (HOMA-IR) was obtained in a subset of children at age 8 years. Children were asked to fast for at least 8 h. Fasting blood glucose was determined locally by a pathology laboratory. Fasting insulin was determined centrally using the Mercodia Ultrasensitive Insulin ELISA (Uppsala, Sweden), a solid-phase two-site enzyme immunoassay, as described in the manufacturer's instructions.

For analysis, data on height, weight, and BMI at follow-up were adjusted for sex and exact age at examination and were expressed as standard deviation scores (SDS) from the mean using German reference data derived from over 34,000 children (7,8). The association between weight-SDS, height-SDS, BMI-SDS, and genotype for each SNP was examined using linear regression, with genotypes coded as 0, 1, or 2 risk alleles and, as a covariate, the type 1 diabetes status of the mother when appropriate. Interaction between birth weight and the *HHEX-IDE* or *CDKAL1* genotypes was tested by the general linear model. Data were also stratified for birth weight expressed as percentiles of the reference German population adjusted for sex and gestational age (9) using the categories small for gestational age (SGA; birth weight <10th percentile of the reference population; $n = 68$), appropriate for gestational age (AGA; 10th–90th percentile of the reference population; $n = 459$), and large for gestational age (LGA; >90th percentile of the reference population; $n = 120$). Gestational age and sex distribution was similar among

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TABLE 1
Characteristics of the study cohort

	Children of mothers with T1D	Children of fathers with T1D†	All children
n (% male)	386 (48.6)	260 (52.7)	646 (50.2)
Median (IQR) gestation in weeks (range)	39 (38–40)	40 (39–41)	39 (38–40)
Birth weight, g	3,572.5 ± 579	3,465.4 ± 510	3,527.6 ± 553
Median (IQR) birth weight percentile (range)	68 (33–91)	54 (23–74)	60 (28–85)
SGA*	35 (9.1)	33 (12.7)	68 (10.5)
AGA*	256 (66.3)	203 (78.1)	459 (71.1)
LGA*	95 (24.6)	24 (9.2)	119 (18.4)
Birth length, cm	51.2 ± 2.7	51.8 ± 2.4	51.5 ± 2.6
8-year height, cm	131.1 ± 5.6	131.8 ± 5.6	131.4 ± 5.6
8-year height-SDS	0.23 ± 0.96	0.35 ± 0.96	0.28 ± 0.96
8-year weight, kg	28.2 ± 4.8	28.5 ± 5.1	28.4 ± 4.9
8-year weight-SDS	0.11 ± 0.93	0.16 ± 0.95	0.13 ± 0.94
8-year BMI	16.4 ± 2.1	16.3 ± 2.2	16.4 ± 2.2
8-year BMI-SDS	−0.01 ± 1.0	−0.03 ± 1.0	−0.01 ± 1.0

Data are mean ± SD or *n* (%). *SGA, small for gestational age (<10th percentile); AGA, appropriate for gestational age (10th–90th percentile); LGA, large for gestational age (>90th percentile). †Children of fathers with type 1 diabetes (T1D) had a mother without T1D or known other diabetes.

SGA, AGA, and LGA children. The statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Weight, height, and BMI at age 8 years in the cohort were normally distributed and were not significantly different to those of the German reference data (Supplementary Fig. S1, available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db10-0099/DC1, and Table 1). No differences were observed for weight, height, and BMI at age 8 years between children who had a mother with type 1 diabetes and children who had a father with type 1 diabetes and a nondiabetic mother (Table 1).

The type 2 diabetes risk allele at the *HHEX-IDE* locus was associated with reduced BMI-SDS at age 8 years in all children. Per risk allele, the BMI-SDS was lower by 0.17 SDS (95% CI, 0.06–0.28; $P = 0.004$) at age 8 years (Table 2). The association remained significant when the child's maternal diabetes status was included as a covariate ($P = 0.004$). The same association was observed when a second SNP within the *HHEX-IDE* locus (rs10882102) was examined (data not shown). The genotypes at the *CDKAL1* and *SLC30A8* loci were not significantly associated with BMI-SDS in the total cohort.

