

Plasma Resistin Is Associated With Single Nucleotide Polymorphisms of a Possible Resistin Receptor, the Decorin Gene, in the General Japanese Population

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Resistin is an adipokine secreted from adipocytes in mice. We previously reported that a single nucleotide polymorphism (SNP) -420 (rs1862513) in the human resistin gene (*RETN*), is correlated with plasma resistin. Decorin is a multifunctional proteoglycan, and its isoform, lacking 14 amino acids from the N terminal region of mature core decorin, recently was identified as a resistin receptor in mice. To examine whether SNPs in the vicinity of the human decorin gene (*DCN*) are associated with plasma resistin, we cross-sectionally analyzed six tag SNPs selected around *DCN* in the same linkage disequilibrium block in 2,078 community-dwelling Japanese subjects. Plasma resistin was associated with the rs7139228, rs7956537, rs516115, and rs3138167 genotypes in *DCN*. A multiple regression analysis revealed that the genotype of rs7308752 (G/G) or rs516115 (C/C) was associated with decreased plasma resistin after adjusted for age, sex, BMI, and the *RETN* SNP rs1862513. The effect of rs7139228 and rs1862513 seemed to be additive without synergistic interaction. Therefore, plasma resistin was associated with some tag SNPs around *DCN* in the general Japanese population. The possibility that human decorin is a human resistin receptor should be pursued. *Diabetes* 62:649–652, 2013

Insulin resistance is a feature of type 2 diabetes (T2DM). Resistin, which antagonizes insulin action, is an adipokine secreted from adipocytes in mice (1,2). The overexpression of the resistin gene (*RETN*) in the liver causes insulin resistance via elevated plasma levels of resistin in mice (3), whereas mice lacking *RETN* show decreased fasting plasma glucose (4). Serum resistin is increased in obese diabetic mice. The relationship between serum resistin and insulin resistance, T2DM, or adiposity in humans is controversial (5). Some studies found no changes in circulating resistin in obesity, insulin resistance, or T2DM, but others reported a significant

relationship between circulating resistin and these conditions (6,7). In humans, resistin has been reported to be expressed mainly in macrophages and monocytes.

We previously reported that the G/G genotype of a single nucleotide polymorphism (SNP) at -420 (rs1862513), which is located in the promoter region of human *RETN*, was associated with T2DM susceptibility (8). In the general Japanese population, subjects with the G/G genotype of rs1862513 had the highest plasma resistin, followed by those with the C/G and C/C genotypes (9). Rs1862513 explains ~26% of the total variance in plasma resistin. The G/G genotype of rs1862513 in *RETN* increases T2DM susceptibility by enhancing its promoter activity (8–10). At SNP -358 (rs3219175), A is required for G at rs1862513 to confer the highest plasma resistin in the general Japanese population (11). These SNPs in the promoter region of *RETN* could affect plasma resistin as *cis* factors.

Decorin is an extracellular matrix protein belonging to a family of small leucine-rich proteoglycans. The core decorin protein is attached to a dermatan or chondroitin glycosaminoglycan chain (12). Decorin is a component of connective tissue that binds to type I collagen and affects matrix assembly. Furthermore, decorin has been shown to bind transforming growth factor- β , epidermal growth factor, and the insulin-like growth factor-1 receptor (13,14). The human decorin gene (*DCN*) was mapped to 12q23, spans more than 38 kb, and contains 8 exons with large introns (15). A fragment of decorin, produced by proteolytic cleavage, lacking the glycosaminoglycan attachment site, and therefore devoid of carbohydrate chains, recently was identified as a receptor for resistin in mice (16). If decorin or its isoform is also a receptor for resistin in humans, polymorphisms of *DCN* could affect plasma resistin.

In view of this, to determine the association between *DCN* SNPs and circulating resistin, we cross-sectionally analyzed 2,078 Japanese subjects. Plasma resistin was associated with tag SNPs in the vicinity of *DCN*.

RESEARCH DESIGN AND METHODS

Subjects. In this cross-sectional study, 2,078 community-dwelling Japanese subjects were recruited during a community-based annual medical check-up. We previously analyzed rs1862513 in *RETN* and plasma resistin in these subjects (9). The clinical characteristics of the subjects are shown in Table 1. The study was approved by the ethics committee of the Ehime University Graduate School of Medicine, and informed consent was obtained from all subjects.

