A meta-analysis of genome-wide association studies for adiponectin levels in East Asians identifies a novel locus near WDR11-FGFR2

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Blood levels of adiponectin, an adipocyte-secreted protein correlated with metabolic and cardiovascular risks, are highly heritable. Genome-wide association (GWA) studies for adiponectin levels have identified 14 loci harboring variants associated with blood levels of adiponectin. To identify novel adiponectin-associated loci, particularly those of importance in East Asians, we conducted a meta-analysis of GWA studies for adiponectin in 7827 individuals, followed by two stages of replications in 4298 and 5954 additional individuals. We identified a novel adiponectin-associated locus on chromosome 10 near WDR11-FGFR2 (P = 3.0 × 10^{-14}) and provided suggestive evidence for a locus on chromosome 12 near ORBS1-LALBA (P = 1.2 × 10^{-7}). Of the adiponectin-associated loci previously described, we confirmed the association at CDH13 (P = 6.6 × 10^{-156}), ADIPOQ (P = 1.8 × 10^{-22}), PEPD (P = 3.6 × 10^{-12}), CMIP (P = 2.1 × 10^{-10}), ZNF664 (P = 2.3 × 10^{-7}) and GPR109A (P = 7.4 × 10^{-6}). Conditional analysis at ADIPOQ revealed a second signal with suggestive evidence of association only after conditioning on the lead SNP (P_{\text{initial}} = 0.020; P_{\text{conditional}} = 7.0 × 10^{-7}). We further confirmed the independence of two pairs of closely located loci (<2 Mb) on chromosome 16 at CMIP and CDH13, and on chromosome 12 at GPR109A and ZNF664. In addition, the newly identified signal near WDR11-FGFR2 exhibited evidence of association with triglycerides (P = 3.3 × 10^{-4}), high density lipoprotein cholesterol (HDL-C, P = 4.9 × 10^{-3}) and body mass index (BMI)-adjusted waist–hip ratio (P = 9.8 × 10^{-5}). These findings improve our knowledge of the genetic basis of adiponectin variation, demonstrate the shared allelic architecture for adiponectin with lipids and central obesity and motivate further studies of underlying mechanisms.

INTRODUCTION

Adiponectin is an adipocyte-secreted protein and blood adiponectin levels are positively associated with high density lipoprotein cholesterol (HDL-C) concentration and negatively correlated with the risk of type 2 diabetes (T2D), glucose, insulin, insulin resistance, triglycerides and anthropometric measures of obesity (1–3). Twins and family studies demonstrated an estimated 30–70% heritability for circulating adiponectin levels (4–6). A recent multi-ethnic meta-analysis of genome wide association (GWA) studies, including ~40 000 Europeans, ~4200 African Americans and ~1800 East Asians, identified 10 novel loci associated with adiponectin levels (7), in addition to the previously reported ADIPOQ, CDH13, ARL15 and FER (8–14). A multi-SNP genotype risk score that accounted for 5% of the variance of adiponectin levels exhibited significant association with T2D and markers of insulin resistance, suggesting a shared allelic architecture of adiponectin and other metabolic traits (7).

To date, only variants at CDH13 and ADIPOQ exhibited significant association at P < 5 × 10^{-8} in studies of Asians (11,12,14,15). Large-scale meta-analysis of these and other GWA studies should increase the statistical power to detect and confirm additional loci. The CDH13 signal that was initially identified in Asians and had a consistently stronger genetic effect in this population than in Europeans suggested that the genetic contributions may differ across populations (7,11,12,15). Meta-analyses of GWA studies in East Asians for T2D, body mass index (BMI), blood pressure and other metabolic traits have identified novel loci that show Asian-specific associations either due to differences in allele frequencies or due to genuine heterogeneity of genetic effects across continental populations (16–20).

Allelic heterogeneity is frequently observed in large genetic association studies (21–23). A deep resequencing of ADIPOQ in Europeans revealed seven variants exerting independent effects on the adiponectin level (24). A previous GWA study for adiponectin in Koreans suggested the existence of two signals at CDH13, but did not evaluate their independence (12). Two pairs of adiponectin loci are located <2 Mb apart, including CDH13 and CMIP at 16q23.2–23.3 and GPR109A and ZNF664 at 12q24.31; however, it is unclear whether these two nearby loci are independent of each other. Although a physical distance is frequently used to define independent signals, genomic regions have been reported with LD that extended >1 Mb (25,26). These findings motivated our analysis of closely co-localized adiponectin loci to evaluate independence.

We carried out the first meta-analysis of GWA studies for adiponectin in East Asians of the Asian Genetic Epidemiology...
RESULTS

The meta-analysis included three stages, including GWA discovery and two stages of follow-up of selected SNPs (Supplementary Material, Fig. S1). Descriptions of collection, phenotyping and genotyping for study samples in each participating cohort are shown in the Supplementary Material, text and Table S1. The results of meta-analyses using the inverse-variance weighted and sample size-weighted meta-analysis methods were similar. No substantial difference was observed in results analyzed from Models 1 and 2, with or without the adjustment for BMI. We showed results based on Model 1 that accounted for BMI and meta-analyzed using an inverse-variance weighted method.

