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Association of Variants in RETN With Plasma Resistin Levels and Diabetes-Related Traits in the Framingham Offspring Study

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OBJECTIVE—The RETN gene encodes the adipokine resistin. Associations of RETN with plasma resistin levels, type 2 diabetes, and related metabolic traits have been inconsistent. Using comprehensive linkage disequilibrium mapping, we genotyped tag single nucleotide polymorphisms (SNPs) in RETN and tested associations with plasma resistin levels, risk of diabetes, and glycemic traits.

RESEARCH DESIGN AND METHODS—We examined 2,531 Framingham Offspring Study participants for resistin levels, glycemic phenotypes, and incident diabetes over 28 years of follow-up. We genotyped 21 tag SNPs that capture common (minor allele frequency >0.05) or previously reported SNPs at \( r^2 > 0.8 \) across RETN and its flanking regions. We used sex- and age-adjusted linear mixed-effects models (with/without BMI adjustment) to test additive associations of SNPs with traits, adjusted Cox proportional hazards models accounting for relatedness for incident diabetes, and generated empirical \( P \) values \((P_e)\) to control for type 1 error.

RESULTS—Four tag SNPs (rs1477341, rs4804765, rs1423096, and rs10401670) on the 3' side of RETN were strongly associated with resistin levels (all minor alleles associated with higher levels, \( P < 0.05 \) after multiple testing correction). rs14041670 was also associated with fasting plasma glucose \((P = 0.02, \text{BMI adjusted})\) and mean glucose over follow-up \((P = 0.01; \text{BMI adjusted})\). No significant association was observed for adiposity traits. On meta-analysis, the previously reported association of SNP −420C/G (rs1862513) with resistin levels remained significant \((P = 0.0009)\) but with high heterogeneity across studies \((P < 0.0001)\).

CONCLUSIONS—SNPs in the 3' region of RETN are associated with resistin levels, and one of them is also associated with glucose levels, although replication is needed. Diabetes 58: 750–756, 2009

A dipose tissue is now recognized as a prolific endocrine organ. In the past few years, several proteins, called adipokines, produced by adipose tissue have been discovered (1). In the process of unraveling the link between obesity and development of diabetes, various adipokines have been suspected to contribute to the pathogenesis of insulin resistance. Resistin is a 12.5-kDa polypeptide that belongs to the resistin-like molecule family of cysteine-rich proteins (2). In murine models, it is produced mainly by adipocytes, and it has been proposed to link obesity with diabetes (3). In humans, adipocytes seem to contribute to only a small fraction of the resistin production (4), and macrophages are considered the predominant source of circulating resistin (5,6). Adipose tissue of obese individuals is characterized by increased infiltration by macrophages (7), which have been proposed to contribute to the proinflammatory state that is characteristic of insulin resistance. Some population studies (8–10) have shown that resistin levels are indeed associated with metabolic risk factors and insulin resistance, suggesting that resistin may play an important role in the pathophysiology of diabetes.

The gene encoding resistin (RETN) is located on chromosome 19p13. Genetic variants in RETN have been examined by many groups, and it is estimated that up to 70% of the variation in circulating resistin levels can be explained by genetic factors (11). Several single nucleotide polymorphisms (SNPs) have been associated with resistin levels (9,12–14). However, associations between RETN and BMI or other measures of adiposity have shown very inconsistent results (13,15–21). Polymorphisms in RETN also have been associated with indexes of insulin resistance in some reports (21,22), but lack of replication and null associations (13,19) have raised questions regarding the robustness of these findings. Moreover, most of the analyses examining common variation in RETN and risk of type 2 diabetes have been negative (9,13,16,23–27), with nominal associations only emerging in subanalyses (28,29). The inconsistencies in those studies might be due to low power afforded by small samples or poor coverage of the gene and its flanking sequences.

To address those limitations, we conducted fine mapping of RETN to test if any of the SNPs in or around the gene are associated with resistin levels, diabetes incidence, or glycemic and obesity traits in the Framingham Offspring Study, a large representative community sample. Our goal was to confirm or refute previous reports of association and possibly uncover novel SNP associations.
using comprehensive tag SNP linkage disequilibrium (LD) mapping.

**RESEARCH DESIGN AND METHODS**

The Framingham Offspring Study is a large community-based prospective cohort study designed to investigate cardiovascular disease risk factors. This analysis includes 2,531 participants (including 285 pedigrees and 1,445 unrelated individuals) who were followed over 28 years on a periodic basis (from exam 1 [1971–74] up to exam 7 [1998–2001]). Each exam cycle included anthropometric measurements, a physical exam, and blood samples related to cardiovascular risk factors. The study was approved by the institutional review boards of Massachusetts General Hospital, Boston University, and the Massachusetts Institute of Technology; written informed consent, including consent for genetic analyses, was obtained from all study participants.