SNP typing. We selected six SNPs—rs7139228, rs7956537, rs7308752, rs516115, rs3138167, and rs545666—for genotyping as tag SNPs in the 10 kb region around *DCN*, using HapMap2 Rel24, CHB+JPT. These SNPs were analyzed by a TaqMan probe assay (Applied Biosystems Co., Ltd., Foster City, CA)

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TABLE 1
Characteristics of the population studied (n = 2,078)

Characteristics	
Sex (men/women), n	914/1,164
Age (years)	62 ± 13
BMI (kg/m ²)	23.4 ± 3.2
Systolic blood pressure (mmHg)	139 ± 22
Diastolic blood pressure (mmHg)	82 ± 12
Total cholesterol (mg/dL)	203 ± 35
Glucose (mg/dL)	98 ± 21
Insulin (μU/mL)*	6.7 ± 5.0
HOMA-IR‡	1.6 ± 1.4
Resistin (ng/mL)	11.5 ± 6.6
Decorin (ng/mL)†	6.84 ± 2.11

Values are means ± SD unless otherwise indicated. *Of the total 2,078 subjects, 2,017 had immunoreactive insulin measured. †Of the total 2,078 subjects, 2,074 had decorin measured. ‡HOMA-IR (homeostasis model assessment insulin resistance index) was calculated as glucose (mg/dL) × insulin (μU/mL) ÷ 405; n = 1,875.

using commercially available primers and probes purchased from the Assay-on-Demand system. The genotype call rates were 99.8 (rs7139228), 99.5 (rs7956537), 99.7 (rs7308752), 99.7 (rs516115), 99.6 (rs3138167), and 99.7% (rs138167). Linkage disequilibrium (LD) coefficients were calculated using the Haploview software program (17).

Measurement of plasma resistin and decorin. Fasting plasma resistin was measured using a human resistin ELISA kit (LINCO Research Inc., St. Charles, MO), according to the manufacturer's recommended protocol. The assay was linear for concentrations below 0.16 ng/mL. Inter- and intra-assay coefficients of variation were 6.9 and 1.7% (low levels) and 7.2 and 8.1% (high levels), respectively. Fasting plasma decorin values were measured using a human decorin ELISA kit (R&D Systems, Inc., Minneapolis, MN), according to the manufacturer's recommended protocol with minor modification. The inter- and intra-assay coefficients of variation were 14.9 and 9.1%, respectively.

Statistical analysis. The mean values for plasma resistin among the genotypes were assessed by ANOVA. To assess the isolated effects of SNPs in *DCN* and rs1862513 on plasma resistin, multiple regression analyses were performed using these SNPs as independent variables (adjusted for age, sex, and BMI) and plasma resistin as a dependent variable. To assess the interaction between each SNP in *DCN* and rs1862513 in *RETN*, multiple regression analyses were performed involving plasma resistin as a dependent variable, and each of the SNPs in *DCN*, rs1862513, their interactions, and adjustments for age, sex, and BMI were included as independent variables. We performed the analysis by comparing major alleles (A) and minor alleles (B) of SNPs in *DCN*, where AA = 0, AB = 1, and BB = 2. The rs1862513 genotype, C/C, C/G, and G/G were denoted by two dummy variables (c1, c2) and set as (0, 0), (1, 0), and (0, 1), respectively. A multiple testing correction was performed using a Benjamini-Hochberg correction with false discovery rate (FDR) set to 0.05 (18) in ANOVA and multiple regression analysis. The interaction between the rs1862513 genotype (C/C, C/G, and G/G) and rs7139228 (G/G, G/A, and A/A) in *DCN* on plasma resistin was assessed by ANCOVA. All analyses were performed with the JMP 7.0 software program (SAS Institute, Cary, NC). Null hypotheses were rejected at a level of significance of *P* < 0.05.

