Adiponectin exhibits its biological effects through adiponectin receptors (AdipoR1 and AdipoR2), which are distributed in the kidneys, and activation of those receptors could prevent or ameliorate diabetic nephropathy. This study aimed to evaluate the associations between AdipoR single nucleotide polymorphisms (SNPs) and kidney function in an elderly Japanese population.

Methods: A total of 271 elderly Japanese volunteers underwent anthropometric and laboratory tests (cystatin C-based eGFR and total and high molecular weight adiponectin levels at baseline and a follow-up visit). Genotype data were obtained for the selected 7 and 5 AdipoR1 and AdipoR2 SNPs, respectively.

Results: In a cross-sectional analysis at baseline, we found a significant association between the AdipoR2 SNP rs12230440 and kidney function; eGFRcys tended to increase as the number of carriers of T alleles increased after adjustment for covariates and Bonferroni correction, although the association of the SNP and annual eGFR decline could not be identified in the longitudinal data. Regarding the variants rs16850797, rs11061925, and rs10773983, each of the allele G, allele C, and allele G showed nominally significant associations with higher eGFRcys. However, this failed to reach significance after Bonferroni correction.

Conclusion: Here, an AdipoR2 SNP was associated with kidney function, suggesting that the effects of this polymorphism on adiponectin receptor may affect kidney function in the elderly Japanese population.
Adiponectin is a major adipokine secreted by adipose tissue that plays an important role in regulating glucose and fat metabolism by enhancing insulin sensitivity and decreasing free fatty acid production. Adiponectin exhibits its biological effects through adiponectin receptors (AdipoR), including AdipoR1 and AdipoR2, both of which contain 7 transmembrane domains and are topologically distinct from the G protein-coupled receptor. AdipoR1 mediates increases in 5'-adenosine monophosphate-activated protein kinase, and AdipoR2 activates peroxisome proliferator-activated receptor (PPAR)-α. AdipoR1 is widely expressed in muscle tissue, whereas AdipoR2 is expressed predominantly in the liver. In addition, other studies have shown that AdipoR1 and AdipoR2 are distributed in the kidneys, and their activation could prevent and ameliorate diabetic nephropathy, especially type 2 diabetes mellitus (T2DM). Indeed, rats with CKD had increased renal expression of AdipoR1 and AdipoR2, which indicates that renal injury may cause compensatory upregulation of AdipoR1 and AdipoR2 in the kidneys to abate further injury. These renoprotective effects may partly be explained by ameliorating glomerular endothelial cell and podocyte injury by activating the AMP-activated protein kinase/PPAR-α pathway through AdipoR. Recent studies have demonstrated that AdipoR polymorphisms are associated with coronary artery disease, intima media thickness, and endothelial dysfunction. Thus, we hypothesized that AdipoR polymorphism might affect kidney function via AdipoR activation signaling.

However, the association of AdipoR1 and AdipoR2 polymorphisms with kidney function in the elderly general population has not been fully understood. In this study, we evaluated the association of polymorphisms of AdipoR1 and AdipoR2 genes—7 single nucleotide polymorphisms (SNPs) for AdipoR1 (rs7539542, rs1342387, rs16850797, rs12045862, rs16850799, rs2275737, and rs1539355) and 5 SNPs for AdipoR2 (rs11061925, rs10773983, rs10773986, rs10773988, and rs12230440)—with kidney function, as measured by cystatin C, in community-dwelling elderly adults.

**Methods**

**Study Design**

This is a prospective observational study of community-dwelling elderly adults aimed to evaluate the hematologic changes accompanying increasing age. All participants provided written informed consent to participate during their first visit and the study protocol was approved by the Ethics Committee of Nihon University School of Medicine in accordance with the Declaration of Helsinki. This study was conducted from 2004 to 2015 in Ogano-machi, a town of approximately 12,000 residents located in Saitama Prefecture, Japan. Volunteers were recruited based on the method outlined in a previous report. By 2015, 1034 residents had participated in the study. Of these participants, subjects who were followed for more than two times (between 2004 and 2015) were enrolled. Subjects who did not undergo baseline or follow-up blood sampling were excluded. Frozen sera, collected at two different times from a single subject and stored at −80°C, were used to measure the serum total adiponectin, glycated albumin, albumin, and cystatin C. In cases where >2 samples were drawn from a subject, we used the sample collected at the time point furthest away from the baseline.