Joint regression analysis showed that 8-year BMI was associated with both birth weight percentile ($P < 0.0001$) and the *HHEX-IDE* gene ($P = 0.01$) also when adjusted for maternal diabetes status. We therefore stratified the children on the basis of their gestational age- and sex-corrected birth weight percentile into small (<10th percentile), appropriate (10th–90th percentile) and large (>90th percentile) for gestational age and analyzed the BMI–gene relationships. Strikingly, there was a very strong association between BMI and the *HHEX-IDE* genotypes in the LGA children ($P = 0.0003$), but not in the SGA and AGA children (Fig. 1*A*; supplementary Tables S1–S3 in an online appendix). A similar association was also observed with *CDKAL1* genotypes ($P = 0.0001$, Fig. 1*B*; supplementary Tables S1–S3). For *CDKAL1*, significant interaction was shown between birth weight category and genotype in the general linear model ($P < 0.01$). For both genes, the type 2 diabetes susceptibility genes were associated with lower BMI-SDS at age 8 years in children born LGA, with the strongest effects seen in children who were

TABLE 2
BMI-SDS at age 8 years in relation to fetal genotype in children of parents with type 1 diabetes

	BMI-SDS, mean (95% CI)			Effect per allele BMI-SDS (95% CI)	§*P*	†*P* adjusted
	Fetal genotype (no. of T2D risk alleles)					
Locus	0	1	2			
HHEX-IDE	0.25 (0.06–0.45)	−0.04 (−0.15–0.08)	−0.12 (−0.26–0.01)	0.17 (0.06–0.28)	0.004	0.004
	n = 104	*n* = 318	*n* = 218			
CDKAL1	0.11 (−0.13–0.34)	−0.05 (−0.17–0.07)	−0.01 (−0.13–0.11)	0.03 (−0.14–0.09)	0.67	0.69
	n = 74	*n* = 284	*n* = 88			
SLC30A8	0.08 (−0.20–0.35)	-0.09 (−0.21–0.03)	0.02 (−0.09–0.14)	0.03 (−0.09–0.16)	0.60	0.54
	n = 54	*n* = 277	*n* = 305			
Birth weight	SGA	AGA	LGA			
	−0.33 (−0.57–0.10)	−0.06 (−0.15–0.03)	0.32 (0.15–0.49)		<0.001	<0.001
	n = 70	*n* = 507	*n* = 132			

§The association BMI-SDS and genotype for each SNP was examined using linear regression, with genotypes coded as 0, 1, or 2 risk alleles. The association BMI-SDS and birth weight was examined using linear regression, with birth weight coded as SGA (small for gestational age; <10th percentile), AGA (appropriate for gestational age; 10th–90th percentile), or LGA (large for gestational age; >90th percentile). †Adjusted for proband (children who have a mother with type 1 diabetes or children without a mother with type 1 diabetes).

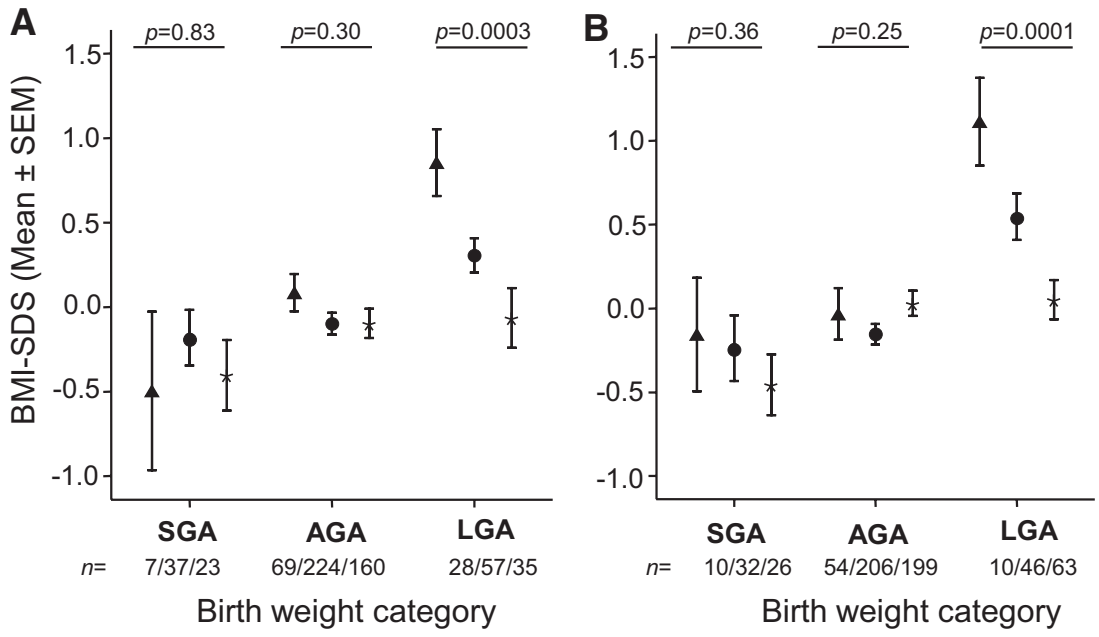

FIG. 1. Association between BMI-SDS at age 8 years and the number of type 2 diabetes risk alleles at the *HHEX-IDE* locus (*A*) or *CDKAL1* locus (*B*) after stratification for birth weight. ▲, ●, and × represent children with 0, 1, and 2 type 2 diabetes susceptibility alleles, respectively.

