Genetic Variation in *CDH13* Is Associated With Lower Plasma Adiponectin Levels but Greater Adiponectin Sensitivity in East Asian Populations

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Variants in the *CDH13* gene have been identified as determinants of blood levels of adiponectin, an insulin-sensitizing adipokine. However, their association with other metabolic risk factors remains unclear. We examined variants at *CDH13* in relation to total and high-molecular-weight (HMW) adiponectin using data from a genome-wide association study performed in 2,434 Singaporean Chinese with replication in up to 3,290 Japanese and 1,610 Koreans. The top signal rs4783244 in *CDH13* showed strong associations with total adiponectin (standardized β [β] = −0.34, 95% CI −0.38 to −0.30, $P = 2.0 \times 10^{-70}$), HMW adiponectin (β = −0.40, 95% CI −0.43 to −0.36, $P = 1.1 \times 10^{-117}$), and the HMW-to-total adiponectin ratio (β = −0.44, 95% CI −0.49 to −0.40, $P = 3.2 \times 10^{-83}$). In the replication study, this single nucleotide polymorphism explained 4.1% of total and 6.5% of HMW adiponectin levels. No association was observed between rs4783244 and metabolic traits associated with insulin resistance before adjustment for HMW adiponectin levels. After adjustment for HMW adiponectin levels, the minor allele was associated with lower BMI (β = −0.15, 95% CI −0.19 to −0.11, $P = 3.5 \times 10^{-14}$), homeostasis model assessment-insulin resistance index (β = −0.16, 95% CI −0.20 to −0.12, $P = 9.2 \times 10^{-16}$), and triglycerides (β = −0.16, 95% CI −0.19 to −0.12, $P = 1.3 \times 10^{-16}$) and with higher HDL (β = 0.16, 95% CI 0.12 to 0.19, $P = 2.1 \times 10^{-17}$). *CDH13* variants strongly influence plasma total and HMW adiponectin levels in East Asian populations but appear to alter adiponectin sensitivity, resulting in better metabolic health than expected based on circulating adiponectin levels. ***Diabetes* 62:4277–4283, 2013**

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Adiponectin is a protein abundantly secreted by adipose tissue with anti-inflammatory (1) and insulin-sensitizing properties (2). Blood levels of adiponectin are inversely associated with obesity (3), insulin resistance (4), and risk of type 2 diabetes (5). Genetic determinants account for a substantial proportion of the variation in plasma adiponectin (6), and genome-wide association studies (GWAS) have identified several loci associated with plasma adiponectin (7–10). Adiponectin exists in several forms in the blood. High-molecular-weight (HMW) adiponectin has shown stronger associations with insulin sensitivity and suppression of hepatic glucose production than other forms of adiponectin (11). Few existing GWAS have included both total and HMW adiponectin and compared the associations. This may be pertinent because *CDH13* has been identified to code for T-cadherin, a specific receptor for hexameric and HMW adiponectin (12). In addition, the effects of variants at the *CDH13* locus on insulin resistance and other metabolic risk factors remain unclear.

We therefore conducted a GWAS of total and HMW adiponectin in a Singaporean Chinese population. With an extension to other East Asian populations, we also examined the effects of *CDH13* variants in relation to insulin resistance and associated metabolic traits.

RESEARCH DESIGN AND METHODS

Study populations. Participants from several studies conducted in East Asians were used for the analyses presented here. These included 2,282 Chinese living in Singapore from the Singapore Prospective Study Program (SP2) (13), 3,290 Japanese from the Nomura study (14) and the Ehime University Hospital Antiaging Center (AAC) study (15), and 1,610 Koreans from the Yangpyeong Cohort Study (16). Detailed descriptions of these studies are included in the Supplementary Data.

Laboratory analyses and genotyping. Fasting blood samples were obtained in all studies, and concentrations of total adiponectin, HMW adiponectin, and metabolic variables were measured with acceptable coefficients of variation. Details of the methods used are included in the Supplementary Data. Insulin resistance and β-cell function were calculated using homeostasis model assessment-insulin resistance (HOMA-IR) and HOMA–β-cell function (HOMA-B) indices.