**Data Collection**

As in our previous study, participants were asked to answer a standard questionnaire and were measured for height, body weight, body mass index (BMI), waist circumference, and blood pressure. Non-fasting blood samples were drawn from all participants using the antecubital vein, and laboratory parameters measured at the annual evaluations included serum high molecular weight (HMW) adiponectin, high-density lipoprotein (HDL) cholesterol levels, total cholesterol levels, and triglyceride levels. HMW adiponectin levels were determined by the chemiluminescent enzyme immunoassay using a Lumipulse® f analyzer (FujiRebio, Tokyo, Japan). The intra-assay and inter-assay coefficients of variation were 5.2–6.9% and 2.8–4.5%, respectively. Direct measurement of HDL cholesterol was conducted at a central laboratory (SRL Inc., Tokyo, Japan). In addition to the above-mentioned measurement of parameters, in 2016 we thawed the baseline sera samples that had been stored at −70°C to −80°C and measured additional parameters, including serum cystatin C, total adiponectin, creatinine, albumin, and GA levels at baseline, and compared them to the follow-up values. Serum cystatin C was measured using a colloidal gold particle-enhanced colorimetric immunoassay (Nescauto GC Cystatin C, Alfresa Pharma, Osaka, Japan). The coefficient of variation for the cystatin C assay was ≤10% during the testing period, and the analytical measurement range for cystatin C was 0.20–8.00 mg/L. Total adiponectin was measured by a latex turbidimetric immunoassay using a Human Adiponectin Latex Kit (LSI Medience Corporation, Tokyo, Japan). The coefficient of variation for total adiponectin was ≤10% during the testing period, and the analytical measurement range for total adiponectin was 0.5–25 μg/mL. Albumin was determined by a bromocresol purple dye-binding assay (PureAuto S ALB; Kainos, Tokyo, Japan). GA was measured using the LU-
CICA GA-L kit (Asahi Kasei Pharma Corporation, Tokyo, Japan). Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. Because serum creatinine level is affected by muscle mass, we chose to use cystatin C to calculate eGFR. eGFR by cystatin C (eGFRcys) was calculated using the following equations: eGFRcys in male subjects = (104 × cystatin C $^{-1.094} \times 0.996^{\text{age}}$) − 8; eGFRcys in female subjects = (104 × cystatin C $^{-1.019} \times 0.996^{\text{age}}$ × 0.929) − 8 [27].

Selection of SNPs
To investigate the genetic variability in each gene, we used a tag SNP approach. This tagging approach was applied to the entire set of common genetic variants in the AdipoR1 and AdipoR2 genes with a minor allele frequency (MAF) of ≥ 10% in the Japanese population (JPT) and a minimum $r^2$ threshold of 0.8. The tagging SNPs were selected using the NIEHS LD TAG SNP Selection database (https://snpinfo.niehs.nih.gov/snpinfo/snpntag.html). This process resulted in the selection of 9 and 11 tagging SNPs for the AdipoR1 and AdipoR2 genes, respectively. We chose genotype rs7539542 (UTR variant 3 prime), rs1342387 (intron variant), rs16850797 (intron variant), rs12045862 (intron variant), rs16850799 (intron variant), rs2275737 (intron variant), rs1539355 (intron variant), for AdipoR1 and rs10773983 (intron variant), rs10773988 (intron variant), rs12230440 (intron variant), for AdipoR2 after careful review of the literature and their MAFs in the Japanese population [28-30]. In addition, although they were not tag SNPs, rs11061925 (intron variant) and rs10773986 (intron variant) were evaluated because rs11061925 was shown the relation between the SNP and the metabolic parameter [31], and rs10773986 had high MAF in the Japanese population.