Participants underwent standardized procedures for all anthropometric measurements (weight, height, and waist circumference [at the umbilicus]). BMI was calculated using measured weight (kg) and the square of height (m²). Diabetes was defined by 2003 American Diabetes Association clinical criteria, where case subjects were defined as those who used oral hypoglycemic or insulin therapy at any exam or had a fasting plasma glucose (FPG) ≥7.0 mmol/l at the index exam and FPG ≥7.0 mmol/l at least one prior exam. Fasting resistin levels were measured once at exam 7. For diabetes, we were primarily interested in outcomes and metabolic traits measured over follow-up (time-averaged mean FPG over follow-up [exams 3–7; chosen for measurement stability]), and at the last follow-up (exam 7) including FPG; fasting insulin; homeostasis model assessment of insulin resistance (HOMA-IR) (30); A1C levels; the Gutt 0- to 120-min insulin sensitivity index (31), conducted in a subsample; BMI; waist circumference; visceral adipose tissue (VAT); and subcutaneous adipose tissue (SAT), measured by computed tomography (the latter two conducted in a subsample) (32). FPG was measured immediately with a hexokinase reagent kit (A-gent glucose test; Abott, South Pasadena, CA), and A1C was measured by high-performance liquid chromatography (33). Other plasma analyses were frozen at −80°C until assay: fasting plasma insulin was measured with a human-specific insulin assay (R&D Systems, Minneapolis, MN). Intrassay coefficients of variation were <3% for glucose, 6.1% for insulin, and 0.0% for resistin.

**SNP selection.** We downloaded SNPs from the region of interest (20 kb on the 5’ end plus 10 kb on the 3’ end of RETN) from the phase 2 HapMap database (www.hapmap.org) in January 2006. Due to sparse coverage of the region, we then mined the dbSNP database to choose additional SNPs across the region so as to ensure adequate coverage. We genotyped a set of 58 SNPs in the HapMap European-descent CEU plate, and 27 of them passed quality control (genotyping success rate >95% for all the LD-tagging SNPs (average 98.4%). Consensus rates on a maximally unrelated subset of individuals. The genotyping success rate was >95% for all the LD-tagging SNPs (average 98.4%). Consensus rates on a subset of 254 duplicate individuals reached 99.6%. All the SNPs met HWE (P > 0.001).

**Statistical analysis.** The quantitative traits were regressed against covariates in order to produce Studentized residuals, which were used as the dependent variable in the subsequent genetic models. Two covariate adjustment schemes were used: the first with sex, age, and age² adjustment and the second with BMI added to age and sex to examine the strength of the SNP associations when adjusted for overall adiposity. For resistin levels and glucose-related traits (mean glucose exam 3–7, FPG, fasting insulin, HOMA-IR, A1C, and Gutt 0- to 120-min insulin sensitivity index), we excluded participants with diabetes.

The association between each trait residual and each SNP was assessed using a linear mixed-effects (LME) model implemented in SOLAR (34) to account for the within-family correlation of the trait. Each SNP was included in a model as a fixed effect with additive coding. The models included random effects to account for the covariance between family members; the covariance structure was determined by the degree of relatedness between each relative pair.

To assess SNP associations with type 2 diabetes, we used Cox proportional hazards survival analysis, with diabetes as the outcome and the survival time as the age at the exam at which diabetes was first determined. The survival time of individuals without diabetes was the age at their last exam. The model was implemented with the survival package in R (35), with the same adjustments as in the LME models, with covariates taken at the first exam. Trait correlation among siblings was modeled with a frailty term in the survival model (36).

**RESULTS**

Characteristics of the participants genotyped in the Framingham Offspring Study are presented in Table 1. Overall, 2,531 participants were included in this analysis, 53% were women, and 10% had a diagnosis of diabetes during the 28 years of follow-up. Mean resistin levels measured at exam 7 were 14.1 ± 7.2 ng/dl. The heritability of resistin levels in the Framingham Offspring Study was estimated to be 35% (adjusted for sex, age, age², and BMI). Other metabolic traits measured at exam 7 and the mean glucose levels over exams 3–7 are presented in Table 1. Resistin levels were modestly correlated with BMI (r = 0.16), waist circumference (r = 0.18), VAT (r = 0.15), and SAT (r = 0.13; all correlations age and sex adjusted; all P values < 0.001).