RESULTS

The SNPs rs7139228, rs7956537, rs516115, and rs3138167 in *DCN* were associated with plasma resistin in the general Japanese population. To determine whether plasma resistin is associated with SNPs in *DCN* in the general Japanese population, we examined the relationship between plasma resistin and genotypes of the six selected tag SNPs. Based on a confidence interval analysis, these six SNPs analyzed were in the same LD block (Fig. 1). Plasma resistin was associated with the following genotypes (Table 2): rs7139228 (GG, 11.7 ± 6.7, GA, 10.4 ± 5.5, and AA, 9.2 ± 3.5 ng/mL; *P* = 0.015), rs7956537 (TT, 11.7 ± 6.7, TG, 10.4 ± 5.5, and GG, 9.4 ± 3.4 ng/mL; *P* = 0.020), rs516115 (TT, 12.0 ± 7.1, TC, 11.1 ± 6.3, and CC, 11.0 ± 5.8 ng/mL; *P* = 0.010), and rs3138167

(CC, 11.8 ± 6.9, CT, 10.8 ± 5.8, and TT, 10.6 ± 6.8 ng/mL; *P* = 0.006). After multiple test correction using the Benjamini-Hochberg correction with the FDR set to 0.05, rs7139228, rs516115, rs7956537, and rs3138167 remained significant for association with plasma resistin.

The SNPs rs7308752 and rs516115 in *DCN* were associated with plasma resistin independent of age, sex, BMI, and rs1862513 in *RETN*. To examine isolated effects of the genotypes of *DCN* on plasma resistin, a multiple regression analysis was performed using plasma resistin as a dependent variable and the genotypes of these SNPs, with adjustments for age, sex, BMI, and rs1862513 as independent variables. The rs7139228 (A/A), rs7308752 (G/G), or rs516115 (C/C) genotypes were inversely associated with plasma resistin (unstandardized regression coefficient (β) = -0.76, *P* = 0.040; β = -0.50, *P* = 0.016; and β = -0.47, *P* = 0.011, respectively) (Table 2). After multiple test correction using the Benjamini-Hochberg correction with the FDR set to 0.05, rs516115 and rs7308752 remained significant for association with plasma resistin. When the FDR was set to 0.1, rs7139228 was associated with plasma resistin.

We next examined the effect of a combination of rs7139228 (GG vs. GA+AA) and rs1862513 on plasma resistin. Of the SNPs analyzed, rs7139228 was chosen because it seemed to be most strongly associated with plasma resistin (β = -0.76). Plasma resistin seemed to be highest in subjects with the G/G genotype of rs7139228 and G/G genotype of rs1862513 (Fig. 2). The effect of the two SNPs seemed to be additive, although no synergistic interaction was observed (*P* = 0.308). To assess the interaction between rs1862513 and each of the six SNPs in

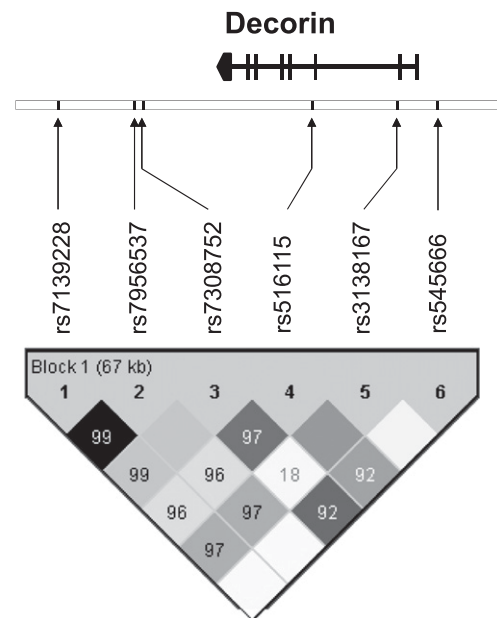


FIG. 1. The six tag SNPs around *DCN* analyzed were in the same LD and were genotyped in 2,078 subjects in the general Japanese population. LD between each pair of these SNPs were analyzed using Haploview software (17). The LD block consisting of these six SNPs was defined by the confidence interval analysis. Each square represents a pairwise value of *D'*, with the standard gradation (black box indicates logarithm of odds (LOD) ≥ 2 and *D'* = 1; boxes with no number indicate LOD < 2 and *D'* < 1; white boxes indicate LOD < 2 and *D'* < 1; and gray boxes indicate LOD ≥ 2 and *D'* < 1). Numbers in the shaded squares are the *r*² values between each pair of SNPs. Two SNPs are located in the intron of *DCN*, and four SNPs are located in the intergenic region of *DCN*.

