Examination of All Type 2 Diabetes GWAS Loci Reveals *HHEX-IDE* as a Locus Influencing Pediatric BMI

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OBJECTIVE—A number of studies have found that BMI in early life influences the risk of developing type 2 diabetes later in life. Our goal was to investigate if any type 2 diabetes variants uncovered through genome-wide association studies (GWAS) impact BMI in childhood.

RESEARCH DESIGN AND METHODS—Using data from an ongoing GWAS of pediatric BMI in our cohort, we investigated the association of pediatric BMI with 20 single nucleotide polymorphisms at 18 type 2 diabetes loci uncovered through GWAS, consisting of *ADAMTS9*, *CDC123-CAMK1D*, *CDKAL1*, *CDKN2A/B*, *EXT2*, *FTO*, *HHEX-IDE*, *IGF2BP2*, the intragenic region on 11p12, *JAZF1*, *KCNQ1*, *LOC387761*, *MTNR1B*, *NOTCH2*, *SLC30A8*, *TCF7L2*, *THADA*, and *TSPAN8-LGR5*. We randomly partitioned our cohort exactly in half in order to have a discovery cohort (n = 3,592) and a replication cohort (n = 3,592).

RESULTS—Our data show that the major type 2 diabetes risk–conferring G allele of rs7923837 at the *HHEX-IDE* locus was associated with higher pediatric BMI in both the discovery (P = 0.0013 and survived correction for 20 tests) and replication (P = 0.023) sets (combined $P = 1.01 \times 10^{-4}$). Association was not detected with any other known type 2 diabetes loci uncovered to date through GWAS except for the well-established *FTO*.

CONCLUSIONS—Our data show that the same genetic *HHEX-IDE* variant, which is associated with type 2 diabetes from previous studies, also influences pediatric BMI. ***Diabetes* 59: 751–755, 2010**

Diabetes affects an estimated 194 million adults worldwide and more than 18 million in the U.S. with chronic complications including microvascular disease and accelerated development of cardiovascular disease. Approximately 90–95% of those affected by diabetes have the type 2 diabetes form of the disease. Hyperglycemia is a key feature of type 2 diabetes and occurs through two possible mechanisms: *1*) abnormal insulin secretion as a result of pancreatic β-cell defects or *2*) insulin resistance in skeletal, muscle, liver, and adipose tissue.

Type 2 diabetes has been the focus of more genome-wide association studies (GWAS) than any other disorder studied to date; such analyses have revealed a number of loci (1–9). The strongest association in European populations has been with a gene established in 2006, namely, the Wnt-signaling pathway member transcription factor 7–like 2 (*TCF7L2*) (10), while in China and Japan, the strongest association has been with the gene encoding potassium channel, voltage-gated, KQT-like subfamily, member 1 (*KCNQ1*) (8,9). The first batch of such studies (1–6) revealed new loci, and with a recent meta-analysis (7) of type 2 diabetes genome-wide single nucleotide polymorphism (SNP) genotype data producing another six loci, there are now 17 genes established in the disease, including *CDKAL1*, *SLC30A8*, and *JAZF1*. *MNTR1B* was first implicated in multiple GWAS of the related trait of fasting glucose and was subsequently associated with type 2 diabetes within the same studies (11–13).

All the type 2 diabetes genes uncovered by GWAS to date have been implicated in primarily impacting insulin secretion, with the exception of the fat mass and obesity-associated gene (*FTO*), which was uncovered as a consequence of a type 2 diabetes GWAS but turned out to be operating through insulin resistance and was therefore primarily an obesity risk factor (14).

A question therefore arises, If specific genomic variants can impact insulin resistance or insulin secretion, can this in turn impact BMI earlier on in life? As such, we sought to examine these type 2 diabetes GWAS findings in a large pediatric cohort with BMI measures and to determine the relative impact of these variants on the trait of interest. We used data from an ongoing GWAS in a cohort of 7,184 European American children with recorded heights and weights randomly partitioned precisely in half in order to have a discovery cohort and a subsequent replication cohort.