homozygous for the susceptibility alleles. Per risk allele, the BMI-SDS was lower by 0.45 SDS (95% CI, 0.22–0.69) for the *HHEX-IDE* gene and by 0.52 SDS (95% CI, 0.26–0.78) for the *CDKAL1* gene in the LGA children. For both the *HHEX-IDE* and the *CDKAL1* genes, a mean BMI above the German reference population mean at 8 years was observed only in the subgroup of children who were LGA and not homozygous for the type 2 diabetes susceptibility alleles. A similar relationship was observed between the *HHEX-IDE* and the *CDKAL1* genes and weight but not height (supplementary Tables S4 and S5, available in an online appendix). No relationship between alleles of the *SLC30A8* gene and BMI-SDS were observed with or without stratification for birth weight (data not shown).

Within the LGA group, both genes were associated with BMI at age 8 years (*HHEX-IDE*, $P = 0.0001$; CDKAL1, $P = 0.0002$) with an adjusted R^2 of 0.21 in the joint regression model. Thus, the combination of alleles from both genes showed a dramatic association between the number of type 2 diabetes susceptibility alleles and lower BMI in LGA children (Fig. 2, supplementary Figure S2A and supplementary Table S6, available in an online appendix). LGA children with no type 2 diabetes susceptibility alleles at the *HHEX-IDE* and *CDKAL1* loci had BMIs almost two SDS above the population average, whereas children who had four susceptibility alleles had BMIs that were at or below the population average. Across all birth weight strata, an increased mean 8-year BMI was only seen in children who were LGA and had two or less of the type 2 diabetes susceptibility alleles for *HHEX-IDE* and *CDKAL1*. These findings were consistent in children who had a mother with type 1 diabetes ($P < 0.0001$) and children who had a father with type 1 diabetes and a nondiabetic mother ($P = 0.008$), and no evidence of interaction between maternal diabetes status and genotype on 8-year BMI was observed. Examination of weight and height in relation to these gene combinations in LGA children found an association with weight and weight-SDS ($P = 0.0002$; supplementary Figure S2B and supplementary Table S7, available in an online appendix) corresponding to a weight difference of ~ -2 kg per risk allele and resulting in >8 kg difference between LGA children with no risk alleles (mean weight, 35.7 kg) and those with all four risk alleles (mean weight, 27.5 kg). No association was observed with height-SDS ($P = 0.51$; data not shown). HOMA-IR was available at age 8 years in 63 LGA children. With this limited data, a similar, but not significant, trend was observed between the number of type 2 diabetes susceptibility alleles at the *HHEX-IDE* and *CDKAL1* loci and both fasting insulin and HOMA-IR (supplementary Figure S3, available in an online appendix).

DISCUSSION

An association between the recently identified type 2 diabetes susceptibility genotypes and growth during child-

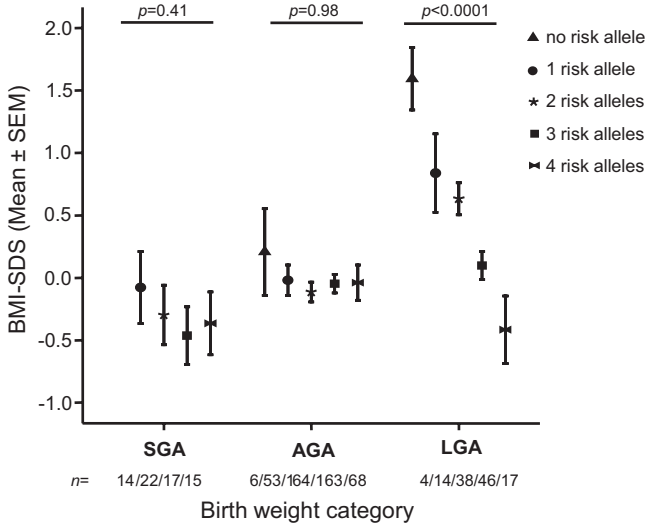

FIG. 2. Association between BMI-SDS at age 8 years and the number of type 2 diabetes risk alleles at the *HHEX-IDE* locus and the *CDKAL1* locus after stratification for birth weight.

hood was identified. Analysis of weight, height, and BMI in a cohort of children showed that type 2 diabetes susceptibility genotypes at the *HHEX-IDE* and *CDKAL1* loci were associated with reduced BMI and weight at age 8 years. The associations were interactive with birth weight status, suggesting that these genes contribute to both fetal and childhood growth patterns.