Stage 1 GWA discovery

The meta-analysis of seven GWA studies including 7827 East Asians in discovery stage revealed three loci significantly associated with the adiponectin level at \( P < 5.0 \times 10^{-8} \) (Table 1, Supplementary Material, Fig. S2). These loci included the previously described \( CDH13 \) (rs4783244, \( P = 2.0 \times 10^{-104} \)) and \( ADIPOQ \) (rs10937273, \( P = 1.1 \times 10^{-22} \)), and a novel signal on chromosome 10, \( \sim 300 \) kb from \( WDR11 \) and \( \sim 300 \) kb from \( FGFR2 \) (rs3943077, \( P = 1.2 \times 10^{-9} \)) (Table 1). Our data also showed suggestive evidence of association (\( P < 10^{-4} \)) for four novel signals at \( KCNH8 \) (rs12714975, \( P = 1.2 \times 10^{-6} \)), \( OR8S1-LALBA \) (rs11186618, \( P = 1.7 \times 10^{-5} \)), \( HIVEP2 \) (rs12211360, \( P = 1.0 \times 10^{-5} \)) and \( GAL3ST1 \) (rs6518702, \( P = 4.5 \times 10^{-5} \)). In addition, the signals previously reported in Europeans at \( CMIP, PEPD, ZNF664, GPR109A \) and \( IRS1 \) also exhibited suggestive association with adiponectin at \( P < 10^{-4} \) in East Asians (Table 1). The AGEN evidence of adiponectin association at other previously reported loci are described in Supplementary Material, Table S2. Furthermore, we did not observe evidence of sex-specific signals at \( P < 5 \times 10^{-5} \), and all \( P \)-values for heterogeneity between sexes were \( > 10^{-8} \) (uncorrected for multiple testing). All loci associated with the adiponectin level in the sex-combined analysis and all loci previously reported in other populations exhibited \( P \) for heterogeneity \( > 0.02 \) in East Asians (Supplementary Material, Table S3).

Stage 2 in silico follow-up

A total of 115 SNPs exhibiting genome-wide significant or suggestive association (\( P < 10^{-4} \)) in Stage 1 were tested for association with adiponectin level in three additional cohorts including up to 4298 individuals (Table 1). The meta-analysis of 10 cohorts consisting of 12 125 East Asians in combined Stages 1 and 2 confirmed the novel adiponectin locus near \( WDR11-FGFR2 \) (\( P = 1.8 \times 10^{-13} \)). Four loci \( KCNH8, OR8S1-LALBA, HIVEP2 \) and \( GAL3ST1 \) that exhibited association at \( P < 10^{-4} \) in Stage 1 also provided suggestive evidence of association in Stages 1 and 2 combined analysis with \( P \)-values between 2.8 \( \times 10^{-7} \) and 7.6 \( \times 10^{-6} \). In addition to \( CDH13 \) and \( ADIPOQ \), associations for SNPs at the previously reported \( PEPD \) (rs889140, \( P = 3.6 \times 10^{-15} \)) and \( CMIP \) (rs2925979, \( P = 2.1 \times 10^{-10} \)) loci reached genome-wide significance in Stages 1 and 2 combined meta-analysis. We also observed associations for SNPs at \( ZNF664 \) (rs1187415, \( P = 2.3 \times 10^{-7} \)) and \( GPR109A \) (rs10847980, \( P = 7.4 \times 10^{-6} \)), whereas little evidence of association was observed at \( IRS1 \) (\( P = 1.4 \times 10^{-3} \)).

Stage 3 further follow-up

To further examine the possible novel signals that exhibited genome-wide significant or suggestive evidence of association in Stages 1 and 2 combined meta-analysis (\( P < 10^{-5} \)), five SNPs were investigated in four additional cohorts including up to 5954 individuals (Table 1). The meta-analysis combining all 14 cohorts including 18 079 individuals in the discovery and two follow-up stages provided additional evidence for the signal near \( WDR11-FGFR2 \) which had already achieved genome-wide significance in Stages 1 and 2 (\( P = 3.0 \times 10^{-14} \)), Fig. 1A). The data also provided supporting yet still suggestive evidence of another locus near \( OR8S1-LALBA \), which did not reach but approximated to the genome-wide significance (\( P = 1.2 \times 10^{-5} \)) (Fig. 1B). However, the Stages 1, 2 and 3 combined meta-analysis did not strongly support the association at \( HIVEP2, GAL3ST1 \) and \( KCNH8 \), which showed less evidence of association despite an increased statistical power when additional subjects were included in the analysis (Table 1).

Conditional analysis

To explore the presence of additional signals at adiponectin-associated loci, we performed conditional analyses at \( WDR11-FGFR2, ADIPOQ, GPR109A, ZNF664, CDH13, CMIP \) and \( PEPD \) loci by conditioning on the lead SNP at each of the seven loci and testing the residual association with all remaining SNPs within \( \pm 500 \) kb flanking regions of the lead SNPs. We also carried out conditional analyses to evaluate independence of the association for signals at two pairs of closely located (<2 Mb) loci, \( GPR109A \) and \( ZNF664 \) on 12q24.31, and at \( CMIP \) and \( CDH13 \) on 16q23.2-23.3. Meta-analysis of the seven cohorts in Stage 1 revealed a second signal near \( ADIPOQ \) exhibiting suggestive evidence of association only after conditioning on the lead SNP rs10937273 (\( EIF4A2-rs266719: P_{\text{initial}} = 0.020, P_{\text{conditional}} = 7.0 \times 10^{-7} \)); Table 2, Supplementary Material, Fig. S3). The other six loci each had only one signal (\( P_{\text{conditional}} > 10^{-4} \)) within the \( \pm 500 \) kb flanking region of the index SNPs. We next performed conditional analysis on the 2 Mb genomic region (chr12: 121.4–123.4 Mb) that included \( GPR109A \) and \( ZNF664 \). When we conditioned on \( ZNF664 \) rs1187415, the second best signal in this region was rs10847980 near \( GPR109A \), with no reduction of association in both magnitude and significance (Table 2, Supplementary Material, Fig. S4A and B). In reciprocal conditional analysis accounting for \( GPR109A \) rs10847980, the effect size and \( P \)-value of association for rs1187415 did not change (Table 2, Supplementary Material, Fig. S4A and C). When both rs1187415 and rs10847980 were included in
### Table 1. Loci associated with adiponectin