Loci selected had been discovered directly from published type 2 diabetes GWAS. We therefore queried for

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known variants at the 18 type 2 diabetes–associated loci of *ADAMTS9*, *CDC123-CAMK1D*, *CDKAL1*, *CDKN2A/B*, *EXT2*, *FTO*, *HHEX-IDE*, *IGF2BP2*, the intragenic region on 11p12, *JAZF1*, *KCNQ1*, *LOC387761*, *MTNR1B*, *NOTCH2*, *SLC30A8*, *TCF7L2*, *THADA*, and *TSPAN8-LGR5* with respect to their correlation with pediatric BMI.

RESEARCH DESIGN AND METHODS

Our study cohort consisted of 7,184 singleton children of European ancestry with systematically recorded height and weight. All subjects were consecutively and randomly recruited from the greater metropolitan area of Philadelphia from 2006 to 2009 at The Children's Hospital of Philadelphia; i.e., participants were not specifically targeted for obesity-related traits. The study was approved by the institutional review board of The Children's Hospital of Philadelphia. Parental informed consent was given for each study participant for both the blood collection and subsequent genotyping.

Genotyping. We performed high throughput genome-wide SNP genotyping using the Illumina Infinium II HumanHap550 or Human 610 BeadChip technology (Illumina, San Diego, CA) at The Children's Hospital of Philadelphia's Center for Applied Genomics as described previously (15). The overall genomic control value was 1.036. The SNPs analyzed survived the filtering of the genome-wide dataset for SNPs with call rates <95%, minor allele frequency <1%, missing rate per person >2%, and Hardy-Weinberg equilibrium $P < 10^{-5}$.

Most loci described from GWAS published to date have been found using either the Affymetrix or Illumina platform. In the event a locus was reported using both the Illumina and Affymetrix arrays, we used the SNPs present on the Illumina array. In the event of a signal only being described on the Affymetrix array, we either already had the SNP on our Illumina array or identified and used the best surrogate SNP available based on the CEPH (Centre d'Etude du Polymorphisme Humain) from Utah (CEU) HapMap (supplemental Table 1, which can be found in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db09-0972/DC1). We used two SNPs at the *CDKAL1* (rs4712523 and rs7756992; $r^2 = 0.677$) and *HHEX-IDE* (rs1111875 and rs7923837; $r^2 = 0.698$) loci as the association with type 2 diabetes from various GWAS reported different SNPs, which were in imperfect linkage disequilibrium (LD) with each other. rs3751812 at *FTO* was included as a positive control as we have previously reported the association with this SNP and both pediatric obesity and pediatric BMI (16,17).

Analysis: normalization of BMI. BMI percentiles were defined using the standard Centers for Disease Control (CDC) growth chart *z* scores that take into account age and sex. All subjects were biologically unrelated and were between 2 and 18 years of age. All subjects were between ±3 SDs of CDC corrected BMI; i.e., outliers ($n = 356$) were excluded to avoid the consequences of potential measurement error or Mendelian causes of extreme obesity.

Association. We queried the data for the SNPs of interest in our pediatric sample. All statistical analyses were carried out using the software package PLINK (version 1.05) (18). We applied PLINK to the generation of genome-wide identical by state estimates between all subjects and then generated multidimensional scaling (MDS) plots for visual examination of population outliers. To help interpret the population genetic analysis, we included 924 HapMap3 individuals from 11 populations as positive control subjects into the MDS analysis. The individuals of European ancestry were selected by the principal component one of >0.04 and principal component two of >0.01. Comparing self-identified ancestry with the MDS-inferred ancestry confirmed the reliability of MDS to identify genetically inferred individuals of European ancestry.

By treating the normalized BMI *z* score as a quantitative trait, association analysis for each SNP was carried out using linear regression (additive model) with the SNP included as an independent variable (coded as 0, 1, and 2). With 3,592 subjects in the discovery cohort, the powers to detect 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, and 1% variation at the $\alpha = 0.0025$ level were 27.0, 49.0, 68.2, 82.0, 90.6, 97.9, and 99.6%, respectively.