Genotyping in SP2 was done on three different arrays (Illumina HumanHap 550, 610 Quad, and 1Mduov3 BeadChips; http://www.illumina.com). Details on genotyping and quality control measures are included in the Supplementary Data. For replication, blood-derived genomic DNA of a Japanese and Korean sample was used. The *CDH13* single nucleotide polymorphism (SNP)

rs4783244 was analyzed by a TaqMan probe assay (Applied Biosystems Co., Ltd., Foster City, CA) using commercially available primers and probes purchased from the Assay-on-Demand system (C_10076301_10).

Statistical analysis. We standardized adiponectin and other metabolic variables to mean of 0 and variance of 1 to facilitate cross-study comparisons. Multiple linear regression analysis, based on additive and general genetic models, was used with different adiponectin forms and metabolic risk factors (log-transformed if necessary) as the dependent variable, and genotype, age, and sex were used as independent variables. In addition, for metabolic traits, multivariable models that also included HMW adiponectin (or total adiponectin) and BMI were evaluated. Results across studies were combined by a fixed-effect meta-analysis. Population structure in Singaporean Chinese was assessed by principal component analysis. A Bonferroni-corrected threshold $\alpha \leq 5 \times 10^{-8}$ was considered genome-wide significant, and $\alpha \leq 0.005$ was used as a cutoff for the tests on rs4783244 and 10 metabolic variables (calculated as 0.05/10). All tests were two-sided.

RESULTS

Characteristics of the participants in each study are summarized in Table 1. Singaporeans were generally younger than Japanese and Korean participants, whereas Koreans had a higher BMI, higher triglyceride levels, higher HOMA-IR, and lower HDL levels than the other populations. The substantial differences in adiponectin levels among study populations may be partly due to differences in laboratory methods and have been addressed by standardization of adiponectin levels in the data analysis. As expected, blood adiponectin levels were inversely correlated with insulin resistance (measured by HOMA-IR or fasting insulin), fasting glucose, triglycerides, and C-reactive protein and directly correlated with HDL in our study populations (Supplementary Table 1).

In the GWAS in Singaporean Chinese, signals reaching genome-wide significance (5×10^{-8}) mapped exclusively to the *CDH13* and *ADIPOQ* gene (Supplementary Figs. 1 and 2). Associations for selected SNPs from these two genes and SNPs from other genes previously reported to be associated with adiponectin levels are listed in Supplementary Table 2. The strongest signal in *CDH13* was rs4783244, located in the intron region. With regard to other previously reported loci, associations with total and HMW adiponectin levels reached genome-wide significance for *ADIPOQ* (rs10937273), and we observed nominally significant associations for *GPR109A* (rs601339), *CMIP* (rs2925979), and *PEPD* (rs731839) (Supplementary Table 2). The principal components were not correlated with total or HMW adiponectin levels (Supplementary Fig. 3 and Supplementary Table 3). For subsequent analyses, we focused on the top hit *CDH13* SNP rs4783244.

In the combined data from Singaporean Chinese, Japanese, and Korean cohorts, total adiponectin levels significantly decreased by 0.34 SD on the log scale for each additional T allele rs4783244 in *CDH13* (95% CI −0.38 to −0.30, $P = 2.0 \times 10^{-70}$; Table 2). This *CDH13* variant was even more strongly associated with HMW adiponectin levels (standardized β [β] = −0.40, 95% CI −0.43 to −0.36, $P = 1.1 \times 10^{-117}$) and the HMW-to-total adiponectin ratio (β = −0.44, 95% CI −0.49 to −0.40, $P = 3.2 \times 10^{-83}$) based on the Singaporean Chinese and Japanese data. Adjustment for BMI did not substantially affect these effect estimates, and similar results were obtained for the general genetic model (Supplementary Table 4). The *CDH13* rs4783244 variant explained more than 4% of variation in total adiponectin (Singapore: 4.5%, Korea: 5.5%, Japan: 4.1%) and more than 6% of variation in HMW adiponectin levels (Singapore: 8.3%, Japan: 6.5%).