<table>
<thead>
<tr>
<th>Locus/ nearby gene</th>
<th>Index SNP</th>
<th>Chr Position (hg18)</th>
<th>Stage 1 ( (n = 7827) ) Effect/ non-effect alleles</th>
<th>Stages 1 + 2 ( (n = 12125) ) Effect/ non-effect alleles</th>
<th>Stages 1 + 2 + 3 ( (n = 18079) ) Beta (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Novel locus exhibiting GWA with adiponectin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WDR11-FGFR2</td>
<td>rs3943077</td>
<td>10 122 935 076 A/G</td>
<td>0.567 0.09 (0.02) 1.2E-09</td>
<td>0.09 (0.01) 1.8E-13</td>
<td>0.07 (0.01) 3.0E-14</td>
</tr>
<tr>
<td><strong>Loci exhibiting suggestive association with adiponectin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR8S1-LALBA</td>
<td>rs11168618</td>
<td>12 47 219 500 T/C</td>
<td>0.137 -0.10 (0.02) 1.7E-05</td>
<td>-0.08 (0.02) 1.1E-06</td>
<td>-0.06 (0.01) 1.2E-07</td>
</tr>
<tr>
<td>HIVEP2</td>
<td>rs12211360</td>
<td>6 143 161 525 A/G</td>
<td>0.966 -0.21 (0.05) 1.0E-05</td>
<td>-0.21 (0.04) 2.8E-07</td>
<td>-0.16 (0.03) 5.5E-06</td>
</tr>
<tr>
<td>KCNH8</td>
<td>rs12714975</td>
<td>3 19 060 378 C/G</td>
<td>0.047 0.21 (0.04) 1.2E-06</td>
<td>0.16 (0.04) 7.6E-06</td>
<td>0.12 (0.03) 8.9E-05</td>
</tr>
<tr>
<td>GALST1</td>
<td>rs6518702</td>
<td>22 29 278 752 T/C</td>
<td>0.249 -0.08 (0.02) 4.5E-05</td>
<td>-0.06 (0.01) 5.2E-06</td>
<td>-0.04 (0.01) 5.3E-04</td>
</tr>
<tr>
<td><strong>Known loci with previous evidence of association with adiponectin ( (P &lt; 10^{-4} \text{ in stage 1}) )</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDH13</td>
<td>rs4783244</td>
<td>16 81 219 769 T/G</td>
<td>0.360 -0.34 (0.02) 2.0E-10</td>
<td>-0.33 (0.01) 6.8E-165</td>
<td>n.a. n.a.</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>rs10937273</td>
<td>3 188 032 389 A/G</td>
<td>0.404 0.15 (0.02) 1.1E-22</td>
<td>0.12 (0.01) 1.8E-22</td>
<td>n.a. n.a.</td>
</tr>
<tr>
<td>PEPD</td>
<td>rs889140</td>
<td>19 38 580 840 A/G</td>
<td>0.450 0.07 (0.02) 8.4E-06</td>
<td>0.08 (0.01) 3.6E-12</td>
<td>n.a. n.a.</td>
</tr>
<tr>
<td>CMP</td>
<td>rs2992979</td>
<td>16 80 092 291 T/C</td>
<td>0.411 -0.07 (0.02) 5.3E-06</td>
<td>-0.08 (0.01) 2.1E-10</td>
<td>n.a. n.a.</td>
</tr>
<tr>
<td>ZNF664</td>
<td>rs1187415</td>
<td>12 113 057 482 C/G</td>
<td>0.920 -0.14 (0.03) 1.2E-06</td>
<td>-0.11 (0.02) 2.3E-07</td>
<td>n.a. n.a.</td>
</tr>
<tr>
<td>GPR109A</td>
<td>rs10847980</td>
<td>12 121 935 875 T/G</td>
<td>0.771 -0.08 (0.02) 7.2E-06</td>
<td>-0.06 (0.01) 7.4E-06</td>
<td>n.a. n.a.</td>
</tr>
<tr>
<td>IRS1</td>
<td>rs7558386</td>
<td>2 227 270 383 A/G</td>
<td>0.341 -0.06 (0.02) 7.8E-05</td>
<td>-0.04 (0.01) 1.4E-03</td>
<td>n.a. n.a.</td>
</tr>
</tbody>
</table>

*EAF, effect allele frequency based on the data in Stage 1.

**Effect direction of each individual studies in the order of SP2_1M, SP2_610 K, SP2_550 K, KCPS-II, CLHNS, NHAPC Beijing, and NHAPC Shanghai in Stage 1, Ansan, KING_GWAS, SAPPHIRE in Stage 2 and followed by KING_noGWAS, ACC, Nomura and SMHS in Stage 3 if the cohorts were included in the analysis.*
conditional analysis, the association for all other SNPs in the 2 Mb region were not significant (all $P_{\text{conditional}} > 10^{-4}$ in stage 1 meta-analysis), providing no evidence for a third signal at this region. Similarly, when rs2925979 at CMIP was conditioned on rs4783244 at the strong signal CDH13, and vice versa, little change of association was observed, indicating two independent loci at 16q23.2–23.3 (Table 2, Supplementary Material, Fig. S5).