TABLE 2

Associations between the decorin SNPs and plasma resistin in the general Japanese population SNP

Position	Allele (major/minor)	Genotype frequency	Plasma resistin (ng/mL)			P (ANOVA)	Regression analysis				
			AA	AB	BB		Coded allele (= B)	β	SE	P	
rs7139228	191513311	G/A	1,842/221/10	11.7 \pm 6.7	10.4 \pm 5.5	9.2 \pm 3.5	0.015	A	-0.76	0.37	0.040
rs7956537	91526402	T/G	1,841/221/11	11.7 \pm 6.7	10.4 \pm 5.5	9.4 \pm 3.4	0.020	G	-0.69	0.37	0.062
rs7308752	91527181	A/G	1,261/698/111	11.7 \pm 6.9	11.1 \pm 6.2	11.2 \pm 5.5	0.130	G	-0.50	0.21	0.016
rs516115	91557292	T/C	965/872/239	12.0 \pm 7.1	11.1 \pm 6.3	11.0 \pm 5.8	0.010	C	-0.47	0.18	0.011
rs3138167	91572415	C/T	1,470/534/69	11.8 \pm 6.9	10.8 \pm 5.8	10.6 \pm 6.8	0.006	T	-0.36	0.23	0.123
rs545666	91580359	T/C	1,425/589/54	11.5 \pm 6.8	11.4 \pm 6.3	12.2 \pm 6.0	0.613	C	-0.27	0.24	0.260

The data are presented as mean \pm SD. ANOVA was used for statistical analysis. Multiple regression analysis involving plasma resistin (nanograms per milliliter) as a dependent variable, with age, sex (male = 0, female = 1), BMI, and genotypes of *DCN* and *RETN* SNP-420 as independent variables, was performed as described in RESEARCH DESIGN AND METHODS. β , unstandardized regression coefficient of plasma resistin. Boldface indicates statistical significance. SE, standard error.

DCN, multiple regression analyses were performed involving plasma resistin as a dependent variable and rs1862513, the SNPs in *DCN*, their interactions, and adjustments for age, sex, and BMI as independent variables. The interactions between rs1862513 and each of the six SNPs in *DCN* were not found after multiple test correction using the Benjamini-Hochberg correction (data not shown). Therefore, the rs7308752 and rs516115 genotypes in *DCN* were associated with plasma resistin independent of age, sex, BMI, and rs1862513 in *RETN*.

The six SNPs in *DCN* were not associated with plasma decorin in the general Japanese population. To determine whether plasma decorin is associated with SNPs in *DCN* in the general Japanese population, we examined the relationship between plasma decorin and genotypes of the six selected tag SNPs in 2,074 subjects. Plasma decorin was not associated with each genotype of the six SNPs in ANOVA and multiple regression analysis after multiple test corrections (Supplementary Table).

DISCUSSION

In this study involving 2,078 subjects from the general Japanese population, plasma resistin was associated with four tag SNPs located in the vicinity of *DCN* (rs7139228, rs79566402, rs516115, and rs3138617) in the same LD block. A multiple regression analysis adjusted for age, sex, and BMI indicated that plasma resistin was associated with two tag SNPs (rs7308752 and rs516115) independent of rs1862513. No synergistic interaction was found between the SNPs around *DCN* and rs1862513.

Some of the tag SNPs around *DCN* were associated with plasma resistin in the general Japanese population. Although the genotype of rs1862513 is tightly associated with plasma resistin, the effect of the SNPs around *DCN* on plasma resistin was independent of rs1862513. We previously reported that plasma resistin also is associated with T2DM susceptibility SNPs, namely, *THADA* (rs7578597) and *PPARG* Pro12Ala (rs1801282) via a *trans*-acting effect (19,20). Plasma resistin is associated with rs1862513 and rs3219175, both of which are located in the promoter region of *RETN*, via a *cis*-acting effect (11,20). Plasma resistin seems to be regulated by *cis*- and *trans*-acting SNPs, which merits further investigation as an acceptable model for protein quantitative trait locus.