Previous studies (10–16) have shown that birth weight is associated with growth and BMI during childhood. Consistent with these studies, SGA children in our cohort were ~2 kg lighter and LGA children were 2 kg heavier than AGA children at age 8 years (data not shown). There was, however, also a very striking relationship between the *HHEX-IDE* and *CDKAL1* genotypes and 8-year BMI that was found in LGA children. Both genes contributed independently to reduce BMI and weight to around normal in the LGA children but not in the AGA children. Thus, our findings suggest that the type 2 diabetes susceptibility genes *HHEX-IDE* and *CDKAL1* influence homeostasis of body mass when there has been excessive fetal growth. Potentially relevant to this affirmation is that over half the children in our cohort were affected by maternal diabetes, a state that is associated with increased fetal growth via mechanisms that include increased fetal insulin production (17). These children are no longer exposed to diabetic glycemic variations after delivery and are therefore interesting to compare to children of nondiabetic mothers. In this regard, the associations between the *HHEX-IDE* and *CDKAL1* genes and 8-year BMI were consistent in LGA children from mothers with diabetes and children who had a father with type 1 diabetes and a mother without known diabetes. Therefore, although it cannot be excluded that the LGA children from the nondiabetic mothers were also exposed to hyperglycemic stimuli during fetal growth, the associations between genes and BMI appear to be independent of hyperglycemia during pregnancy, further supporting the notion that the genes influence childhood growth in addition to fetal growth.

Our findings are inconsistent with a recent report on children (18). Zhao et al. found increased BMI associated with the type 2 diabetes susceptibility allele of the *HHEX-IDE* gene and no association between BMI and SNPs of the *CDKAL1* gene. It should be noted that, in their study, the association between increased BMI and the *HHEX-IDE* gene was only observed in children aged 2–6 years and not in older children, whereas we examined children at the age of 8 years. Moreover, inconsistent with ours and other studies (4,5), they did not find an association between the *HHEX-IDE* gene and birth weight in their cohort. Finally, because our associations were limited to children who were LGA, it is possible that these would be missed in a cohort that is not overly represented by LGA children.

The relationship of our findings to type 2 diabetes susceptibility and pathogenesis is unclear. Many have shown that SGA is associated with increased type 2 diabetes risk (19–22), and some have also suggested that LGA is associated with increased risk (23–25). The relationship of type 2 diabetes susceptibility genes with growth and BMI appears complex, and there is no general rule for the direction of the effect of type 2 diabetes susceptibility and BMI. Ours and previous studies consistently show that SGA is associated with reduced weight, height, and BMI during childhood (10–16). Our data further show that having the full complement of type 2 diabetes susceptibility genotypes for two genes protects against increased BMI at age 8 years. Analogous to this, the protective variant of the type 2 diabetes susceptibility gene *PPARG2* is associated with increased BMI (26–28). Thus, while type 2 diabetes is generally associated with increased BMI, there are examples where increased BMI can be associated with reduced type 2 diabetes risk. It is possible that, in such examples, large fat deposits may protect against accumulation in the liver and muscle in children with protective alleles. It is also possible that, although BMI is not increased, other characteristics such as adiposity or insulin sensitivity may be already affected in the children (29,30), or that different gene effects are seen in the subset of children with increased adiposity (28) or under certain dietary conditions such as was found for peroxisome proliferator–activated receptor-γ (31). Relevant to our cohort, which has an increased load of type 1 diabetes–associated genetic susceptibility, it is possible that the relative contribution of genes such as *HHEX-IDE* and *CDKAL1* to pathogenesis may be outweighed by a series of other genes. Finally, longer follow-up of our and, in particular, type 2 diabetes–susceptible cohorts will be required to ascertain if the association of lower weight and BMI with the type 2 diabetes susceptible alleles for the *HHEX-IDE* and *CDKAL1* genes persists or changes after puberty and in adulthood.

In conclusion, we show that the fetal programming associated with the type 2 diabetes susceptibility genes *HHEX-IDE* and *CDKAL1* has prolonged effects during childhood as evidenced by the influence of birth weight status on BMI and weight at age 8 years, and that further programming in association with these genes occurs during childhood when there has been excess fetal growth. These data indicate that there is important genetic control of childhood weight that may act through mechanisms associated with insulin release and action. The relationship of these genetic factors to weight control during childhood appears inconsistent to their association with type 2 diabetes later in life, a finding that requires validation and longer follow-up of cohorts that are susceptible for type 2 diabetes.

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C.W. designed the study and the concept, performed acquisition of data, undertook statistical analysis, provided interpretation of the results, wrote and edited the manuscript, and provided critical review of the manuscript for intellectual content. E.B. designed the study and the concept, performed statistical analysis, provided interpretation of the results, wrote the manuscript, and provided critical review of the manuscript for intellectual content. H.G. performed the genotyping and wrote the manuscript. L.H. performed acquisition of data and wrote the manuscript. T.I. performed the genotyping, wrote the manuscript, and provided critical review of the manuscript for intellectual content. A.Z. was the principal investigator, designed the study and concept, undertook the statistical

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