Studies in 3,523 Norwegians and Meta-Analysis in 11,571 Subjects Indicate That Variants in the Hepatocyte Nuclear Factor 4α (HNF4A) P2 Region Are Associated With Type 2 Diabetes in Scandinavians

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OBJECTIVE—Recent publications have found an association between common variants near the hepatocyte nuclear factor 4α (HNF4A) P2 promoter and type 2 diabetes in some populations but not in others, and the role for HNF4A in type 2 diabetes has remained unclear. In an attempt to address these inconsistencies, we investigated HNF4A single nucleotide polymorphisms (SNPs) in a large population-based sample and included a meta-analysis of published studies.

RESEARCH DESIGN AND METHODS—We genotyped 12 SNPs in the HNF4A region in a Norwegian population–based sample of 1,644 individuals with type 2 diabetes and 1,879 control subjects (the Nord-Trøndelag Health Study [HUNT] 2). We combined our data with all previously published case/control studies and performed a meta-analysis.

RESULTS—Consistent with initial studies, we found a trend toward association for the SNPs rs1884613 (odds ratio [OR] 1.17 [95% CI 1.03–1.35]) and rs2144908 (1.21 [1.05–1.38]) in the P2 region and for rs4812831 (1.21 [1.02–1.44]), located 34 kb downstream of the P2 promoter. Meta-analysis, comprising 12,292 type 2 diabetic case and 15,519 control subjects, revealed a nonsignificant OR of 1.05 (95% CI 0.98–1.12) but with significant heterogeneity between the populations. We therefore performed a subanalysis including only the data for subjects from Scandinavia. Among the 4,000 case and 7,571 control Scandinavian subjects, a pooled OR of 1.14 (1.06–1.23), $P = 0.0004$, was found for the SNP rs1884613.

CONCLUSIONS—Our results suggest that variation in the HNF4A region is associated with type 2 diabetes in Scandinavians, highlighting the importance of exploring small genetic effects in large, homogenous populations. ***Diabetes*** **56:3112–3117, 2007**

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HUNT, Nord-Trøndelag Health Study; LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

Genetic variants in the hepatocyte nuclear factor 4α (HNF4A) gene may be involved in type 2 diabetes development. HNF4A encodes a transcription factor with an important role in hepatocyte and pancreatic transcriptional regulation. The two promoters, P1 and P2, are located 45.5 kb apart on chromosome 20q. While HNF4A transcripts in the liver are primarily of P1 origin, the P2 promoter drives expression in the pancreas, where it regulates genes involved in insulin secretion and glucose homeostasis (1–3). The importance of HNF4A in glucose metabolism is further reflected by maturity-onset diabetes of the young-1, which is caused by mutations in HNF4A and characterized by impaired insulin secretion and monogenic inheritance (4–7). Several type 2 diabetes studies have shown linkage to the 20q region, and two initial reports found evidence for association between HNF4A and type 2 diabetes, highlighting the genetic segment surrounding the P2 promoter as the prime candidate region (8,9). Subsequent studies have shown conflicting results between different populations (8–21). Thus, it is still not established whether the HNF4A locus harbors heritable variation involved in development of type 2 diabetes. Meta-analyses may prove useful to evaluate such conflicting results. Recently, such analyses have revealed that common genetic variations in TCF7L2, PPARG, and KCNJ11 explain part of the heritable fraction of type 2 diabetes (22–25). Extensive meta-analysis for HNF4A P2 has not been undertaken. We therefore decided to genotype a Norwegian case/cohort sample of 3,827 individuals for 12 HNF4A single nucleotide polymorphisms (SNPs) and to combine the results with all previously published studies in a meta-analysis of P2 promoter SNPs as risk factors for type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study subjects were participants aged ≥20 years in an extensive population-based study (the Nord-Trøndelag Health Study [HUNT]) from 1995–1997 [HUNT 2]) (26). Case subjects who were GAD antibody–positive and had diabetes onset before age 40 years or before age 30 years with insulin treatment initiated during the first year of diagnosis or had continuously been on insulin treatment since the year of diagnosis were excluded due to suspected type 1 diabetes. For 459 diabetic subjects with no GAD antibody measurements, subjects with diabetes onset before age 40 years were excluded. The study groups finally consisted of 1,644 subjects with type 2 diabetes and 1,879 nondiabetic (self-reported) control subjects. The study was approved by the regional committee for research ethics and the Norwegian Data Inspectorate and performed according to the Declaration of Helsinki.