**Characterization of novel loci**

We looked up the lead SNPs near WDR11-FGFR2 and OR8S1-LALBA loci for evidence of adiponectin association in the publicly released data of ADIPOGen European discovery meta-analysis (http://www.mcgill.ca/genepi/adiopogen-consortium). The SNP rs3943077 near WDR11-FGFR2 showed consistent direction of allelic effect, but did not exhibit strong evidence of association ($P = 0.093$) in $> 29$ 000 Europeans (Table 3). Despite a lower allele frequency of rs3943007 in ADIPOGen (A allele = 0.24) compared with that in AGEN (A allele = 0.57), the European study has a $> 96\%$ power to detect the effect size ($\beta = 0.07$) observed in AGEN at a threshold of $P < 5 \times 10^{-8}$. The differences in allele frequency and significant level of association suggested that variants at WDR11-FGFR2 might have a larger genetic effect on levels
CMIP-CDH13 were available in AGEN or other consortia (Table 3). We found that the adiponectin-increasing allele of rs3943077 at $WDR11-FGFR2$ was significantly associated with decreased triglycerides ($P = 3.3 \times 10^{-5}$) and increased HDL-C ($P = 4.9 \times 10^{-4}$) levels in East Asians from the AGEN consortium. The SNP rs11618618 at $OR8S1-LALBA$ exhibited a borderline association with HDL-C in East Asians ($P = 0.040$). In addition, the A allele of rs3943077 associated with increased adiponectin was associated with decreased WHRadjBMI in East Asians ($P = 9.8 \times 10^{-3}$). GIANT data including up to 77,000 Europeans also showed a borderline association between rs3943077 and WHRadjBMI ($P = 0.013$) with consistent direction of effect.

The novel signal near $WDR11-FGFR2$ explained 0.6% of the total variation in adiponectin. To assess whether this signal could be refined, we investigated additional variants within ± 500 kb of rs3943077 by testing the association of SNPs imputed from the 1000 Genomes Project in a subset of 3778 individuals from the Singapore prospective study program (SP2) _1M, SP2 _610 and the Cebu Longitudinal Health and Nutrition Survey (CLHNS) that had imputed data available. The most strongly associated SNP (rs72631105, EAF = 0.632, $\beta = 0.13$, $P = 5.4 \times 10^{-7}$) was located 30 kb away and in a moderate LD ($r^2 = 0.63/0.89$ in Genomes Project Phase 1 ASN) with rs3943077 (EAF = 0.541, $\beta = 0.10$, $P = 1.4 \times 10^{-8}$) (Supplementary Material, Fig. S6). All seven variants that exhibited stronger evidence of association were located 0.16–35 kb from rs3943077 and were not present in the HapMap reference panel. Six of these variants were in moderate to high LD ($r^2 \geq 0.63–1.00$) with rs3943077, except rs10886862 (EAF =

Table 2. Regions with multiple signals or independent loci associated with adiponectin ($P_{conditional} < 10^{-4}$)

<table>
<thead>
<tr>
<th>Index SNP</th>
<th>Chr</th>
<th>Position</th>
<th>Effect/ non-effect alleles</th>
<th>EAF</th>
<th>Main effect analysis(^a)</th>
<th>Conditional analysis(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$\beta$ (SE) $P$</td>
<td>$\beta$ (SE) $P$</td>
</tr>
<tr>
<td><strong>ADIPOQ</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10937273</td>
<td>3</td>
<td>188 032 389</td>
<td>A/G</td>
<td>0.404</td>
<td>0.15 (0.02) 5.7E-23</td>
<td>0.16 (0.02) 6.9E-26</td>
</tr>
<tr>
<td>rs266719</td>
<td>3</td>
<td>187 984 342</td>
<td>T/C</td>
<td>0.096</td>
<td>0.06 (0.03) 0.020</td>
<td>0.13 (0.03) 7.0E-07</td>
</tr>
<tr>
<td><strong>GPR109A-ZNF664</strong></td>
<td>12</td>
<td>123 057 482</td>
<td>C/G</td>
<td>0.920</td>
<td>−0.14 (0.03) 1.0E-06</td>
<td>−0.14 (0.03) 1.2E-06</td>
</tr>
<tr>
<td>rs1187415</td>
<td>12</td>
<td>121 953 876</td>
<td>T/G</td>
<td>0.771</td>
<td>−0.08 (0.02) 6.8E-06</td>
<td>−0.08 (0.02) 9.6E-06</td>
</tr>
<tr>
<td><strong>CMIP-CDH13</strong></td>
<td>16</td>
<td>81 219 769</td>
<td>T/G</td>
<td>0.450</td>
<td>−0.34 (0.02) 9.5E-106</td>
<td>−0.34 (0.02) 1.8E-106</td>
</tr>
<tr>
<td>rs4783244</td>
<td>16</td>
<td>80 092 291</td>
<td>T/C</td>
<td>0.411</td>
<td>−0.07 (0.02) 5.1E-06</td>
<td>−0.07 (0.02) 4.8E-06</td>
</tr>
</tbody>
</table>

\(^a\)The standard errors (SEs) and $P$-values in Stage 1 main effect analysis were not corrected for genomic control, thus the statistics can be compared with those from the regional conditional analyses.