Single-Nucleotide Polymorphism Analysis
Genomic DNA was extracted from peripheral blood leukocytes by the phenol-chloroform method [32]. Genotyping was performed using the TaqMan® SNP genotyping assay mix (40×) containing primers (final concentration, 331.2 nmol/L) and probes (final concentration, 73.6 nmol/L). Thermal cycling was performed using the GeneAmp 7700 system (Applied Biosystems, Foster City, CA, USA) under the following conditions: 50 cycles of 95°C for 2 min and 95°C for 10 min, and 50 cycles of 95°C for 15 s and 60°C for 1 min. Each 96-well plate contained 80 DNA samples of unknown genotype and four reaction mixtures containing reagents without DNA as controls, which were a necessary part of the 7700 signal processing system as outlined in the TaqMan® Allelic Discrimination Getting Started Guide (Applied Biosystems, Foster City, CA, USA). The plates were read on the 7500 Real-time PCR System (version 1.4; Applied Biosystems, Foster City, CA, USA). Genotypes were determined visually based on the dye component fluorescent emission data depicted on X-Y scatter plots by the sequence detection system software. Genotypes were also determined automatically by the software’s signal processing algorithms. The results of each scoring method were saved in separate output files for subsequent comparisons [33].

SNP Quality Control
SNP-level quality control metrics were applied prior to the analyses. All genotyping SNPs showed: a call rate ≥ 95%, MAF ≥ 10%, Hardy–Weinberg equilibrium (HWE) $p > 0.05$. Supplementary Table 1 shows the characteristics, MAF, and HWE $P$-values for the AdipoR1 and AdipoR2 SNPs.

Statistical Analyses
SPSS version 24 (SPSS Inc, Chicago, IL) was used for descriptive statistical analysis. Participant characteristics were summarized by the medians (interquartile range: 25–75 percentile) for continuous variables and percentages for categorical variables. The Mann–Whitney $U$ test was used to compare the two groups. Comparisons for categorized variables were tested with the Fisher exact test. Associations between AdipoR1 and AdipoR2 SNPs and the continuous variables (eGFRcys, total adiponectin, and HMW adiponectin) were tested using linear regression of additive (2 vs. 1 vs. 0 risk alleles) models of inheritance respectively adjusted for age, gender, BMI, MAP, total cholesterol, HDL cholesterol, GA, antidiabetic medications, and antihypertensive medications. In addition, the association of annual eGFRcys decline and the SNP which was significantly associated with baseline eGFRcys was tested via a logistic regression analysis of recessive (2 vs. 0/1 risk alleles) and dominant (2/1 vs. 0 risk alleles) models of inheritance and via linear regression of additive (2 vs. 1 vs. 0 risk alleles) models of inheritance adjusted for
Table 1. Baseline characteristics of the study participants

|                          | Total (n=271) | eGFRcys ≥ 60 mL/min/1.73 m² (n=216) | eGFRcys < 60 mL/min/1.73 m² (n=55) | P value |
|--------------------------|--------------|---------------------------------|----------------------------------|---------|
| Age, years               | 73.0 (69.0-77.0) | 72.0 (68.0-76.9)               | 76.0 (73.0-80.5)                 | <0.0001 |
| Sex, male %             | 28.4 (77/271) | 26.9 (58/216)                  | 34.5 (19/55)                     | 0.26    |
| Body mass index, kg/m²  | 23.0 (21.2-24.7) | 22.9 (21.2-24.7)             | 23.4 (21.2-25.5)                | 0.38    |
| Current smoking status, % | 12.5 (34/271) | 12.0 (26/216)                 | 14.5 (8/55)                     | 0.62    |
| SBP, mmHg (n=268)       | 143.0 (131.5-154.0) | 143.0 (130.0-154.0)          | 143.0 (136.0-158.0)             | 0.21    |
| DBP, mmHg (n=270)       | 77.0 (70.0-84.0) | 76.0 (70.0-84.0)              | 78.0 (72.0-82.0)                | 0.30    |
| MAP, mmHg (n=269)       | 98.3 (91.8-107.8) | 97.7 (90.7-108.0)            | 99.3 (94.3-107.7)              | 0.17    |
| GA, %                    | 15.0 (14.2-16.0) | 15.1 (14.2-16.0)              | 15.0 (14.1-16.5)               | 0.83    |
| Total cholesterol, mg/dL | 202.0 (180.5-227.0) | 205.0 (183.0-227.0)          | 187.0 (170.3-224.8)             | 0.037   |
| HDL cholesterol, mg/dL   | 55.5 (45.0-64.0)  | 57.0 (46.0-66.0)              | 49.0 (38.5-57.0)                | <0.0001 |
| LDL cholesterol, mg/dL   | 116.8 (97.4-139.2) | 117.8 (99.6-138.4)           | 113.8 (90.1-144.5)             | 0.73    |
| TG, mg/dL                | 130.5 (96.0-177.0) | 130.0 (96.0-174.0)           | 135.0 (101.0-189.0)            | 0.36    |
| Total adiponectin, ng/mL  | 11.8 (8.7-17.8)  | 12.0 (8.6-17.4)               | 10.7 (8.7-18.9)                 | 0.83    |
| HMW adiponectin, ng/mL    | 7.0 (4.4-10.7)    | 7.1 (4.4-10.9)                | 6.6 (4.3-9.8)                   | 0.29    |
| Cystatin C, mg/L         | 0.93 (0.83-1.05)  | 0.89 (0.81-0.98)              | 1.22 (1.13-1.38)                | <0.0001 |
| eGFRcys, mL/min/1.73 m²  | 70.5 (61.6-82.1)  | 74.6 (67.3-84.6)              | 50.9 (45.5-56.1)                | <0.0001 |
| Antihypertensive medication, % | 40.0 (108/271) | 38.4 (83/216)               | 45.5 (25/55)                    | 0.34    |
| Antidiabetic medication, % | 7.8 (20/271)     | 6.9 (15/216)                 | 9.1 (5/55)                     | 0.59    |