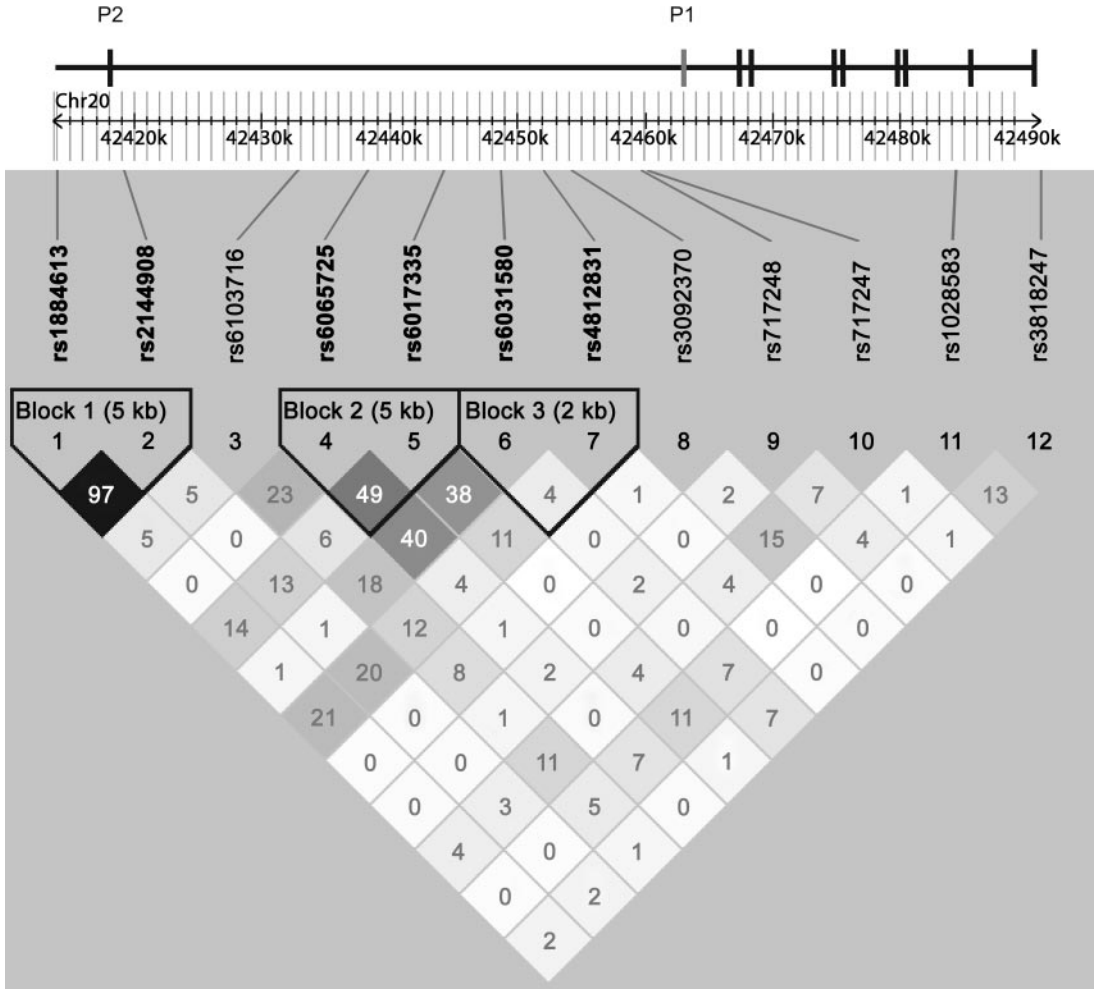

FIG. 1. LD plot across the HNF4A locus in the Norwegian population. The HNF4A coding exons and the P2 promoter are illustrated with black crossbars on the top line and the location of the P1 promoter with a gray crossbar. The twelve successfully genotyped SNPs are listed below the line. The bottom part of the figure presents an LD plot based on the r^2 measure. Each diamond represents the strength of pairwise r^2, with black indicating strong LD and logarithm of odds score. The pairwise r^2 values are written in the boxes. There are three two-marker haplotype blocks, as suggested by the Gabriel et al. method. The leftmost block contains the P2 promoter. The two rightmost SNPs located within the coding region of the gene show very little LD with the promoter region SNPs. The LD plot was produced by Haploview, version 3.2, software.