With 21 tag SNPs selected by a tagging approach that set an r² > 0.8, we were able to capture 96% (26 of 27 SNPs) that passed quality control in the CEU plates) of SNPs in the region of interest at an r² > 0.8 and 100% at an r² > 0.7 (see supplementary Table 1 for details regarding coverage [available at http://diabetes.diabetesjournals.org/cgi/content/full/db08-1339/DC1]). Average distance between tag SNPs was 1.5 kb. The tag SNPs are shown in Table 2, with their tag SNPs selected by a tagging approach that set an r² > 0.8ments (available at http://diabetes.diabetesjournals.org/cgi/content/full/db08-1339/DC1)]. Average distance between tag SNPs was 1.5 kb. The tag SNPs are shown in Table 2, with their tag SNPs selected by a tagging approach that set an r² > 0.8.
The 3' end of RETN and was fully captured by our tagging approach, with our last downstream SNP being on the 3' side of MCEMP1. The LD map for the tagging SNPs in the Framingham population is shown in supplementary Fig. 2.

Circulating resistin levels were measured in 1,877 geno-

typed participants without diabetes. The associations for each tag SNP with resistin levels is illustrated in Fig. 1. The mean resistin level for each genotype and the nominal (uncorrected) and empirical (corrected for the number of SNPs) P values for each tag SNP are presented in Table 3. We found that the minor alleles at four tag SNPs (rs1477341, rs4804765, rs1423096, and rs10401670) in the

FIG. 1. Negative log base 10 of the P value for genetic associations for resistin levels under the additive model (left Y-axis), graphed versus SNPs in the RETN region arranged by chromosomal position (X-axis). The continuous line marked by the right Y-axis indicates the recombination rate. The RETN and C19orf59 (also known as mast cell–expressed membrane protein 1 [MCEMP1]) genes are shown by the horizontal arrows at the bottom of the plot. * traits adjusted for sex and age; †, additional adjustment for BMI.

| SNP identification | Position (NCBI 35) | Relation to the RETN gene | Other name | Call rate | HWE P | Strand Major allele | Minor allele | MAF |
|--------------------|-------------------|---------------------------|------------|-----------|--------|-------------------|--------------|-----|
| rs794070           | 7620814           | 5' of promoter            |            | 0.97      | 0.32   | +                 | T            | 0.21|
| rs11883223         | 7628636           | 5' of promoter            |            | 0.99      | 0.11   | −                 | G            | 0.17|
| rs2081075          | 7629461           | 5' of promoter            |            | 0.97      | 0.28   | +                 | G            | 0.29|
| rs10418380         | 7630540           | 5' of promoter            |            | 0.95      | 0.76   | +                 | A            | 0.32|
| rs10413807         | 7630628           | 5' of promoter            |            | 0.99      | 0.69   | −                 | G            | 0.21|
| rs12460483         | 7636594           | 5' of promoter            |            | 1.00      | 0.71   | −                 | G            | 0.12|
| rs12450044         | 7638406           | Promoter                  |            | 0.99      | 0.15   | −                 | C            | 0.14|
| rs7408174          | 7638955           | Promoter                  |            | 0.97      | 0.54   | −                 | T            | 0.31|
| rs1862513          | 7639793           | Promoter                  | −420C/G    | 1.00      | 0.57   | −                 | G            | 0.29|
| rs3219177          | 7640369           | Intron 2                  | IVS2 + 30C/T| 0.99      | 0.35   | −                 | C            | 0.21|
| rs3745367          | 7640511           | Intron 2                  | IVS2 + 181G/A| 0.99   | 0.67   | +                 | G            | 0.24|
| rs3219178          | 7640951           | Intron 3                  | IVS3 + 167C/G| 0.97   | 1.00   | +                 | C            | 0.42|
| rs10422065         | 7641089           | Intron 3                  |            | 0.99      | 1.00   | −                 | C            | 0.14|
| rs3745368          | 7641297           | 3' UTR                    | 3' UTR + 62G/A| 0.98   | 1.00   | −                 | G            | 0.002|
| rs3745369          | 7641475           | 3' of 3' UTR              |            | 0.99      | 0.80   | +                 | G            | 0.50|
| rs1477341          | 7642769           | 3' of 3' UTR              |            | 0.99      | 0.87   | −                 | A            | 0.44|
| rs4804765          | 7643840           | 3' of 3' UTR              |            | 0.98      | 0.64   | −                 | G            | 0.33|
| rs1423096          | 7645177           | 3' of 3' UTR              |            | 0.99      | 0.53   | +                 | G            | 0.09|
| rs10401670         | 7648802           | 3' of 3' UTR*             |            | 0.98      | 0.75   | −                 | C            | 0.43|
| rs11882592         | 7649975           | 3' of 3' UTR*             |            | 0.98      | 0.07   | −                 | C            | 0.18|
| rs10411016         | 7651043           | 3' of 3' UTR              |            | 0.98      | 0.79   | −                 | T            | 0.49|