Data are shown as medians (25th and 75th percentile). SBP systolic blood pressure; DBP diastolic blood pressure; MAP mean arterial pressure; GA, glycated albumin; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; TG, triglyceride; HMW adiponectin, high molecular weight adiponectin; eGFRcys, cystatin C-based estimated glomerular filtration rate.

Results

Baseline Characteristics of the Study Participants

The baseline characteristics of the study participants according to eGFRcys are shown in Table 1. Of the 271 participants, 216 had an eGFRcys ≥ 60; the rest had values < 60. The participants’ ages were significantly higher in the group with eGFRcys < 60 than in that with eGFRcys ≥ 60 (76.0 vs. 72.0 years, P < 0.0001). Total cholesterol and HDL cholesterol were significantly higher in the eGFRcys ≥ 60 group than in the eGFRcys < 60 group (205.0 mg/dL vs. 187.0 mg/dL, P = 0.037; 57.0 mg/dL vs. 49.0 mg/dL, P < 0.001). There were no statistically significant differences in sex, smoking status, BMI, SBP, DBP, MAP, GA, LDL cholesterol, TG, total adiponectin, HMW adiponectin, antihypertensive medications, and antidiabetic medications between the two groups.

Associations of AdipoR1 and AdipoR2 gene Polymorphisms with Kidney Function, Total Adiponectin, and HMW Adiponectin Levels

The associations between AdipoR gene SNPs and kidney function, total adiponectin, and HMW adiponectin levels are presented in Table 2. The variant rs 12230440 was found to be significantly associated with...
Table 2. Association of ADIPOR1 and ADIPOR2 SNPs with eGFRcys, total adiponectin, and HMW adiponectin

| SNPs          | eGFRcys          | Log Total adiponectin | Log HMW adiponectin |
|---------------|------------------|-----------------------|---------------------|
|               |                  | eGFRcys (β (SE), P value) | Log Total adiponectin (β (SE), P value) | Log HMW adiponectin (β (SE), P value) |
| rs16750799    | C/T              | 0.0023 (0.022), 0.28 | 1                   | -0.0024 (0.030), 0.94 | 1 |
| rs10773986    | A/G              | 0.0016 (0.020), 0.43 | 1                   | 0.026 (0.028), 0.36 | 1 |
| rs10773988    | A/G              | 0.0031 (0.025), 0.90 | 1                   | -0.025 (0.035), 0.47 | 1 |
| rs12230440    | T/G              | 0.0035 (0.018), 0.94 | 1                   | 0.035 (0.026), 0.18 | 1 |
| rs11061925    | C/T              | 0.0075 (0.018), 0.67 | 1                   | -0.0032 (0.025), 0.90 | 1 |
| rs10773983    | A/G              | 0.0064 (0.017), 0.71 | 1                   | 0.016 (0.024), 0.52 | 1 |
| rs10773986    | A/G              | 0.0054 (0.017), 0.75 | 1                   | -0.0063 (0.024), 0.80 | 1 |
| rs10773988    | A/G              | 0.0013 (0.017), 0.45 | 1                   | -0.013 (0.024), 0.58 | 1 |
| rs12230440    | T/G              | 0.0136 (0.019), 0.44 | 1                   | 0.0251 (0.026), 0.85 | 1 |