Genotyping. SNPs were genotyped according to the manufacturers' instructions using Sequenom's MassARRAY iPLEX System. Markers genotyped are depicted in Fig. 1.

Statistical methods. To examine the allelic association of each particular SNP with diabetes, we used a logistic regression model with age, sex, and BMI as cofactors, as implemented in PLINK software (http://pngu.mgh.harvard.edu/purcell/plink/). Supplementary Table 1 (available in an online appendix located at http://dx.doi.org/10.2337/db07-0513) presents the data without adjustment for the cofactors mentioned above. All SNPs examined were consistent with Hardy-Weinberg equilibrium in the control samples. Haplotype frequency estimates and haplotype comparisons were performed using Unphased software (27).

Considering a risk allele frequency of 18% and a multiplicative model, we had ~61% power to detect an odds ratio (OR) of 1.14 at the 0.05 level (Genetic Power Calculator [http://pngu.mgh.harvard.edu/~purcell/gpc/]). For the meta-analysis, we searched Medline to collect all published literature on HNF4A P2 polymorphisms and checked the reference lists of the retrieved articles. We found 12 type 2 diabetes case/control studies on the three HNF4A P2 polymorphisms rs1884613, rs1884614, and rs2144908. When needed, we contacted the corresponding authors to obtain exact genotype counts for all studies. We did not include the Japanese samples from Hara et al. (17) because detailed genotype counts for that study were unavailable. The Silander et al. (9) study was excluded from the meta-analysis since the same individuals were included in an extended study published recently by the same group (19). For the meta-analysis, we applied a random-effect model as implemented by the "metan" command in Stata (version 8.0; Stata, College Station, TX), with the estimate of heterogeneity taken from the Mantel-Haenszel model, and analyzed all data using Stata. Family studies were not included in the overall meta-analysis, but results are presented in supplementary Table 2 for comparison (as presented in publications or via personal communication). *P* values presented were not corrected for the number of tests performed.

RESULTS

Trend toward an association between SNPs near the HNF4A P2 promoter and type 2 diabetes. The demographic characteristics of the study subjects are described in Table 1. Based on reported associations in previous studies, we focused our study on the most commonly studied P2 promotor region SNPs and the region upstream of HNF4A (10 SNPs altogether). Two commonly studied SNPs within the gene were also included (Fig. 1). Genotype analysis confirmed a linkage disequilibrium (LD) pattern in the Norwegian population similar to that in other populations (including HapMap data), with a block of tight LD covering the P2 promoter region and relatively weak LD with and within the HNF4A gene (13).

The allelic association results from the Norwegian case/cohort data are summarized in Table 2 (adjusted for age, sex, and BMI) and in further detail in supplementary Table 1. There was a trend toward increased OR for the rare alleles at markers rs1884613 (OR 1.17 [95% CI 1.03–1.35])

TABLE 1
Clinical characteristics of the study samples

	Type 2 diabetic subjects	Control subjects
Samples (*n*)	1,644	1,879
Sex (male/female)	767/877	886/993
Age at diagnosis (years)	58.4 ± 15.1	—
Age at examination (years)	68.4 ± 12.1	56.3 ± 18.4
BMI (kg/m^2)	29.2 ± 4.8	26.5 ± 4.2
Serum cholesterol (mmol/l)	6.2 ± 1.3	6.1 ± 1.3
Serum triglycerides (mmol/l)	2.5 ± 1.6	1.9 ± 1.2
Serum HDL (mmol/l)	1.2 ± 0.4	1.4 ± 0.4
Random serum glucose (mmol/l)	9.6 ± 4.2	5.4 ± 1.4

Data are means ± SD unless otherwise indicated.

and rs2144908 (1.21 [1.05–1.38]), genotyped in most of the previously reported studies, and rs4812831, located 34 kb downstream of the P2 promoter (1.21 [1.02–1.44]).