At a Bonferroni-corrected threshold of $P \leq 0.005$, no significant association between rs4783244 in *CDH13* and metabolic risk factors was observed in Singaporean Chinese or in Japanese (model 1; Table 3). Because *CDH13* is known to code for a receptor for HMW adiponectin, we reassessed these associations after adjustment for HMW adiponectin levels (model 2; Table 3). In a meta-analysis of the Singaporean Chinese and Japanese samples, the minor allele T in rs4783244 was significantly associated with lower BMI (β = −0.15, 95% CI −0.19 to −0.11, $P = 3.5 \times 10^{-14}$), lower HOMA-IR (β = −0.16, 95% CI −0.20 to −0.12, $P = 9.2 \times 10^{-16}$), higher HDL (β = 0.16, 95% CI 0.12 to 0.19, $P = 2.1 \times 10^{-17}$), and lower triglycerides (β = −0.16, 95% CI −0.19 to −0.12, $P = 1.3 \times 10^{-16}$) after adjustment for HMW adiponectin levels (Fig. 1*A*). After further adjusting for BMI, associations were weaker but remained significant for HOMA-IR (β = −0.09, 95% CI −0.12 to −0.05, $P = 5.4 \times 10^{-7}$), HDL (β = 0.12, 95% CI 0.09 to

TABLE 1
Characteristics of the study populations

	Singaporean Chinese n = 2,282	Japanese n = 3,290	Koreans n = 1,610
Age (years)	47.6 (10.9)	63.4 (11.6)	61.0 (10.5)
Males, n (%)	1,055 (46.2)	1,365 (41.5)	667 (41.4)
BMI (kg/m^2)	22.8 (3.6)	23.3 (3.2)	24.6 (3.3)
Total adiponectin (μg/mL)*	3.27 (2.28–4.78)	9.10 (6.40–13.40)	7.15 (4.74–10.57)
HMW adiponectin (μg/mL)	1.14 (0.65–1.93)	4.40 (2.70–7.20)	—
HMW-to-total adiponectin ratio	0.35 (0.27–0.43)	0.41 (0.35–0.47)	—
HOMA-IR	1.16 (0.77–1.79)	1.21 (0.80–1.89)	2.20 (1.63–2.98)
HOMA-B (%)	100.0 (67.6–147.0)	56.7 (38.1–83.6)	102.1 (71.2–135.7)
Fasting glucose (mmol/L)	4.7 (4.4–5.0)	5.3 (5.0–5.7)	5.3 (5.0–5.8)
Fasting insulin (mU/L)	5.6 (3.8–8.4)	5.1 (3.4–7.7)	9.2 (6.9–11.8)
Cholesterol (mmol/L)			
LDL	3.10 (2.58–3.67)	3.18 (2.62–3.72)	3.11 (2.56–3.65)
HDL	1.43 (1.21–1.69)	1.63 (1.34–1.94)	1.15 (1.00–1.33)
Total	5.15 (4.58–5.78)	5.40 (4.80–6.00)	5.12 (4.50–5.72)
Triglycerides (mmol/L)	1.08 (0.76–1.60)	1.05 (0.78–1.48)	1.45 (1.06–2.09)
C-reactive protein (mg/L)	0.8 (0.4–1.9)	0.5 (0.3–1.0)	0.9 (0.5–1.8)

Data are represented as mean (SD) for age and BMI and as median (interquartile range) for all of the other metabolic variables. *Total adiponectin levels were only available for a subset of the Japanese sample (n = 1,266).

0.16, $P = 5.4 \times 10^{-12}$), and triglycerides (β = −0.12, 95% CI −0.16 to −0.09, $P = 2.2 \times 10^{-11}$; Fig. 1*B*). These associations were not driven by population admixture in Singaporean Chinese (Supplementary Table 5) and were significant but weaker when we adjusted for total adiponectin instead of HMW adiponectin (results not shown). A sensitivity analysis found minimal difference in effect estimates between fixed- and random-effect meta-analysis, and the estimates retained genome-wide significant with random-effect analysis.

DISCUSSION

Our study replicates previously reported associations of variants at the *CDH13*, *ADIPOQ*, *GPR109A*, *CMIP*, and *PEPD* loci with blood adiponectin levels (10). Furthermore, we found that rs4783244 at the *CDH13* locus, which encodes a receptor for hexameric and HMW adiponectin, was more strongly associated with HMW adiponectin than total adiponectin, explaining more than 6% of the variation in HMW adiponectin levels in East Asians.