\(^b\)Reciprocal conditional analyses were performed; The effect sizes and $P$-values in conditional analysis for one SNP were conditioned on the other, and vice versa. EAF, effect allele frequency.

Table 3. Association of the novel and suggestive loci with adiponectin and obesity-related traits in other consortium

<table>
<thead>
<tr>
<th>Trait</th>
<th>Consortium</th>
<th>Ethnicity</th>
<th>$WDR11-FGFR2$-rs3943077</th>
<th>$OR8S1-LALBA$-rs11168618</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Direction(^a)</td>
<td>Direction(^b)</td>
<td>$P$</td>
<td>$N$</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>ADIPOGen</td>
<td>European</td>
<td>+</td>
<td>+</td>
<td>0.093</td>
<td>29 202</td>
</tr>
<tr>
<td>TG</td>
<td>AGEN</td>
<td>East Asian</td>
<td>−</td>
<td>+</td>
<td>3.3E-04</td>
<td>8311</td>
</tr>
<tr>
<td>HDL-C</td>
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<td>+</td>
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<td>+</td>
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<td>32 380</td>
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<tr>
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<td>European</td>
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<td>−</td>
<td>0.013</td>
<td>77 165</td>
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</table>

\(^a\)The directions of effect are based on the alleles (rs3943077-A; rs11168618-C) associated with increased adiponectin levels in this study. The A allele frequency of rs3943077 is 0.57 in AGEN and 0.24 in AdipoGen; the C allele frequency of rs11168618 is 0.86 and 0.46 in AGEN and AdipoGEN, respectively. TG: triglycerides; TC: total cholesterol; WC: waist circumference; WCadbBMI: BMI-adjusted waist circumference; WHR: waist–hip ratio; WHRadbBMI: BMI-adjusted waist–hip ratio.
Five SNPs tested (data not shown). However, luciferase reporter assays in differentiated adipocytes showed no allelic difference in transcriptional activity for the five SNPs tested (data not shown). At least four LD proxies of rs3943077 are located at or near enhancer marks in adipose and liver (data not shown). These markers may introduce uncertainty into the association results, though they were not significant in the three-stage meta-analyses provided convincing evidence of a novel adiponectin-associated locus near **ADIPOQ** and **ZNF664**. Our index SNP rs4783244 is highly correlated with the lead SNP from the 1000 Genomes imputation in a subset of the 1000 Genomes Project Phase 1 ASN, thus the significance of residual association increased when accounting for the other signal. An SNP–SNP interaction might underlie the association. Prior evidence and functional assessment of the second signal suggests possible mechanisms that link **FGFR2b** and **FGFR2c** in the processes of adipocyte hyperplasia and hypertrophy and affects hypertrophy of mature adipocytes (33). An increase in the size of mature adipocytes dysregulates the expression of adipokines, including adiponectin (37). Hence, the involvement of **FGFR2b** and **FGFR2c** in the processes of adipocyte hyperplasia and hypertrophy suggests possible mechanisms that link **FGFR2** to adiponectin regulation.

While consistent evidence supports the adiponectin association with variants in or near **ADIPOQ** in diverse populations, the most strongly associated SNPs are not shared across studies. The lead SNP rs6810075 reported in Europeans by **ADIPOQGen**, though also significantly associated with adiponectin in East Asians (β = 0.12, P = 4.7 × 10⁻¹⁶, effect allele frequency = 0.55), exhibited weaker evidence of association compared with that for our index SNP rs10937273 (β = 0.15, P = 1.1 × 10⁻²², effect allele frequency = 0.41). The magnitude and significance level for rs6810075 were substantially attenuated (β = 0.01, P<sub>conditional</sub> = 0.36) when conditioning on our index SNP rs10937273. The two variants were moderately correlated, with LD estimates of r²/D = 0.58/1.00 and 0.44/1.00 in the 1000 Genomes Project Phase 1 ASN and EUR, respectively. Therefore, rs10937273 and rs6810075 likely represent the same signal at **ADIPOQ**.

However, there is a suggestion of a secondary signal rs266719 located ~60 kb upstream of **ADIPOQ** at **EIF4A2**, the gene encoding Eukaryotic initiation factor 4A (EIF4A), which has been shown to regulate the expression of C/EBPδs that affect adipocyte differentiation, adipogenesis and insulin sensitivity (39). Genetic variants may affect adiponectin levels by influencing **EIF4A2** expression or by acting more distantly on **ADIPOQ** expression. The identification of this second signal that showed association with adiponectin only after conditioning on the lead signal suggests allelic heterogeneity at this locus but a complex pattern of association (40). The trait-lowering allele of rs266719 (C allele frequency = 0.904) is coupled with the trait-increasing allele of rs10937273 (A allele frequency = 0.404) on the same haplotype (LD r²/D = 0.03/0.77; frequencies of rs266719–rs10937273 haplotypes: CG: C = 0.559, CA = 0.360, TG = 0.077 and TA = 0.007, 1000 Genomes Project Phase 1 ASN), thus the significance of residual association increased when accounting for the other signal. An SNP–SNP interaction might underlie the association. Prior evidence and functional assessment of the second signal suggests possible mechanisms that link **FGFR2** to adiponectin regulation.