Haplotypes were estimated for the three associated markers rs1884613, rs2144908 (both near the P2 promoter), and rs4812831 (supplementary Table 3). The results suggest that the at-risk P2 alleles are associated only when combined on the same haplotype with the A-allele at rs4812831 ($P = 0.02$). Similar haplotype frequency estimates were found with Haploview and PLINK software (data not shown).

Meta-analysis shows that variation in the HNF4A P2 region is associated with type 2 diabetes in Scandinavians. Although the *P* values presented would not remain significant after correction for multiple testing, our study of a Norwegian population–based sample suggests an association between SNPs near the HNF4A P2 promoter and diabetes. To more extensively assess the role of variation in the HNF4A P2 region, we therefore performed a meta-analysis on all published studies including the present data.

We found 14 PubMed-listed studies testing for association between common HNF4A variation and type 2 diabetes (8–21). The case/control studies covered 15 different samples, consisting of 27,811 subjects from various ethnic groups. Four family-based samples were also found. No common single SNP had been genotyped across all studies, but all studies included at least one of three SNPs surrounding the HNF4A P2 promoter (rs1884613, rs1884614, and rs2144908). From our own data (Fig. 1), the HapMap data, and previous publications, it is evident that rs1884613, rs1884614, and rs2144908 are virtually interchangeable ($r^2 \sim 1.0$), and, therefore, it is valid to use any of the three SNPs in an overall meta-analysis. We chose to use allele counts for the most commonly used marker, rs1884613, in all studies where it was genotyped and markers rs1884614 or rs2144908 in consecutive order for studies lacking rs1884613.

Figure 2 presents the meta-analysis plot of the common allelic OR from 12,292 type 2 diabetic case and 15,519 control subjects from all 15 samples. Nine samples showed a trend of elevated OR for the minor allele, two showed no trend, and four revealed a trend in the opposite direction. The combined OR estimate for the minor allele among case compared with control subjects was not significant (OR 1.05 [95% CI 0.98–1.12]; $P = 0.17$). However, a statistical test for homogeneity of the odds revealed evidence for heterogeneity between the studies ($P = 0.009$). We therefore restricted the analysis to Scandinavian samples only, since they are considered to share similar genetic background. In this sample of 4,000 case and 7,571 control subjects, we did not find any evidence for heterogeneity of the odds ($P = 0.85$). The results showed a significant association between type 2 diabetes and the minor allele at rs1884613 (1.14 [1.06–1.23]; $z = 3.56$, $P = 0.0004$). Furthermore, all family-based samples trended toward increased risk associated with the minor alleles (supplementary Table 2).

We also performed a Scandinavian meta-analysis on rs3818247 (located in the 3′ part of the gene), for which all Scandinavian samples were genotyped. This result was not significant ($P = 0.13$). Influence plot and funnel plot analyses did not show evidence for publication bias in any test strata (data not shown).

DISCUSSION

Here, we present data from a combined sample of 11,571 Scandinavian individuals that support a role in type 2 diabetes for common variants near the HNF4A gene. Our results highlight the power and limitations of meta-analyses in genetic association studies. On its own, the results from the Norwegian cohort were suggestive but inconclusive. By combining results from several populations with similar genetic background, we gained power to detect an association with a relatively small effect size (OR 1.14; $P =$

TABLE 2
Comparisons of allele frequencies in the Norwegian sample of 1,644 type 2 diabetic and 1,879 control subjects

Marker	Position (bp)†	Minor/major allele	Minor allele frequency		Allelic OR*	
			Case subjects	Control subjects	OR (95% CI)	*P*
rs1884613	−3925	G/C	0.198	0.181	1.17(1.03–1.35)	0.02
rs2144908	1377	A/G	0.197	0.178	1.21(1.05–1.38)	0.007
rs6103716	15290	C/A	0.339	0.338	1.03(0.92–1.16)	0.57
rs6065725	20675	A/G	0.314	0.316	0.99(0.88–1.11)	0.89
rs6017335	26485	A/G	0.486	0.467	1.06(0.96–1.18)	0.26
rs6031580	30941	A/G	0.272	0.280	0.96(0.85–1.08)	0.46
rs4812831	33920	A/G	0.113	0.097	1.21(1.02–1.44)	0.03
rs3092370	35763	A/G	0.469	0.482	0.93(0.83–1.03)	0.16
rs717248	41265	G/A	0.030	0.032	0.96(0.70–1.32)	0.81
rs717247	41444	G/A	0.301	0.313	0.93(0.83–1.05)	0.24
rs1028583	66421	T/G	0.354	0.358	0.98(0.88–1.10)	0.76
rs3818247	73140	T/G	0.330	0.347	0.92(0.82–1.03)	0.15

*Calculations based on logistic regression with age, BMI, and sex as cofactors. †Position relative to start of the HNF4A P2 promotor (according to Goldenpath: hg17; dbSP: build 123).