Alleles listed as major/minor allele; Multiple linear regression model for eGFRcys adjusted for age, gender, body mass index, mean arterial pressure, total cholesterol, high-density lipoprotein cholesterol, glycated albumin, antihypertensive medications, and antidiabetic medications. Multiple linear regression model for total and HMW adiponectin adjusted for age, gender, body mass index, total cholesterol, high-density lipoprotein cholesterol, and glycated albumin. ADIPOR, adiponectin receptor; SNP, single nucleotide polymorphism; eGFRcys, cystatin-based estimated glomerular filtration rate; HMW adiponectin, high-molecular-weight adiponectin; SE, standard error; Bonferroni Corr, Bonferroni Correction.

eGFRcys (analysis of recessive and dominant models for rs12230440 is shown in Supplementary Table 2). The analysis showed that eGFRcys tended to increase as the number of carriers of T alleles increased after adjustments for age, gender, BMI, MAP, GA, total-cholesterol, HDL-cholesterol, antihypertensive medication, and antidiabetic medication and after Bonferroni correction (β = 3.57, corrected P = 0.034). In the case of the variants rs16850797, rs11061925, and rs10773983, each of the G allele, allele C, and allele G showed a nominally significant association with higher eGFRcys as well. However, this failed to reach the significance threshold after Bonferroni correction (corrected P = 0.13, 0.46, and 0.072).

In the prospective analysis, for which the average follow-up period was 4.59 years, median annual eGFRcys decline was −1.7 ml/min/1.73 m². There was no significant association between rs12230440 variants and annual eGFRcys decline after multivariable adjustments when analyzed using recessive (P = 0.39), dominant (P = 0.28), and additive (P = 0.16) models of inheritance (Table 3).

We could not detect significant associations between the AdipoR1 and AdipoR2 variants and HMW adiponectin levels. On the other hand, total adiponectin levels tended to significantly decrease as the number of major alleles G of the SNPs rs16850797 and rs16750799 increased. However, this failed to reach the significance threshold after Bonferroni correction (corrected P = 0.22 and 0.23).

**Associations of Common Haplotypes of AdipoR2 with Kidney Function**

To study the combined effect of AdipoR2 SNPs in the present study, the haplotype analysis only included combinations of those AdipoR2 variants that were significantly or nominally associated with baseline eGFRcys (i.e., rs11061925, rs10773983, and rs12230440). The haplotype analysis predicted three common haplotypes (frequency >5%). The most probable haplotype (CGT) had an estimated global frequency of 61%. As shown in Table 4, the haplotype of TAG had significant association with eGFRcys, which reached the significance threshold after Bonferroni correction and adjustment for all the covariates (β = −3.83, corrected P = 0.019).

**Discussion**

In this study, we analyzed the associations of genetic variants of AdipoR1 and AdipoR2 genes and haplotypes of the AdipoR2 gene with kidney function and adiponectin level in elderly Japanese populations. One of the main findings was the significant association...
A study population revealed that an intronic variant, rs767870, is associated with coronary artery disease, intima-media thickness, and endothelial dysfunction. In addition to 13 other AdipoR2 SNPs, this variant is also associated with fasting plasma triglyceride concentrations in Mexican and Finnish subjects. Other reports, studying the Finnish population, have demonstrated that AdipoR2 SNPs in rs11061937 and rs1058322 were associated with CVD risk. Furthermore, patients with an inherent homozygosity for the rare alleles rs11061946 and rs11061973 displayed an increased risk of converting from impaired glucose tolerance to T2DM.

One of the causes of the association between AdipoR SNPs and CVD risk might be described by the influence that AdipoR SNPs assume over the interaction between monocytes/macrophages and adiponectin, which is of critical importance in the anti-atherosclerotic protection offered by adiponectin. Chronic inflammation is of key importance in the process of renal interstitial fibrosis via monocytes/macrophages. Taking into consideration that rs11061937 and rs11061946 are SNPs tagged to rs12230440, which has been demonstrated in the present study to be associated with kidney function, one can hypothesize that the AdipoR2 SNP affects—albeit to an undetermined degree—fibrotic replacement in the renal interstitium under chronic inflammation.