### DISCUSSION

This study is the largest GWAS meta-analysis conducted for adiponectin association in populations of East Asian ancestry to date. The three-stage meta-analyses provided convincing evidence of a novel adiponectin-associated locus near **WDR11-FGFR2**. Our data also suggested a potential new locus near **OR8S1-LALBA** that did not reach traditional threshold of GWA significance. In addition to confirming the previously described loci of **CDH13** and **ADIPOQ**, the discovery of a novel adiponectin-associated locus near **ZNF664** suggests possible mechanisms that link **FGFR2** to adiponectin regulation. The three-stage meta-analyses provided convincing evidence of a novel adiponectin-associated locus near **ADIPOQ** and **ZNF664**. Our index SNP rs4783244 is highly correlated with the lead SNP from the 1000 Genomes imputation in a subset of the 1000 Genomes Project Phase 1 ASN, thus the significance of residual association increased when accounting for the other signal. An SNP–SNP interaction might underlie the association. Prior evidence and functional assessment of the second signal suggests possible mechanisms that link **FGFR2** to adiponectin regulation.

Our data from conditional analysis demonstrate that the locus **CDH13** is independent of **CMIP** located 1 Mb away (7), but did not support the previous evidence of two signals at **CDH13** (rs3865188, rs3865186, r²/D = 0.34/0.97) (12) (Supplementary Material, Fig. S7). Our index SNP rs4783244 is highly correlated with the previously reported first signal rs3865188 (LD r²/D = 0.90/0.97), and conditioning on this signal substantially attenuated the association with the previously described second signal (rs3865186, P<sub>initial</sub> = 2.3 × 10⁻⁴⁹, P<sub>conditional</sub> = 0.058). Although the pairwise LD is modest, conditional analysis suggested that the second signal could be explained by the initial signal. The signal at **CDH13** consistently has been reported to regulate the expression of C/EBPδs that affect adipocyte differentiation, adipogenesis and insulin sensitivity (39). Genetic variants may affect adiponectin levels by influencing **EIF4A2** expression or by acting more distantly on **ADIPOQ** expression. The identification of this second signal that showed association with adiponectin only after conditioning on the lead signal suggests allelic heterogeneity at this locus but a complex pattern of association (40). The trait-lowering allele of rs266719 (C allele frequency = 0.904) is coupled with the trait-increasing allele of rs10937273 (A allele frequency = 0.404) on the same haplotype (LD r²/D = 0.03/0.77; frequencies of rs266719–rs10937273 haplotypes: CG: C = 0.559, CA = 0.360, TG = 0.077 and TA = 0.007, 1000 Genomes Project Phase 1 ASN), thus the significance of residual association increased when accounting for the other signal. An SNP–SNP interaction might underlie the association. Prior evidence and functional assessment of the second signal suggests possible mechanisms that link **FGFR2** to adiponectin regulation.
European ancestry (7–10,13). At CDH13, the index SNPs from our East Asian samples (rs4783244) and the ADIPOGen Europeans (rs12922394) are weakly correlated (LD $r^2/D' = 0.36/0.71$ and 0.04/0.75 in the 1000 Genomes Project Phase 1 ASN and EUR, respectively) and have varied allele frequencies (rs4783244: 0.36 in East Asians and 0.46 in Europeans; rs12922394: 0.24 in East Asians and 0.07 in Europeans). Similarly, the lead SNP rs12051272 from the ADIPOGen multi-ethnic meta-analysis was common in Asians (minor allele frequency, MAF = 0.33), but rare in Europeans and African Americans (MAF = 0.03 for both) (7), and the pairwise LD between rs12051272 and rs4783244 differs across populations ($r^2/D' = 0.95/0.99, 0.03/1.00$ and $0.10/1.00$ in the 1000 Genomes Project Phase 1 ASN, EUR and AFR, respectively). These varied allele frequencies and LD structures may explain the differences in strength of genetic association across continental populations. The differences may also be influenced by differing environmental exposures that modulate the effect of a gene (42).

In this study, we also generalized the adiponectin association with GPR109A and ZNF664 at 12q24.31 to populations of East Asian ancestry, and confirmed that the two loci located ~1 Mb apart were independently associated with adiponectin. The ZNF664 index SNPs identified in Europeans (rs7133378) and East Asians (rs1187415) were in moderate to high LD ($r^2/D' = 0.64/1.00$ and 0.90/1.00 in the 1000 Genomes Project Phase 1 ASN and EUR, respectively), suggesting that both the groups shared the same signal. At GPR109A, the lead SNP rs10847980 identified in this study was ~200 kb away from the European index rs601339 and these two SNPs were weakly correlated ($r^2/D' = 0.02/0.31$ and 0.03/0.30 in the 1000 Genomes Project Phase 1 ASN and EUR). The SNP rs601339 only exhibited borderline association with adiponectin in East Asians ($P_{\text{initial}} = 0.014$), and this association can be explained by rs10847980 ($P_{\text{conditional}} = 0.20$ for rs601339). The differences in lead SNPs from the different populations might reflect different frequencies, different causal variants or that index SNPs may be only correlated with one or more underlying causal variants not analyzed. Further study of biological mechanisms is warranted to determine whether the signals at GPR109A and ZNF664 act independently on distinct genes or on the same gene. Among nearby candidates, GPR109A has been shown to be required for niacin-stimulated adiponectin secretion (44).