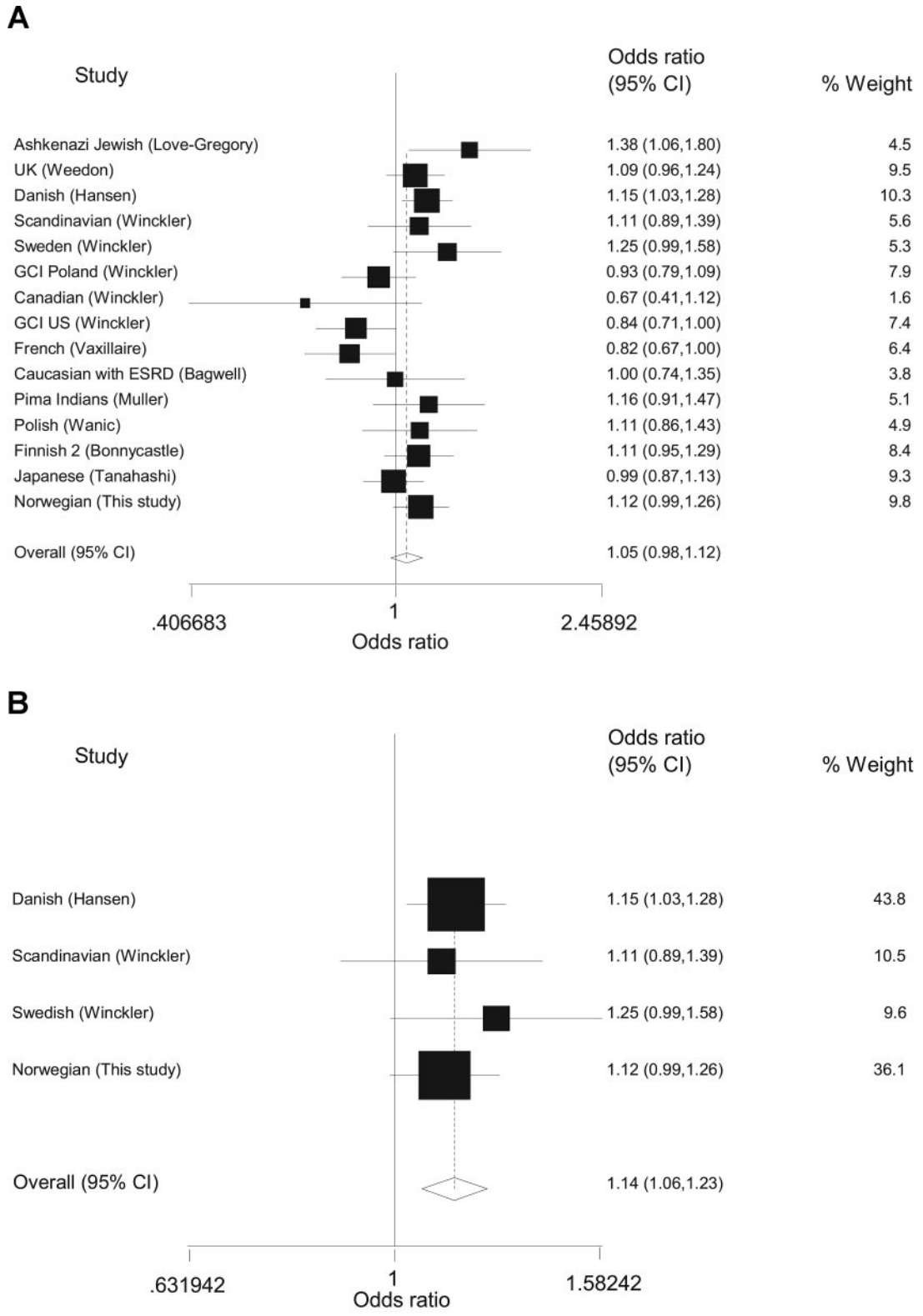

FIG. 2. Meta-analysis plot of HNF4A case/control studies. *A*: Meta-analysis plot of all case/control populations comprising 12,292 type 2 diabetic and 15,519 control subjects. Allelic OR 1.05 (95% CI 0.98–1.12), $P = 0.17$. Evidence of heterogeneity was detected between samples ($P = 0.009$). *B*: Meta-analysis plot among the 4,000 Scandinavian case and 7,571 control subjects. OR 1.14 (1.06–1.23), $P = 0.0004$ was found for the SNP rs1884613. The ORs for the pooled analyses were calculated using a random-effect model.

0.0004), which current genome-wide association studies are not powered to detect. However, in contrast to the two most consistently replicated type 2 diabetes polymorphisms of similar size effects, KCNJ11(E23K) and PPARG (P12A) (22,23), we failed to identify an overall association for the HNF4A P2 promoter SNPs in the total pooled sample. Whereas the former SNPs are probably the etiological variants themselves, there is limited evidence to

suggest that the tested HNF4A P2 promoter region SNPs have a direct biological role. Hence, if the SNPs tested are markers for an as yet not genotyped causal variant, varying patterns of LD in different populations could mirror the apparently conflicting results. Other reasons for the detected heterogeneity could possibly be different clinical ascertainment criteria between studies. However, apart from a younger mean age of diabetes onset in the French study and a higher average BMI in the U.S. Genomics Collaborative Inc. sample compared with those of other samples included in the meta-analysis, we did not find a consistent explanation.

Our study was not designed to cover all the variation in the region, since we did not have sufficient power to fine-map a locus with an effect in the range estimated from previous studies. The Winckler et al. (13) report, along with recent HapMap data, clearly illustrates that no study has managed to capture most of the extensive variation in the region. We therefore focused our tagging efforts on the region between the P2 and P1 promoters not extensively covered by previous studies. Interestingly, apart from the P2 region SNPs, we also found a similar-sized association for rs4812831, located 34 kb downstream of the P2 promoter.