* Located in chromosome 19 open reading frame 59 (C19orf59), also known as mast cell–expressed membrane protein 1 (MCEMP1).
3’ region of RETN were associated with higher resistin levels (all \( P < 0.05 \)). Since some of those SNPs were in moderate LD in the Framingham cohort (see supplementary Table 6 for specific D’ and \( r^2 \) values), we conducted multiple SNPs models. When models were examined with various combinations of these SNPs, rs4804765 and rs1423096 had independent associations with resistin levels and rs4804765 explained the association of the two other SNPs (rs1477341 and rs10401670). The best-fitting model included rs4804765 and rs1423096 and explained 1.5% of the variance in resistin levels.

One of these SNPs in the 3’ region, rs10401670, was also associated with mean glucose over follow-up (\( P_e = 0.02 \), after BMI adjustment \( P_e = 0.01 \)) and FPG at exam 7 (\( P_e = 0.10 \), after BMI adjustment \( P_e = 0.02 \)); its minor T allele was associated with higher glucose levels, concordant with a potential effect of its association with higher resistin levels. Two other SNPs showed associations with FPG at exam 7 (rs1423096, \( P_e = 0.049 \); and rs10413807, \( P_e = 0.02 \)) but did not remain significant after adjustment for BMI. No other associations were observed in the glycemic or adiposity traits (\( P_e > 0.05 \)) (see supplemental Table 3 for details).

Diabetes incidence was analyzed over the 28 years of follow-up. None of the SNPs offered convincing association with diabetes survival (all \( P \) values \( \geq 0.05 \)) (see supplementary Table 2). Because a previous study reported that IVS2 +181G/A was associated with diabetes when an interaction with BMI was added to the model (28), we conducted diabetes incidence analysis with a BMI interaction term included in the model for this SNP, but even with this more refined replication attempt we did not detect a significant association. We also explored the effect of BMI on the association between rs10401670 and diabetes incidence: adding a BMI \( \times \) rs10401670 term to the LME model revealed a significant interaction (\( P = 0.02 \)), and the \( P \) value for the main effect for rs10401670 reached nominal significance (\( P = 0.01 \)).

The promoter SNP −420C/G (rs1862513) has been investigated by many groups, some examining its association with resistin levels (9,11,13,14,38) and a few with diabetes (29,39) or adiposity (15–18). The analysis of −420C/G (rs1862513) in the Framingham Offspring Study did not show an association with any of the traits measured, including resistin levels. To help attempt to discriminate low power from a true null association, we conducted a meta-analysis of the association of SNP −420C/G (rs1862513) with resistin levels. The details of each population included in the meta-analysis (9,11,13,14,38) and our results are presented in Table 4. The minor C allele seemed to be associated with higher resistin levels; this effect was mainly driven by the largest Japanese study. Heterogeneity was highly significant (\( P < 0.0001 \)). The divergence between studies could be due to differences in ethnic background, age, sex distribution, diabetes status, or other characteristics. When we removed the diabetic subjects from the analysis, heterogeneity was still present.

### DISCUSSION

We have demonstrated that circulating resistin levels are associated with SNPs in the 3’ region of RETN (rs1477341, rs4804765, rs1423096, and rs10401670) in a large, representative community sample. Among the four SNPs that were associated with resistin levels, rs4804765 and rs1423096 showed independent association according to multiple SNP models. One of those, rs10401670, was also associated with mean fasting glucose and FPG at exam 7. Moreover, rs10401670 was nominally associated with diabetes incidence when including a BMI interaction term in the model. No SNP showed significant association with adiposity traits.

### Association with resistin and glucose levels.

Previous reports of association of SNPs within the RETN gene region targeted specific known SNPs and thus achieved
only partial coverage; our extensive mapping in and around the RETN gene in a large sample has allowed us to reveal novel associations. The four SNPs associated with resistin levels are all located in the 3' region, downstream of RETN. SNPs outside of the coding sequence can influence transcription or mRNA stability and thus affect transcript levels. We tried to explore the functional role of those SNPs located in the 3' region of RETN by mining publicly available or private genome-wide expression quantitative trait loci datasets, including one obtained from subcutaneous and omental adipose tissue (E.E. Schadt, personal communication). Unfortunately, the fixed marker arrays utilized in these studies do not include our SNPs of interest or any SNPs in moderate to strong LD fixed marker arrays utilized in these studies do not include (Schadt, personal communication). Unfortunately, the

The most commonly reported associations with BMI (r² = 0.58) with rs3219175 (also in the promoter region), which is monomorphic in the HapMap CEU population.