However, rs4783244 at the *CDH13* locus was not associated with other metabolic traits, which would be expected based on its association with adiponectin levels, if circulating adiponectin causally influences insulin resistance.

Results from previous studies also provided little support for an association between variants at the *CDH13* locus and metabolic traits. In Filipino women, no significant associations with metabolic risk factors were detected for rs3865188 in *CDH13* (linkage disequilibrium [LD] with rs4783244, $r^2 = 0.85$) except for a nominal association ($P = 0.042$) with waist circumference (9). A Swedish study similarly reported that rs11646213, a SNP upstream of *CDH13* in minimal LD with rs4783244 ($r^2 = 0.08$), was not associated with metabolic risk factors (17). In a Taiwanese study, the significant associations between rs4783244 and waist circumference, glucose, and triglyceride levels did not remain after adjustment for BMI, although the adiponectin-lowering T allele was paradoxically still associated with a reduced risk for diabetes, the metabolic syndrome, and stroke (18).

After adjustment for total and HMW adiponectin levels, the *CDH13* allele associated with lower blood adiponectin levels was associated with a better metabolic profile, including lower BMI, lower insulin resistance based on fasting insulin measures, lower triglyceride levels, and higher HDL levels. Japanese researchers recently reported an association between another *CDH13* SNP (rs12051272) and BMI, fasting insulin, fasting glucose, HOMA-IR, and fasting triglycerides only after controlling for adiponectin levels (19). This SNP is close to and in moderate LD ($r^2 = 0.66$) with rs4783244, which we studied. Together, the data suggest a complex relationship among variants at the *CDH13* locus and metabolic traits that is only evident after controlling for their effects on blood adiponectin levels.

The association between the variants at *CDH13* and plasma HMW adiponectin may be explained by the function of the T-cadherin receptor that it encodes. T-cadherin is a receptor for hexameric and HMW adiponectin that is expressed in the vasculature (20), cardiac myocytes (21), and epithelial cells in the lung (22). We believe that the T allele at rs4783244 is associated with increased binding of HMW adiponectin to the T-cadherin receptor, resulting in the sequestration of HMW adiponectin in these tissues and thus removing it from the blood. Consistent with this explanation, ablation of the T-cadherin receptor increased

TABLE 2
Association between rs4783244 in *CDH13* and different forms of adiponectin

Population	Total adiponectin			HMW adiponectin			HMW-to-total adiponectin ratio		
	N	β (95% CI)	*P* value	*N*	β (95% CI)	*P* value	*N*	β (95% CI)	*P* value
Singaporean Chinese	2,282	−0.32 (−0.37 to −0.26)	2.7×10^{-27}	2,282	−0.43 (−0.48 to −0.37)	1.7×10^{-51}	2,282	−0.48 (−0.54 to −0.43)	9.7×10^{-62}
Japanese	1,266	−0.34 (−0.42 to −0.27)	4.2×10^{-19}	3,290	−0.38 (−0.42 to −0.34)	3.3×10^{-64}	1,266	−0.36 (−0.44 to −0.29)	1.7×10^{-19}
Koreans	1,610	−0.37 (−0.44 to −0.30)	2.4×10^{-25}	—	—	—	—	—	—
Meta-analysis	5,158	−0.34 (−0.38 to −0.30)	2.0×10^{-70}	5,572	−0.40 (−0.43 to −0.36)	1.1×10^{-117}	3,548	−0.44 (−0.49 to −0.40)	3.2×10^{-83}

Results are based on linear regression with rs4783244 as the independent variable, adjusted for age and sex. Total and HMW adiponectin were natural log-transformed, and all the adiponectin forms were standardized to the *z*-scores. rs4783244 genotypes refer to GG, GT, and TT, with GG as the reference. An additive genetic model is assumed, and each β represents the effect of one copy of the T allele on the respective form of adiponectin.