It has been suggested that the relevance of resistin in humans could be different from that in mice. Human resistin is expressed predominantly in monocytes and macrophages, and expression in adipose tissue is derived from inflammatory cells (21). It has been shown that resistin induces the production of inflammatory cytokines in human macrophages and that inflammatory stimuli induce expression of the resistin gene (22). Mice with humanized resistin, in which human resistin is expressed in macrophages, show adipose tissue inflammation and insulin resistance (23). Inflammation is now increasingly recognized to be involved in the pathogenesis of insulin resistance and T2DM, and human resistin could link inflammation and insulin resistance.

Decorin is recognized as a secreted multifunctional proteoglycan involved in cell adhesion, migration, and proliferation. Decorin also binds to C1q as a regulator, resulting in the regulation of inflammatory responses. Decorin and C1q were reported to be involved in adipose tissue inflammation, which could lead to insulin resistance (24). Most recently, it was reported that a proteolytic isoform of decorin (Δ DCN) was expressed on adipocyte stromal cell surfaces and serves as a functional resistin receptor in mice (16). The findings of the current study

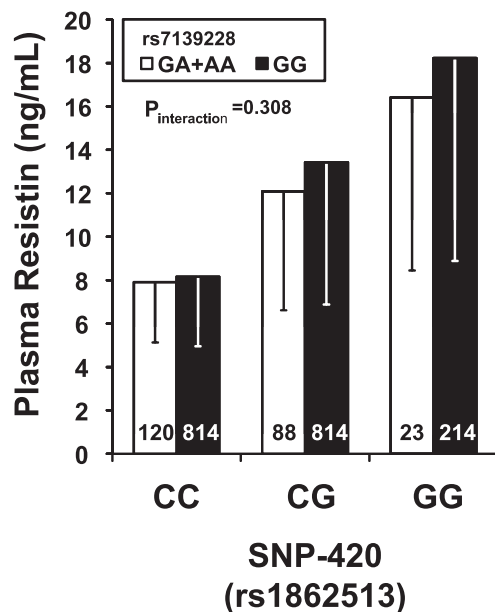


FIG. 2. Plasma resistin according to the *DCN* rs7139228 genotype and *RETN* rs1862513 genotype. Plasma resistin according to *DCN* rs7139228 (GA+AA and GG) and *RETN* rs1862513 genotype (CC, CG, and GG) is shown. Values are means \pm SD. The numbers of subjects are shown in the columns. Interaction between the *DCN* rs7139228 and *RETN* rs1862513 genotypes were assessed by ANCOVA.

indicate the existence of a significant association between tag SNPs around *DCN* and plasma resistin. The possibility that human decorin is a human resistin receptor should be pursued.

In this study, plasma decorin was not associated with each genotype of the six tag SNPs in *DCN* in the general Japanese population. These SNPs are located in introns of *DCN* or intergenic regions and potentially could affect *DCN* expression. Whether decorin located on the cell surface but not in plasma might be associated with these SNPs merits further investigation.

It also was reported that decorin is expressed in adipose tissue in humans and that plasma decorin was elevated in subjects with T2DM (25). In a previous study, we reported that plasma resistin was higher in subjects with T2DM (10). Although the association between plasma resistin and plasma decorin was expected, no association was found in this study (data not shown). Possible isoform and multimer formation of decorin in the plasma should be analyzed.

In summary, plasma resistin was associated with tag SNPs around *DCN* in the general Japanese population. How plasma resistin is affected by these SNPs, and whether decorin or its isoform is a receptor for resistin in humans, remain unknown. Further studies will be required to clarify these points.

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H.On. designed the experiments, researched data, contributed to discussion, and wrote the manuscript. Y.Tab. designed the experiments, researched data, and contributed to discussion. R.Kawamu. researched data and contributed to discussion. J.O. researched data. W.N. and Y.Tal. contributed to discussion. M.O. and T.N. researched data. R.Kawamo., K.K., and T.M. reviewed the manuscript. H.Os. designed the experiments, contributed to discussion, and reviewed and edited the manuscript. H.On., Y.Tab., and H.Os. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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