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Meta-analysis identifies common variants associated with body mass index in East Asians

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Abstract

Multiple genetic loci associated with obesity or body mass index (BMI) have been identified through genome-wide association studies conducted predominantly in populations of European ancestry. We conducted a meta-analysis of associations between BMI and approximately 2.4 million SNPs in 27,715 East Asians, followed by *in silico* and *de novo* replication in 37,691 and 17,642 additional East Asians, respectively. We identified ten BMI-associated loci at the genome-wide significance level ($P<5.0\times10^{-8}$), including seven previously identified loci (*FTO*, *SEC16B*, *MC4R*, *GIPR/QPCTL*, *ADCY3/RBJ*, *BDNF*, and *MAP2K5*) and three novel loci in or near the *CDKAL1*,*PCSK1*, and *GP2* genes. Three additional loci nearly reached the genome-wide significance threshold, including two previously identified loci in the *GNPDA2* and *TFAP2B* genes and a new locus near *PAX6*, which all had $P<5.0\times10^{-7}$. Findings from this study may shed light on new pathways involved in obesity and demonstrate the value of conducting genetic studies in non-European populations.

Since 2007, genome-wide association studies (GWAS) have contributed to a major leap forward in understanding the genetic basis of obesity[1–11]. To date, 37 genetic loci associated with obesity or body mass index (BMI) have been identified through these GWAS. However, virtually all of these studies were conducted in populations of European ancestry and included limited data from Asian populations[9, 11]. Asians, which account for over 60% of the world's population, have a greater percentage of body fat and higher metabolic

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disease risk than European-ancestry individuals with the same BMI[12]. Therefore, studies conducted in Asian populations not only allow an evaluation of whether genetic markers of obesity identified in North American and European populations can be generalized to Asians, but also facilitate the dissection of the genetic architecture of obesity and the identification of genetic variants of particular importance to Asians.

We began with an initial genome-wide association meta-analysis using BMI as the primary outcome based on approximately 2.4 million genotyped or imputed SNPs generated from eight GWAS including 27,715 East Asians (stage I). This was followed by an *in silico* replication analysis conducted among 37,691 East Asians from an additional seven GWAS (stage II) and subsequently a *de novo* replication conducted among 17,642 East Asians from three studies (stage III). All of these studies were conducted in populations of East Asian ancestry; details of the study designs are presented in Supplementary Figure 1 and described in the Supplementary Note and Supplementary Tables 1 to 3.

The stage I meta-analysis was performed using the METAL program (http://www.sph.umich.edu/csg/abecasis/Metal), and study-specific genomic control adjustment was applied (see ONLINE METHODS). The Stage I analysis revealed that three well established loci (*FTO*, *SEC16B*, and *MC4R*) were associated with BMI at or near the genome-wide significance level ($P<5\times10^{-8}$)[13] (Table 1, Figure 1).

In stage II, we analyzed 798 SNPs with a *P* value $<1.0\times10^{-4}$ in stage I and 50 additional SNPs that were previously reported to be associated with BMI in studies conducted in European-ancestry populations but that did not reach $P<1.0\times10^{-4}$ in stage I. Seven additional GWAS conducted in East Asian populations participated in stage II and provided regression analysis results for the selected SNPs. These data, along with the stage I meta-analysis results, were combined again in meta-analyses using methods similar to stage I with adjustment for both study-specific genomic control inflation and estimated residual inflation for the stage I meta-analysis results, which was 1.056 (see ONLINE METHODS). Analysis of combined data from stages I and II revealed that the index SNPs in six previously reported loci (*FTO*, *SEC16B*, *MC4R*, *GIPR/QPCTL*, *ADCY3/RBJ*, and *BDNF*) were genome-wide significant ($P<5.0\times10^{-8}$) and in three other previously reported loci (*GNPDA2*, *TFAP2B*, and *MAP2K5*) were near genome-wide significant ($P<5.0\times10^{-7}$) in East Asians (Table 1, Supplementary Table 4). In addition, the index SNPs in nine other previously reported loci were associated with BMI in the East Asian data at the nominal significance level ($P<0.05$) (Supplementary Table 4).