TABLE 3
Association between rs4783244 in *CDH13* and metabolic traits with and without adjustment for HMW adiponectin levels

	Singaporean Chinese			Japanese		
Metabolic trait	Model 1 (age and sex)	Model 2 (& HMW adiponectin)	Model 3 (& BMI)	Model 1 (age and sex)	Model 2 (& HMW adiponectin)	Model 3 (& BMI)
BMI						
β (95% CI)	−0.04 (−0.10 to 0.02)	−0.21 (−0.27 to −0.15)	—	0.02 (−0.03 to 0.07)	−0.11 (−0.16 to −0.06)	—
P value	0.166	2.7×10^{-11}	—	0.494	1.7×10^{-5}	—
HOMA-IR						
β (95% CI)	−0.06 (−0.12 to 0.00)	−0.23 (−0.29 to −0.17)	−0.12 (−0.18 to −0.07)	0.04 (−0.01 to 0.09)	−0.11 (−0.16 to −0.06)	−0.06 (−0.11 to −0.02)
P value	0.062	4.7×10^{-13}	6.4×10^{-6}	0.137	1.0×10^{-5}	6.6×10^{-3}
HOMA-B*						
β (95% CI)	−0.05 (−0.11 to 0.01)	−0.04 (−0.10 to 0.02)	−0.04 (−0.10 to 0.02)	0.02 (−0.02 to 0.05)	0.06 (0.02–0.09)	0.06 (0.02–0.10)
P value	0.118	0.229	0.207	0.288	2.4×10^{-3}	1.1×10^{-3}
Fasting glucose						
β (95% CI)	0.01 (−0.05 to 0.07)	−0.07 (−0.13 to −0.01)	−0.02 (−0.08 to 0.04)	0.00 (−0.05 to 0.04)	−0.11 (−0.16 to −0.07)	−0.10 (−0.15 to −0.05)
P value	0.725	0.018	0.432	0.851	6.7×10^{-6}	8.3×10^{-5}
Fasting insulin						
β (95% CI)	−0.07 (−0.13 to 0.00)	−0.23 (−0.29 to −0.17)	−0.13 (−0.18 to −0.07)	0.04 (−0.01 to 0.09)	−0.10 (−0.15 to −0.05)	−0.04 (−0.09 to 0.00)
P value	0.037	4.3×10^{-13}	4.5×10^{-6}	0.095	1.8×10^{-4}	0.051
LDL						
β (95% CI)	−0.02 (−0.08 to 0.04)	−0.05 (−0.12 to 0.01)	−0.03 (−0.09 to 0.04)	0.01 (−0.04 to 0.06)	−0.05 (−0.10 to 0.00)	−0.04 (−0.09 to 0.01)
P value	0.461	0.109	0.389	0.630	0.041	0.129
HDL						
β (95% CI)	0.01 (−0.05 to 0.06)	0.18 (0.13–0.24)	0.14 (0.09–0.19)	0.00 (−0.05 to 0.05)	0.14 (0.09–0.19)	0.11 (0.06–0.16)
P value	0.775	6.4×10^{-11}	4.9×10^{-7}	0.959	3.6×10^{-8}	3.6×10^{-6}
Total-C						
β (95% CI)	−0.02 (−0.08 to 0.04)	−0.04 (−0.10 to 0.02)	−0.02 (−0.08 to 0.04)	0.02 (−0.03 to 0.07)	−0.03 (−0.08 to 0.03)	−0.02 (−0.07 to 0.03)
P value	0.524	0.216	0.559	0.509	0.327	0.498
Triglycerides						
β (95% CI)	−0.03 (−0.08 to 0.03)	−0.20 (−0.25 to −0.14)	−0.15 (−0.20 to −0.09)	0.02 (−0.03 to 0.07)	−0.13 (−0.18 to −0.08)	−0.11 (−0.15 to −0.06)
P value	0.396	1.5×10^{-11}	2.0×10^{-7}	0.455	4.5×10^{-7}	2.1×10^{-5}
CRP						
β (95% CI)	0.05 (−0.01 to 0.11)	−0.09 (−0.15 to −0.03)	0.00 (−0.06 to 0.06)	0.01 (−0.04 to 0.06)	−0.09 (−0.15 to −0.04)	−0.07 (−0.12 to −0.02)
P value	0.104	6.5×10^{-3}	0.997	0.775	3.4×10^{-4}	0.010

Results are based on linear regression analysis with rs4783244 and HMW adiponectin level as explanatory variables, adjusted for age and sex. rs4783244 genotypes refer to GG, GT, and TT, with GG as the reference, and the effect of the T allele is assumed to be additive. HMW adiponectin levels and all of the metabolic traits, except BMI and LDL, were natural log-transformed. HMW adiponectin and all the dependent variables in the regression models were standardized to the *z*-scores. Model 1: adjusted for age and sex; model 2: adjusted for the covariates in model 1 plus HMW adiponectin; model 3: adjusted for the covariates in model 2 plus BMI. β represents the SD change in the outcome variable per SD change in the explanatory variable, on the natural log scale if applicable. CRP, C-reactive protein; Total-C, total cholesterol. *Adjusted for HOMA-IR.