RESULTS

In our analysis, 20 SNPs corresponding to the 18 type 2 diabetes loci previously discovered in GWAS of the disorder were investigated, namely, *ADAMTS9*, *CDC123-CAMK1D*, *CDKAL1*, *CDKN2A/B*, *EXT2*, *FTO*, *HHEX-IDE*, *IGF2BP2*, the intragenic region on 11p12, *JAZF1*, *KCNQ1*, *LOC387761*, *MTNR1B*, *NOTCH2*, *SLC30A8*, *TCF7L2*, *THADA*, and *TSPAN8-LGR5* (Table 1).

We randomly partitioned our cohort exactly in half in order to have a discovery cohort ($n = 3,592$) and a replication cohort ($n = 3,592$). Five of these 20 SNPs yielded at least nominally significant association with BMI ($P < 0.05$) in the discovery cohort, representing four different independent loci.

Of these four loci, the minor allele of rs3751812 at the *FTO* locus yielded the strongest association with $P = 3.81 \times 10^{-5}$ and tracked with higher BMI. The direction of effect was also readily replicated in the additional cohort ($P = 5.56 \times 10^{-6}$), yielding a combined $P = 1.05 \times 10^{-9}$.

The major type 2 diabetes–conferring G allele of rs7923837 at the *HHEX-IDE* locus was associated with higher pediatric BMI in both the discovery (unadjusted $P = 0.0013$; Bonferroni correction for 20 variants threshold $P \leq 0.0025$) and replication (unadjusted $P = 0.023$) sets (combined unadjusted $P = 1.01 \times 10^{-4}$). The major C allele of rs1111875 at the same locus was also trending with higher pediatric BMI but did not survive the Bonferroni correction for multiple testing in the discovery cohort.

The other two nominally significant loci in the discovery cohort, rs4402960 at *IGF2BP2* ($P = 0.05$) and rs11257622 at *CDC123-CAMK1D* ($P = 0.024$) failed to replicate in the additional cohort. Association was not detected at all with any of the other type 2 diabetes loci uncovered to date through GWAS.

We also analyzed male and female subjects separately, but the effect of the G allele rs7923837 at the *HHEX-IDE* locus on pediatric BMI did not vary by sex (supplemental Table 2). However, we did look at different age bins and found that the variant was associated with higher pediatric BMI most strongly in the 2- to 6-year-old age bin (supplemental Table 3). By further breaking down the ages into individual years, nominally significant association for this *HHEX-IDE* variant in the same direction was observed at ages 3, 7, 14, and 16 years (supplemental Table 4). However, we did not observe an overall statistical interaction with age, with the interaction *P* values for rs1111875 and rs7923837 being 0.2507 and 0.1076, respectively.

DISCUSSION

If a genomic variant is well established to be associated with a trait that is the consequence of a defect of recognition of insulin by the body or by a fault in the amount of insulin released for the pancreatic islets (i.e., type 2 diabetes), then if these defects are operating at all in childhood, one might expect there to be an impact on BMI in childhood.

With this notion in mind, we queried the existing dataset from our ongoing GWAS of pediatric BMI if any of the type 2 diabetes loci uncovered in GWAS to date played a role in our trait of interest; it should be noted that *PPARG*, *KCNJ11*, and *WFS1* were not included as their discovery with respect to being type 2 diabetes loci predates GWAS and thus have already been more extensively investigated. Our data in fact do show that the same genetic *HHEX-IDE* variant that is significantly associated with type 2 diabetes from previous studies also influences pediatric BMI. Indeed, the major G allele of rs7923837 at the *HHEX-IDE* locus was associated with higher pediatric BMI in both the discovery and replication cohorts, which is the same allele that has been reported to confer risk of type 2 diabetes. This mirrors very well what has been seen with the much