Table 3. Association of rapid eGFRcys decline and SNP of rs12230440

| Continuous outcome | β (SE) | P value by model of inheritance |
|--------------------|--------|---------------------------------|
|                    |        | Recessive | Dominant | Additive |
| Annual eGFRcys decline | 0.27 (0.20) | 0.39 | 0.28 | 0.16 |

Multivariable models adjust for age, gender, body mass index, mean arterial pressure, total cholesterol, high-density lipoprotein cholesterol, glycated albumin, antihypertensive medications, and antidiabetic medications. ADIPOR, adiponectin receptor; eGFRcys, cystatin C-based estimated glomerular filtration rate; F, haplotype frequency; SE, standard error; Bonferroni Corr, Bonferroni Correction.

Table 4. Association of the common haplotype combinations in the ADIPOR2 gene with eGFRcys

| Haplotype | eGFRcys |
|-----------|---------|
|           | β (SE)  | P value | P value (Bonferroni Corr.) |
|           |        |        |                           |
| CGT       | 0.61 | 2.06 (1.08) | 0.059 | 0.71 |
| TAG       | 0.27 | −3.83 (1.12) | 0.0016 | 0.019 |
| CAT       | 0.058 | 0.024 (2.41) | 0.99 | 1 |

The results of the association are listed as the Beta (standard error) (β (SE)) with the corresponding raw P-value. β coefficients represent the change in eGFRcys of each additional risk haplotype. Model adjusted for age, gender, body mass index, mean arterial pressure, total cholesterol, high-density lipoprotein cholesterol, glycated albumin, antihypertensive medications, and antidiabetic medications. ADIPOR, adiponectin receptor; eGFRcys, cystatin-based estimated glomerular filtration rate; F, haplotype frequency; SE, standard error; Bonferroni Corr, Bonferroni Correction.

between the T allele of the rs12230440 SNP with higher eGFRcys, which remained significant even after the adjustment for covariates and Bonferroni correction. Furthermore, we found that carriers of the G allele of rs16850797 and rs10773983, and the C allele of rs11061925, showed a nominally significant association with higher eGFRcys. To our knowledge, this study is the first to analyze the association of AdipoR1 and AdipoR2 with eGFRcys in the elderly general population.

To date, numerous studies have been published providing details on the association between adiponectin and kidney function. With these studies comes the knowledge that patients with CKD have significantly increased levels of serum adiponectin; some studies have even proposed that elevated levels of serum adiponectin serve as a prognostic marker in CKD progression. Others advocate the notion that adiponectin offers kidney protection under CKD conditions. Dissecting the mechanisms of adiponectin at the fine-scale level, we now understand that this unique adipokine exerts its effects via interaction with specific adiponectin receptors, AdipoR1 and AdipoR2.

Although, this study is the first to analyze the association of AdipoR SNPs with kidney function, there are some reports detailing the relationship between AdipoR SNPs and CVD risk. Recently, a cross-sectional study population revealed that an intronic variant, rs767870, is associated with coronary artery disease, intima-media thickness, and endothelial dysfunction. In addition to 13 other AdipoR2 SNPs, this variant is also associated with fasting plasma triglyceride concentrations in Mexican and Finnish subjects. Other reports, studying the Finnish population, have demonstrated that AdipoR2 SNPs in rs11061937 and rs1058322 were associated with CVD risk. Furthermore, patients with an inherent homozygosity for the rare alleles rs11061946 and rs11061973 displayed an increased risk of converting from impaired glucose tolerance to T2DM.

One of the causes of the association between AdipoR SNPs and CVD risk might be described by the influence that AdipoR SNPs assume over the interaction between monocytes/macrophages and adiponectin, which is of critical importance in the anti-atherosclerotic protection offered by adiponectin. Chronic inflammation is of key importance in the process of renal interstitial fibrosis via monocytes/macrophages. Taking into consideration that rs11061937 and rs11061946 are SNPs tagged to rs12230440, which has been demonstrated in the present study to be associated with kidney function, one can hypothesize that the AdipoR2 SNP affects—albeit to an undetermined degree—fibrotic replacement in the renal interstitium under chronic inflammation.