The adiponectin-increasing allele of the WDR11-FGFR2 index SNP was associated with an increased HDL-C, decreased triglycerides and decreased BMI-adjusted WHR in East Asians. This direction of the genetic effects on these traits agrees with the consistently observational positive correlation of adiponectin with HDL-C and the inverse correlation with triglycerides and indices of abdominal obesity (Supplementary Material, Table S4) (45–47). In addition, the more pronounced evidence of SNP association with BMI-adjusted WHR ($P = 9.8 \times 10^{-3}$) compared with BMI ($P = 0.43$) suggests that WDR11-FGFR2 variants directly or indirectly influence abdominal obesity, a better predictor of metabolic and cardiovascular risk (48,49) than the overall obesity. Several other known adiponectin loci also exhibited evidence of association with other metabolic and cardiovascular risks. A SNP rs3786897 at PEPD was previously reported to be associated with the risk of T2D in East Asians (16); this SNP is in complete LD with the adiponectin index rs889140 ($r^2/D' = 0.99/1.00$ in the 1000 Genomes Project Phase 1 ASN), demonstrating a shared signal for adiponectin and T2D in this population. SNPs near ZNF664, associated with HDL-C and triglycerides in Europeans (23), are highly correlated with the adiponectin signal in both Europeans and Asians (rs4765127 and rs1187415, $r^2/D' = 0.97/0.99$ in the 1000 Genomes Project Phase 1 EUR and 0.92/0.96 in 1000Genomes ASN). In addition, the same index SNP rs2925979 at CMIP exhibited association with HDL-C in Europeans (23) and with adiponectin in our data. CMIP also displayed suggestive evidence of association with T2D in East Asians; however, the signals for T2D and adiponectin were weakly correlated ($r^2/D' = 0.14/0.51$ in the 1000 Genomes Project Phase 1 ASN). The South Asian-specific T2D locus ST6GALI (50) was ~100 kb away from ADIPOQ; but the T2D index SNP rs16861329 is not in LD with either of the two adiponectin-associated signals at ADIPOQ (LD $r^2 = 0$). Given our current data, we were unable to determine whether the genetic effect of adiponectin loci on related metabolic traits is due to a pleiotropic effect or through SNP influence on adiponectin. Nevertheless, these findings support the prior suggestions of a shared allelic architecture of adiponectin levels and related metabolic traits (7) and motivate further studies to investigate potential cause–effect relationships between traits (51,52).

In conclusion, this GWAS meta-analysis for adiponectin in East Asians provides the first evidence for a novel locus near WDR11-FGFR2 and expands the understanding of the genetic basis of adiponectin levels at several known loci. The findings that the novel adiponectin locus near WDR11-FGFR2 also displayed association with HDL-C, triglycerides and BMI-adjusted WHR demonstrate the shared allelic architecture for adiponectin with lipid traits and central obesity, and motivate further studies of underlying biological mechanisms.

**MATERIALS AND METHODS**

**Study population and phenotype**

The Asian Genetic Epidemiology Network (AGEN) is a consortium of genetic epidemiology studies of metabolic and cardiovascular diseases and related traits conducted in individuals of East Asian ancestry (http://www.agenconsortium.org/). This AGEN adiponectin study consisted of a total of 18,079 individuals from 14 cohorts that participated in three stages of meta-analysis. The participating cohorts are either population-based ($n = 13$) or family-based ($n = 1$). Stage 1 of GWA discovery consisted of 7827 Chinese, Korean and Filipino individuals from SP2, the Korean Cancer Prevention Study II (KCPS-II), CLHNS and the Nutrition and Health of Aging Population in China (NHAPC). SP2 consisted of three independent cohorts of SP2_1M, SP2_610 K and SP2_550 K genotyped with different platforms. NHAPC included two independent cohorts of NHAPC Beijing and NHAPC Shanghai based on the sites where individuals were recruited. Stage 2 of *in silico* replication included 4298 individuals from the Ansan cohort (Ansan), Kita-Nagoya Genomic Epidemiology Study (KING) and the Stanford Asian Pacific Program in Hypertension and Insulin
Resistance (SAPPHIRE). Stage 3 contains 5954 individuals from three Japanese cohorts of KING, the anti-aging center cohort study (AAC) and Nomura cohort study (Nomura) and one Chinese cohort of Shanghai Men’s Health Study (SMHS).

Plasma or serum adiponectin levels were measured via an enzyme-linked immunosorbent assay method, a latex enhanced immuno turbidimetric assay or Luminex xMAPTM Technology. Total adiponectin was measured in all studies, except Nomura, in which high-molecular weight adiponectin was assessed. Further description of the sample characteristics is given in detail in the Supplementary Material, text and Table S1. The correlation structures between adiponectin and these traits are shown in the Supplementary Material, Table S4. The sex-stratified measures of adiponectin and other metabolic/cardiovascular-related traits are described in Supplementary Material, Table S5. All study protocols were approved by Institutional Review Boards at their respective sites, and written informed consent was obtained from all participants.