TABLE 1
Quantitative association results for the known type 2 diabetes risk alleles with pediatric BMI in the European American cohort (n = 3,592), followed by a replication effort (n = 3,592), and sorted by chromosomal location

					Discovery cohort					Replication cohort					
CHR	SNP	Type 2 diabetes–associated allele	BP	Nearby gene	n	Effect size	SE	Test statistic	P	n	Effect size	SE	Test statistic	P	Combined P
1	rs2793831	C	120235944	*NOTCH2*	3,592	0.03508	0.04637	0.7565	0.449	3,592	0.02797	0.04603	0.6076	0.544	0.3353
2	rs7578597	T*	43644474	*THADA*	3,592	0.01896	0.04632	0.4094	0.682	3,592	0.007494	0.04521	0.1658	0.868	0.6785
3	rs4411878	C*	64678705	*ADAMTS9*	3,591	−0.02394	0.03145	−0.7611	0.447	3,592	0.01207	0.03082	0.3917	0.695	0.8086
3	rs4402960	T	186994389	*IGF2BP2*	3,587	−0.05843	0.0298	−1.961	0.05	3,592	−0.004747	0.02886	−0.1645	0.869	0.1375
6	rs4712523	G	20765543	*CDKAL1*	3,592	0.01223	0.02991	0.4087	0.683	3,592	−0.02724	0.02996	−0.909	0.363	0.7294
6	rs7756992	G	20787688	*CDKAL1*	3,591	0.02923	0.03128	0.9344	0.350	3,592	−0.01428	0.03104	−0.4599	0.646	0.7371
7	rs1635852	C*	27962651	*JAZF1*	3,590	0.009886	0.02783	0.3552	0.722	3,592	−0.01975	0.02778	−0.7108	0.477	0.8058
8	rs13266634	C*	118253964	*SLC30A8*	3,590	0.003039	0.03004	0.1012	0.919	3,588	−0.01446	0.03039	−0.4759	0.634	0.7949
9	rs2383207	A*	22105959	*CDKN2A/B*	3,591	0.04088	0.02787	1.467	0.142	3,592	−0.04318	0.02783	−1.552	0.121	0.9482
10	rs11257622	C	12335345	*CDC123-CAMK1D*	3,580	−0.08373	0.03703	−2.261	0.0238	3,591	0.08785	0.03706	2.37	0.0178	0.9463
10	rs1111875	C*	94452862	*HHEX-IDE*	3,592	0.08005	0.02839	2.82	0.00483	3,592	0.05527	0.02823	1.957	0.0504	7.14×10^{-4}
10	**rs7923837****	**G***	**94471897**	***HHEX-IDE***	**3,592**	**0.0913**	**0.02845**	**3.209**	**0.00134**	**3,592**	**0.06523**	**0.02865**	**2.277**	**0.0229**	$\mathbf{1.01 \times 10^{-4}}$
10	rs7903146	T	114748339	*TCF7L2*	3,592	−0.01407	0.03025	−0.465	0.642	3,592	−0.00646	0.02988	−0.2162	0.829	0.636
11	rs163171	C*	2777641	*KCNQ1*	3,588	−0.03288	0.0328	1.002	0.316	3,588	−0.09764	0.03347	−2.917	0.00355	0.19
11	rs9300039	C*	41871942	*Intragenic*	3,585	−0.08931	0.05007	1.784	0.0746	3,592	0.03837	0.04824	0.7953	0.427	0.07334
11	rs7480010	G	42203294	*LOC387761*	3,591	0.02035	0.03049	0.6673	0.505	3,592	−0.01925	0.0299	−0.6437	0.520	0.9935
11	rs729287	C*	44236666	*EXT2*	3,592	−0.0188	0.03215	0.5849	0.559	3,591	0.0261	0.03194	0.8173	0.414	0.3223
11	rs1387153	T	92313476	*MTNR1B*	3,592	−0.003922	0.0308	−0.1273	0.899	3,592	−0.01709	0.03052	−0.5598	0.576	0.6223
12	rs1353362	C	69899543	*TSPAN8-LGR5*	3,581	−0.01765	0.03074	−0.5743	0.566	3,589	−0.01196	0.03008	−0.3977	0.691	0.4916
16	**rs3751812****	**T**	**52375961**	***FTO***	**3,587**	**0.1159**	**0.0281**	**4.124**	$\mathbf{3.81 \times 10^{-5}}$	**3,592**	**0.1273**	**0.02799**	**4.549**	$\mathbf{5.56 \times 10^{-6}}$	$\mathbf{1.05 \times 10^{-9}}$