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flammmatory conditions. The specific mechanism is unclear, but the susceptibility of AdipoR to adiponectin or the expression of AdipoR might be affected by this intronic SNP. Indeed, AdipoR1 and R2 double-knockout mice diminished adiponectin-binding effects, which are insulin resistance and impaired glucose tolerance, increased inflammation, and oxidative stress\(^{52,53}\). These effects imply the possibility of anti-inflammatory effects on the kidney tissue via AdipoR. The specific mechanisms underlying the regulation of AdipoR1 and AdipoR2 remain an elusive subject; however, altered expression of AdipoR1 and AdipoR2 in various forms of tissue have been reported in numerous pathological conditions\(^{54-57}\). These facts illustrate the possibility of AdipoR regulation being coordinated in an organ-specific manner and that genetic factors are one of the most crucial factors contributing to the expression and regulation of this gene. Consistent with this theory, Halvatsiotis et al. observed that the AdipoR2 variant rs767870 altered AdipoR2 protein expression levels in peripheral monocytes\(^{250}\).

Although the findings of this particular study are unique and offer insight into the association of AdipoR1 and AdipoR2 with eGFRcys, it does have several limitations. First, our study was limited by the relatively small sample population adopted for genetic association studies. This may weaken the discriminatory statistical power to identify true associations of genetic variants and clinical characteristics. Secondly, our study’s participants were mainly restricted to the elderly population. Hence, it is difficult to apply our results to the young or middle aged Japanese populations. The third limitation lies in the fact that urinary protein levels were not evaluated. Urinary protein is a potentially key factor in kidney function decline. Lastly, we could not gather information pertaining to the use of cholesterol-lowering medications taken by the participants in this study. This is an important limitation because the use of such medications may alter serum adiponectin levels.

**Conclusion**

In this study, conducted in an elderly healthy Japanese cohort, we identified significant associations between an AdipoR2 SNP and eGFRcys that suggest a potential effect of AdipoR gene variants on kidney function. These findings contribute to the understanding of the mechanism by which adiponectin exerts its effects on kidney function via AdipoR. However, these associations need further clarification of AdipoR expression at both the genetic and protein levels. Additional studies that focus on the adiponectin pathway and gene-environment interactions in multi-ethnic subjects, will aid us in obtaining a deeper understanding of the biological differences underlying the AdipoR gene and kidney function.

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**References**

This work was partially supported by a grant from the “Strategic Research Base Development” Program for Private Universities, subsidized by the Ministry of Education, Culture, Sports, Science & Technology (MEXT) in Japan (2011), and by a generous donation from the Saitama Prefectural University.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.
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### Supplementary Table 1. MAF and HWE p-values for the studied ADIPOR1 and ADIPOR2 SNPs

| SNP ID (rs#) | CHR | BP      | CR | MAF   | minor | major | HWE   |
|--------------|-----|---------|----|-------|-------|-------|-------|
| rs7539542    | 1   | 202940846 | 1.00 | 0.2018 | C    | G    | 0.8512 |
| rs1342387    | 1   | 202945228 | 1.00 | 0.4564 | C    | T    | 1.0000 |
| rs16850797   | 1   | 202947555 | 1.00 | 0.3218 | C    | G    | 1.0000 |
| rs12045862   | 1   | 202947678 | 1.00 | 0.3691 | C    | T    | 0.6046 |
| rs16850799   | 1   | 202950723 | 1.00 | 0.4982 | A    | G    | 0.1490 |
| rs2275737    | 1   | 202951172 | 1.00 | 0.2382 | A    | C    | 1.0000 |
| rs1539355    | 1   | 202954952 | 1.00 | 0.1255 | G    | A    | 0.4036 |
| rs11061925   | 12  | 1694068  | 1.00 | 0.3327 | T    | C    | 0.1358 |
| rs10773983   | 12  | 1722080  | 1.00 | 0.3527 | A    | G    | 0.2340 |
| rs10773986   | 12  | 1732158  | 1.00 | 0.4927 | G    | A    | 0.9043 |
| rs10773988   | 12  | 1747015  | 1.00 | 0.44   | G    | A    | 0.7135 |
| rs12230440   | 12  | 1747787  | 1.00 | 0.2745 | G    | T    | 0.5442 |