**Diabetes incidence.** We did not find a significant association of any SNP with diabetes incidence, although our sample of incident case subjects was small (n = 244). This is concordant with most of the previous literature (9,13,16,23–27). Our best P value for association with diabetes survival (age and sex adjusted) was seen with SNP rs3745367 (aka IVS2 +181G/A; minor allele A increasing the risk hazard ratio to 1.25 [1.00–1.56]), but in the setting of multiple hypothesis, testing this nominal P value (P = 0.05) cannot convincingly be considered significant. Other reports testing the association between +181G/A and diabetes have been mostly negative (23,25,26); one report showed a positive association in the same direction as our results when including a BMI-gene interaction term in the model (28). Adding a BMI × genotype interaction term to our diabetes incidence model for SNP rs3745367 did not reveal a significant association. In contrast, adding a BMI × genotype interaction term to the model with rs10401670 revealed significant interaction, increasing the significance of the (nominal) P value of its main effect in predicting diabetes incidence. Since we show that several RETN SNPs are associated with circulating resistin levels and that resistin levels are associated with insulin resistance (10), it is possible that a larger sample size might have produced an association with diabetes incidence. Indeed, for a SNP such as rs3745367 of MAF = 0.24 and effect size = 1.25, we had <40% power to detect a significant association with diabetes incidence (see supplemental Table 4). In examining the publicly available meta-analysis of genome-wide association datasets DIAGRAM (http://www.well.ox.ac.uk/DIAGRAM/meta.html), only two SNPs in the region of interest were available (rs11883223, rs7408174) and neither one was associated with diabetes. Unfortunately, those two SNPs have very low LD with rs3745367 (r²<0.10) or the other SNPs associated with resistin levels in our findings (all r²<0.02).

**Adiposity traits.** Reports of RETN associations with BMI or other measures of adiposity in populations of European descent have been inconsistent in the literature (15–20). Some have reported no association (19), while others did so only in subgroup analyses (15–17). The most commonly
investigated variant (−420G allele) has been the subject of several conflicting reports (15–19). Our results are consistent with the notion that RETN is not associated with adiposity as assessed by BMI, waist circumference, or body fat composition measured by computed tomography scan. The correlation of adiposity measurements with resistin levels, but not RETN genetic variation, suggests that fat accumulation influences resistin levels, but RETN variants are not likely to cause weight gain and obesity.

Strengths and limitations. Our study represents a significant advance in its comprehensive coverage of RETN and its flanking regions, moderate to high statistical power with a large number of participants in a general community sample including a family-based component, and standardized phenotyping of anthropometric measurements, diabetes, and metabolic traits over 28 years of prospective follow-up. Nevertheless, this study has a few limitations. Power for diabetes incidence was limited (see supplemental Table 4), especially given our expectation of small effect sizes (hazard ratio <1.4). We had adequate power to detect a small proportion of the variance in quantitative traits explained by common SNPs (see supplementary Table 5); for example, we had 85% power to detect 1% of the variance explained (assuming $\alpha = 0.0001$ and an MAF $\geq 0.05$), but we may have missed smaller effect sizes in our genotype-phenotype correlations for the resistin levels or glycemic traits. Novel associations need independent replication before we can confidently claim they represent true findings. Currently, studies with large numbers of resistin levels measurements and custom genotyping for comprehensive coverage are uncommon. Also, our findings may need to be refined in populations with LD patterns that differ from those of European descent. Finally, genetic associations do not prove that the SNP is the direct cause of the defect; further fine-mapping and functional studies are needed to identify true causal variants.

Conclusion. We have found that SNPs in the 3’ region of RETN are associated with circulating resistin levels in the Framingham Offspring Study. One variant (rs10041670) located in the 3’ region of RETN, but in the second intron of MCEMP1, is associated with both resistin levels and fasting glucose. rs10401670 is also nominally associated with diabetes incidence once a putative interaction with BMI is taken into account. Functional studies are needed to investigate the role of MCEMP1 and to test whether these variants influence RETN expression, resistin production, and/or glucose regulation in appropriate tissues. Our new findings need to be replicated in independent data before we can claim that these associations are real: it appears that custom genotyping will be required.

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