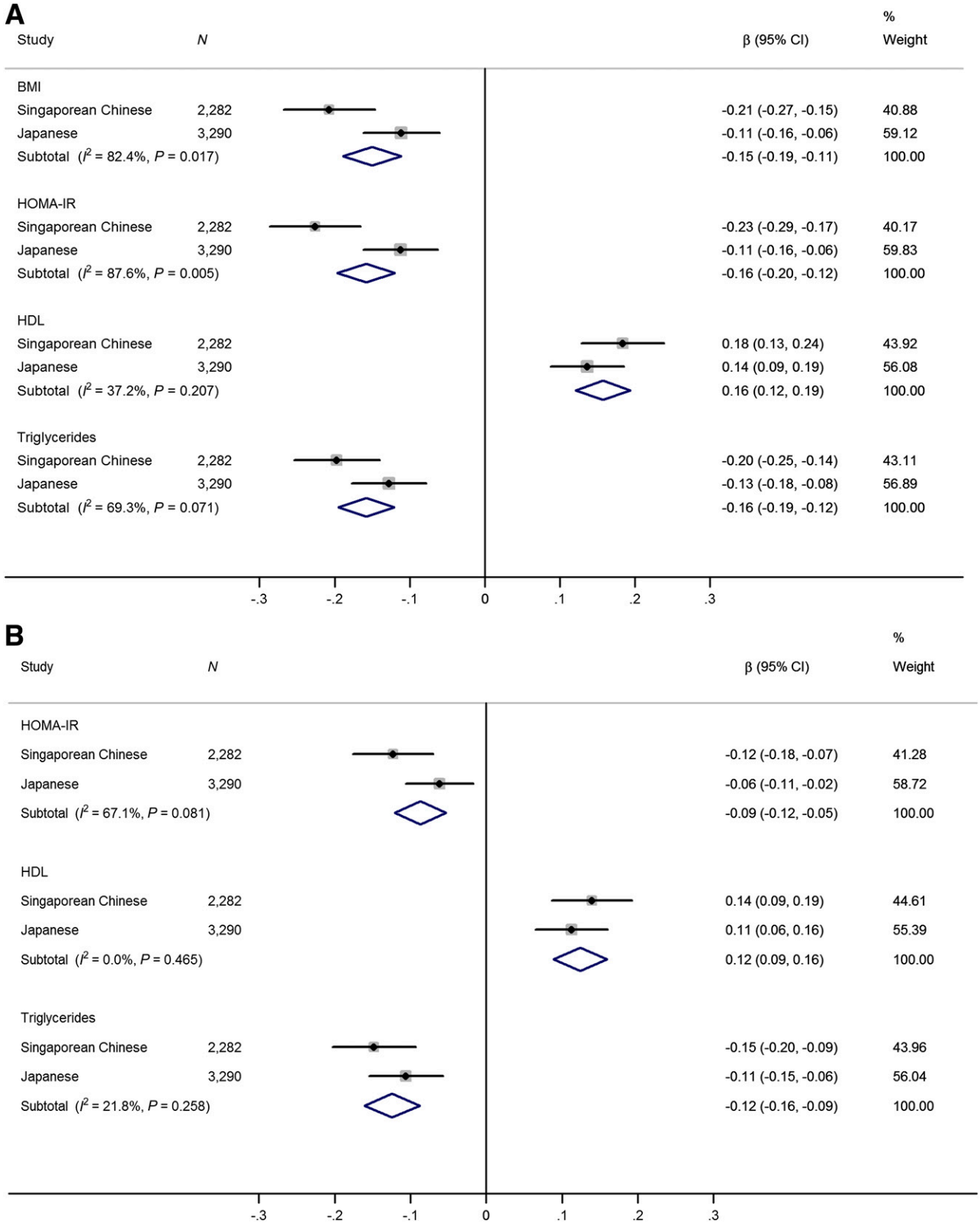

FIG. 1. Effect estimates of rs4783244 in *CDH13* on selected metabolic traits across studies adjusted for age, sex, and HMW adiponectin (*A*) and adjusted for age, sex, HMW adiponectin, and BMI (*B*). HMW adiponectin and levels of HOMA-IR, HDL, and triglycerides were natural log-transformed. HMW adiponectin and all the dependent variables in the regression models were standardized to the *z*-scores. β represents the SD change in the outcome variable per SD change in the explanatory variable, on the natural log scale if applicable. The solid squares denote the mean difference, the horizontal lines represent the 95% CIs, and the diamond denotes the weighted mean differences.

plasma adiponectin levels in mice (20–22). However, this does not explain the paradoxical observation that the T allele at rs4783244, which is associated with lower blood levels of HMW adiponectin, is associated with a more favorable metabolic profile than would be expected based on HMW adiponectin levels.

We hypothesize that the rs4783224 variant at the *CDH13* locus may have an indirect effect on an individual's sensitivity to circulating adiponectin. In this hypothesis, the chronically low levels of plasma adiponectin associated with the T allele may result in upregulation of adiponectin receptors AdipoR1/R2. Consistent with this proposed mechanism, chronic elevation of plasma adiponectin led to downregulation of AdipoR2 in adipose tissue in mice (23). Furthermore, the expression of AdipoR1/R2 was upregulated in insulin-resistant women with polycystic ovary syndrome (24), who would be expected to have low blood adiponectin levels. The greater expression of adiponectin receptors could counterbalance the low adiponectin levels, resulting in the lack of association between rs4783244 and the metabolic profile in unadjusted analyses. However, when the blood adiponectin levels are controlled for, then the greater "adiponectin sensitivity" results in an association between the T allele and a more favorable metabolic profile. Alternatively, effects of *CDH13* on T-cadherin expression and receptor function may directly affect insulin sensitivity. A recent study identified the role of T-cadherin in regulating insulin action in the endothelium such that upregulation of T-cadherin promoted endothelial insulin resistance (25).