Analyses of three-marker haplotypes made up of the two P2 promoter SNPs and rs3818247 suggest that the P2 promoter SNP association might be secondary to LD with a variant on the at-risk haplotype in our Norwegian sample. Although these results remain speculative until they are robustly replicated in other populations, such haplotype effects could potentially explain the conflicting results between populations. Very recently, the group reporting the Finnish association (9) published a combined analysis of their original sample and an extended sample suggesting that the most interesting region might be somewhere downstream of the P2 promoter (19). Furthermore, in the recent French whole-genome association study (28), a weak association for rs2425637, located only 5 kb downstream rs4812831 in the promoter region, was reported. Hence, there is some evidence to support a role for HNF4A promoter region variation in type 2 diabetes, but more comprehensive genotyping both upstream and downstream of the P2 promoter in homogeneous populations is warranted.

We believe that our post hoc Scandinavian stratified meta-analysis is rather conservative, since the Scandinavian population is historically and genetically homogenous (29). The allele frequencies are similar within the population (minor allele frequency range 0.203–0.185 for case subjects and 0.187–0.154 for control subjects). Nevertheless, we cannot rule out selection bias until our results have been confirmed in other samples of Scandinavian ancestry. Interestingly, support for our conclusion is found in a recent Scandinavian study of gestational diabetes mellitus (30), a phenotype likely to share some genetic components with type 2 diabetes. The Scandinavian study reported an equally sized nonsignificant trend toward increased risk (OR 1.14 [95% CI 0.96–1.37]) associated with the minor allele at marker rs2144908. Importantly, the HUNT samples were validated by genotyping known type 2 diabetes risk variants in TCF7L2 and KCNJ11. Results from both loci were very similar to estimates from other Caucasian populations (S.J., H.R., K.M., O.S., A.M., P.R.N., unpublished data).

In conclusion, there seems to be a modest but consistent association between SNPs in a haplotype block covering the P2 promoter in all Scandinavian samples tested. Our data are in agreement with results from other homogeneous populations, such as the Amish and Finnish populations, but different from other populations. This suggests that the SNPs genotyped are not the functional variants and addresses the need for further extensive studies of the HNF4A region.

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