Genotyping, imputation and quality control

Individuals in Stages 1 and 2 were genotyped using commercially available Illumina or Affymetrix genome-wide genotyping arrays. Supplementary Material, Table S1, summarizes the genotyping platforms, quality control criteria across studies, including SNP call rate, sample success rate, Hardy–Weinberg equilibrium and MAF. Imputation of HapMap haplotypes (CHB + JPT for all samples except CHLNS which used CHB + JPT + CEU) of ~2 million SNPs was carried out for each study using IMPUTE or MACH. Additional imputation within ±500 kb flanking region of rs3943077 at WDR11-FGFR2 was performed based on the haplotypes from the 1000 Genomes Project Phase 1 release (November 2010) of all Asian samples (ASN) in a subset of 3778 individuals from three Stage 1 cohorts, including SP2_1M, SP2_610K and CHLNS. SNPs with poor imputation quality (proper info < 0.5 for IMPUTE or Rsq < 0.3 for MACH) were excluded from association analysis. In Stage 3, genotyping for individuals from the KING, noGWAS, ACC and Nomura cohorts (n = 5724) was carried out using TaqMan, and all five SNPs had call rates >98.8%. SNP genotyping and imputation in SMHS (n = 230) were carried out using Affymetrix 6.0 and MACH, respectively. All five SNPs analyzed in SMHS were imputed from phased haplotypes of HapMap (R22 CHB + JPT), with imputation quality (MACH_Rsq) >0.76.

Statistical analysis and SNP prioritization

Association analyses within each cohort

In each individual cohort, adiponectin was natural log transformed to approximate normal distribution. Outliers defined as values greater than mean ± 4 SD were truncated. As the ranges of adiponectin levels substantially varied across studies (Supplementary Material, Table S1), natural log-transformed adiponectin was standardized to z-scores. In population-based studies, multiple linear regression models assuming an additive mode of inheritance were applied to test for association with genotyped or imputed SNPs by accounting for age, sex and BMI in Model 1, and without the adjustment for BMI in Model 2. The family-based study used regression models by the generalized estimating equation approach to adjust for the same covariates while also accounting for correlations among related individuals. Software applied for association analysis in each study is described in Supplementary Material, Table S1.

Meta-analysis of GWAS in Stage 1

The meta-analysis for adiponectin association with ~2.5 million SNPs was performed by two analysts independently each using two different methods of sample size weighted and inverse-variance weighted models implemented in METAL. Prior to meta-analysis, cohort-specific summary statistics were corrected using genomic control (λGC ranges 0.997–1.033), and the overall meta-analytic results were additionally corrected for genomic control (λGC = 1.009). The presence of heterogeneity was assessed by I² statistic and Cochran’s Q-test. After meta-analysis, ~226 000 (9%) SNPs were removed due to an effective sample size of <50% of the total sample size in Stage 1 and/or evidence of heterogeneity across cohorts (P for Cochran’s Q-test < 10−5). We applied the genome-wide association meta-analysis software to perform the sex-specific meta-analysis and test for heterogeneity between sex using the whole genome association data (53, 54).

In silico follow-up in Stage 2

A total of 612 SNPs had a meta-analyzed P-value of <10−4 in either Model 1 or 2. To prioritize SNPs for Stage 2 follow-up, we applied the ‘+–clump’ command implemented in PLINK (55) (http://pngu.mgh.harvard.edu/~purcell/plink/), by setting the LD threshold of r² < 0.1 in HapMap reference panel of CHB + JPT_r23a and disregarding the physical distance between SNPs. A total of 115 SNPs, including 110 clumped SNPs and 5 extra variants at/near each locus of WDR11-FGFR2, CDH13, ADIPOQ, PEPD and ZNF664, were tested for association with adiponectin in 4298 individuals from three cohorts with GWAS data. The cohort-level summary statistics from the in silico follow-up were meta-analyzed with the data from the seven individual cohorts in Stage 1.

Further follow-up in Stage 3

We selected lead SNPs representing the five novel genome-wide significant or suggestive loci (P < 10−5; WDR11-FGFR2, KCNH8, OR8S1-LALBA, HIVEP2 and GAL3ST1) from the Stages 1 and 2 combined meta-analysis, and followed up these loci in 5954 individuals from the four cohorts in Stage 3. Joint meta-analysis was carried out by combining the cohort-level summary statistics from all the 14 individual cohorts in Stages 1, 2 and 3.

Conditional analysis

Conditional analysis was conducted in the seven cohorts in Stage 1 by adding the most strongly associated SNP at a locus into the regression model as a covariate and testing the residual association with all remaining SNPs within ±500 kb flanking regions of the lead SNP. Sequential conditional analyses were performed until the strongest SNP displayed a conditional P-value of >10−4 in meta-analysis of the seven cohorts. Reciprocal conditional analyses were also carried out at two pairs of closely located (<2 Mb) loci, GPR109A and ZNF664 on 12q24.31, and at CMIP and CDH13 on 16q23.2–23.3, to
evaluate the independence of the association for these nearby loci. The regions for conditional analyses and the SNPs used as conditioning variables are shown in Supplementary Material, Table S6.

The explained phenotypic variance was calculated as: $2 \times \text{MAF} \times (1 - \text{MAF}) \times \beta^2_{\text{Z}}$ (56). Regional association plots were created using LocusZoom (57).

**SNP association with lipid and obesity-related anthropometric traits in Asians**

We investigated the evidence of association for the two variants of rs3943077 at WDR11-FGFR2 and rs11618618 at OR8S1-LALBA with lipid and obesity-related anthropometric traits that were available in other AGEN studies (Supplementary Material, text). The on-going AGEN lipids study provided the summary statistics for the SNP associations with triglycerides, HDL-C, LDL-C and total cholesterol in up to 25,413 Asians from 13 cohorts in the discovery stage. Association results for obesity and obesity-related anthropometric traits, including BMI, waist circumference and waist–hip ratio, were provided by the AGEN BMI study, the discovery stage of which consisted of 86,757 Asians from 21 individual studies.

**SUPPLEMENTARY MATERIAL**

Supplementary Material is available at HMG online.

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*Conflict of Interest statement.* None declared.

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