Strengths of our study include the relatively large sample size in a homogeneous Chinese population, replication in independent Japanese and Korean populations, and availability of HMW adiponectin and other metabolic variables in addition to total adiponectin. As a limitation, we are unable to elucidate the underlying biological pathways behind our epidemiological observations.

In summary, our study showed that a genetic variant in *CDH13* explains a substantial part of variation in HMW adiponectin levels in East Asian populations. However, this effect of *CDH13* on circulating HMW adiponectin levels did not appear to translate into effects on metabolic traits related to insulin resistance, suggesting that compensatory mechanisms exist that lead to greater "adiponectin sensitivity." Further mechanistic studies on the complex interaction between *CDH13*, blood adiponectin levels, and metabolic traits are needed to better understand the physiologic significance of these observations.

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H.G. formulated the proposal, performed data analysis, interpreted the results, and drafted the manuscript. Y.-M.K. performed the field survey, collected samples, and analyzed data for the Yangpyeong study. P.C., R.T.-H.O., and X.S. contributed to the SP2 study GWAS data analysis. M.I. and R.K. collected samples for the Japanese studies. M.K.K. supervised the field survey and analyzed data for the Yangpyeong study. K.K. and T.M. collected samples and supervised the study design for the Japanese studies. J.L. designed the SP2 study and supervised data collection. H.On. performed experiments for the Japanese studies. H.Os. supervised the statistical analysis for the Japanese studies. Y.Y.T. supervised the data analysis for the SP2 study. Y.T. collected samples, performed experiments, analyzed data, supervised the Japanese studies, and edited the manuscript. ES.T. designed the SP2 study, conceived the study design, interpreted the results, contributed to the writing of the manuscript, and supervised the project progress. R.M.v.D. conceived the study design, interpreted the results, contributed to the writing of the manuscript, and supervised the project progress. All the authors reviewed and approved the final version of the manuscript. R.M.v.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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