The direction of effect is shown for the type 2 diabetes risk allele in each case. Data in boldface type indicate the combination of statistical significance in the discovery set plus successful replication. *The type 2 diabetes risk allele is the major allele; **$P \leq 0.0025$ in the discovery cohort, i.e., survive Bonferroni correction for number of variants tested. BP, base pair position (dbSNP build 125); effect size, regression coefficient for the test SNP; n, number of individuals tested; P, unadjusted two-sided trend test P value; SE, standard error of the regression coefficient; test statistic, additive model.

more established *FTO* gene reported here and in other studies.

SNP rs7923837 yielded the fourth strongest association with type 2 diabetes in a Canadian/French GWAS carried out on the Illumina HumanHap platform (1). SNPs rs1111875 and rs7923837 yielded the strongest association at the *HHEX-IDE* locus, but it should be noted that they are far from being in perfect LD with each other (r^2 = 0.698), and thus both are included in the current study. However, despite the lack of complete concordance and the large sample size, we were unable to separate the effects of these SNPs as they cannot be considered to be totally independent signals either.

One hypothesis could be that the fetal genotype for rs7923837 is primarily associated with birth weight given that reduced birth weight is often reported to be associated with increased BMI and type 2 diabetes later in life. However, this does not appear to be the case as we have already investigated and reported the role of these type 2 diabetes loci in the context of birth weight in our cohort. Although we have agreed with previous studies that *CDKAL1* is a birth weight-associated gene, we have not observed such an association with *HHEX-IDE* (19). Further, although there is no CDC categorization for the under 2-year-old age-group, we do not observe association between rs7923837 and BMI in this age category following our own normalization (data not shown). The correlation between birth weight and BMI in later childhood is less correlated than in earlier stages, suggesting that the *HHEX-IDE* variant exerts its physiological influence directly rather than as a consequence of a knock-on effect from a primary impact on birth weight. However, we do acknowledge that of the age bins studied, the strongest effect was observed in the 2- to 6-year-old age bin (effect size [SE] = 0.12 [± 0.04]) (supplemental Table 3). But this is not the whole story because at the individual age level, although more limited in terms of power, the impact continues to be observed into the mid-teens (supplemental Table 4).

The assumption in this study is that deficient insulin secretion mediates the effect on childhood BMI, but it is also possible that higher childhood BMI results in impaired insulin secretion later in life. There could indeed be pleiotropic associations from multiple independent mechanisms; however, we were not able to address this as we do not have insulin secretion/sensitivity measures in our study.

From our analysis, apart from *FTO* it is clear that only one of the loci previously reported from type 2 diabetes GWAS plays a role in our phenotype of interest, i.e., pediatric BMI. While this recently discovered locus unveils a new biomolecular pathway not previously studied in the context of type 2 diabetes and obesity, it is also important to note that this and other genetic associations with childhood obesity explain very little of the genetic risk for the pathogenesis of the trait (17); indeed, an estimate of the explained variance of the *HHEX-IDE* and *FTO* loci combined is only 0.98%, suggesting the existence of additional loci whose number and effect size remain mainly unknown. Current knowledge concerning the impact of genetic factors in the determination of pediatric BMI may still be very limited due to both the lack of availability of large pediatric cohorts with GWAS data and methodological difficulties in the analysis of the phenotype that changes with age and depends on many other contributing factors. Once our GWAS is complete, we will have the opportunity to look for other variants in the genome associated with BMI in childhood.

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