MAF, minor allele frequency; HWE, Hardy Weinberg Equilibrium; ADIPOR, adiponectin receptor; SNP, single nucleotide polymorphism; CHR, chromosome; CR, call rate.
Supplementary Table 2. Analysis of recessive and dominant models for rs12230440

|                      | rs12230440 |   |   |                      |                      |                      |                      |
|----------------------|------------|---|---|----------------------|----------------------|----------------------|----------------------|
|                      | GG         | GT| TT| P value for          | P value for          | P value for          | P value for          |
|                      |            |   |   | GG + GT vs TT        | GG vs GT + TT        | GG vs GT + TT        | GG + GT vs TT        |
|                      |            |   |   | (Bonferroni Corr.)   | (Bonferroni Corr.)   | (Bonferroni Corr.)   | (Bonferroni Corr.)   |
| Age, years           | 72.9 (71.4-76.0) | 74.0 (69.0-77.0) | 73.0 (68.0-77.0) | 0.98 | 1 | 0.98 | 1 |
| Sex, male %          | 30.4% (723) | 27.5% (28/102) | 28.8% (42/146) | 0.89 | 1 | 0.82 | 1 |
| Body mass index, kg/m² | 22.9 (21.0-24.8) | 23.2 (21.1-24.9) | 22.9 (21.4-24.6) | 0.82 | 1 | 0.84 | 1 |
| Current smoking status, % | 17.4% (4/23) | 9.8% (10/102) | 13.7% (20/146) | 0.54 | 1 | 0.46 | 1 |
| SBP, mmHg (n = 268)  | 146.0 (132.0-154.0) | 143.0 (130.0-155.3) | 143.0 (131.3-154.0) | 0.86 | 1 | 0.81 | 1 |
| DBP, mmHg (n = 270)  | 79.0 (74.0-86.0) | 76.0 (69.0-85.0) | 77.0 (70.5-82.0) | 0.28 | 1 | 0.065 | 0.78 |
| MAP, mmHg (n = 269)  | 100.3 (95.0-107.7) | 97.5 (90.9-108.0) | 98.2 (91.4-108.0) | 0.56 | 1 | 0.30 | 1 |
| GA, %                | 14.3 (13.4-15.4) | 15.0 (14.1-16.1) | 15.2 (14.5-16.1) | 0.094 | 1 | 0.014 | 0.17 |
| Total cholesterol, mg/dL | 214.0 (180.0-237.0) | 200.0 (177.5-227.3) | 204.0 (181.0-224.0) | 0.98 | 1 | 0.42 | 1 |
| HDL cholesterol, mg/dL | 54.5 (40.8-71.0) | 53.0 (465.0-64.3) | 56.0 (46.0-63.8) | 0.75 | 1 | 0.83 | 1 |
| LDL cholesterol, mg/dL | 118.8 (100.4-143.6) | 115.0 (95.4-140.3) | 118.0 (99.9-138.0) | 0.98 | 1 | 0.67 | 1 |
| TG, mg/dL            | 152.5 (105.8-205.4) | 128.5 (96.0-177.5) | 132.5 (92.0-173.8) | 0.56 | 1 | 0.075 | 0.90 |
| Total adiponectin, ng/mL | 9.8 (8.2-18.9) | 12.1 (8.7-17.6) | 11.8 (8.8-17.9) | 0.85 | 1 | 0.69 | 1 |
| HMW adiponectin, ng/mL | 6.2 (3.3-10.9) | 7.2 (4.5-10.5) | 7.0 (4.4-10.8) | 0.68 | 1 | 0.49 | 1 |
| Cystatin C, mg/L     | 1.01 (0.98-1.16) | 0.91 (0.83-1.11) | 0.93 (0.82-1.02) | 0.060 | 0.72 | 0.0017 | 0.020 |
| eGFRcys, ml/min/1.73 m² | 64.4 (55.2-69.0) | 72.8 (60.0-83.0) | 70.9 (63.8-82.9) | 0.080 | 0.96 | 0.0021 | 0.025 |
| Antihypertensive medication, % | 56.5 (13/23) | 34.3 (35/102) | 7.5 (11/146) | 0.65 | 1 | 0.088 | 1 |
| Antidiabetic medication, % | 0 (0/23) | 8.8 (9/102) | 9.1 (5/55) | 0.92 | 1 | 0.16 | 1 |

Data are shown as medians (25th and 75th percentile). Bonferroni Corr, Bonferroni Correction; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; GA, glycated albumin; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; TG, triglyceride; HMW adiponectin, high molecular weight adiponectin; eGFRcys, cystatin C-based estimated glomerular filtration rate.