We compared two SNPs at each of the three loci *GIPR/QPCTL*, *ADCY3/RBJ*, and *MAP2K5* (Supplementary Table 5), one identified by our study and another by the GIANT consortium (published during the course of our study)[8]. The SNPs at *ADCY3/RBJ* and *MAP2K5* identified in our study are in linkage disequilibrium(LD) with the ones identified by the GIANT consortium. At *GIPR/QPCTL*, the SNP identified by our study, rs11671664, is not in LD in Asians ($r^2=0.026$) and is in weak LD in Europeans ($r^2=0.264$) with the SNP identified by the GIANT consortium, rs2287019. The latter was not in a statistically significant association with BMI in East Asians (see also Supplementary Table 4). Conditional analyses (see ONLINE METHODS) with the two SNPs in each locus included

in the same model for mutual adjustment showed that a statistically significant association with BMI remained only for the SNP identified by our study (Supplementary Table 5), suggesting that the SNP we identified may represent an independent association signal at the same locus in Asians.

The reported effect sizes for BMI-related SNPs in studies of European ancestry populations are usually greater than 3% of the standard deviation of BMI [4]. Given the sample sizes of our study (N=27,715 for stage I and N=65,406 for stages I and II combined), we had adequate statistical power (>0.8) to detect a SNP with such an effect size and with a MAF>0.2 in stage I or a MAF>0.08 in the combined stage I and II data at a significance level of $P<0.05$. The index SNPs in the 19 previously identified loci that were not replicated in our study at $P<0.05$ had either very small effect sizes or very low MAFs (two were not available, seven were monomorphic according to the HapMap Asian data) in East Asians (Supplementary Table 4).

We selected one representative SNP from each of seven loci for further replication, including the four loci at or near the *CDKAL1*, *PCSK1*, *PAX6*, and *GP2* genes that have not previously been reported to be associated with BMI and the three loci at the *GIPR/QPCTL,ADCY3/RBJ*, and *MAP2K5* genes that were reported by the GIANT consortium (the selection of these SNPs was completed before the publication of the GIANT paper)[8](Supplementary Table 4). Replication for these seven SNPs was conducted in stage III using *de novo* genotyping data from three study sites that included a total of 17,642 subjects (Supplementary Table 1 and 2). SNPs at other reported BMI loci that were genome-wide significant in stage I and II data were not included in the stage III *de novo* replication study for cost saving purposes. Stage III analyses found that the direction of the associations between BMI and the seven SNPs were consistent with stages I and II. The final results derived from a meta-analysis of data from all three stages combined, with adjustment for both study-specific genomic control inflation and estimated residual inflation for the stage I meta-analysis results, showed that six SNPs at or near *GIPR/QPCTL,ADCY3/RBJ*, *MAP2K5*, *CDKAL1*,*PCSK1*, and *GP2* were associated with BMI at the genome-wide significance level ($P=1.02\times10^{-8}$ to 5.93×10^{-14}) (Table 1) and SNP rs652722 near the *PAX6* gene nearly reached the genome-wide significance threshold ($P=7.65\times10^{-8}$) (Supplementary Table 6). The explained variances of these SNPs are also presented in Table 1.

We also evaluated the association of BMI with these seven SNPs in data obtained from the GIANT consortium. Three of these SNPs (rs654581, rs4776970, and rs1167166) at the three loci that were recently reported by the GIANT consortium[8] (*AGCY3/RBJ, MAP2K5*, and *GIPR/QPCTL*) and one newly identified SNP (rs261967) near the *PCSK1* gene exhibited a significant association with BMI at $P<0.007$ (=0.05/7, to account for seven tests for seven SNPs) (Supplementary Table 7). Although the effect sizes of these seven loci were smaller than those of the well established variants in the *FTO, MC4R*, and *SEC16B* loci (2.55–4.22 percentile of standard deviation of normal deviate versus 5.51–7.92, Table 1), their effect sizes were larger and the explained variances were bigger among East Asians than among Europeans (Supplementary Table 7, data obtained from the GIANT consortium), with the exception of SNP rs4776970 in the *MAP2K5* gene, which was independently identified by

both our study and the GIANT consortium. The explained variance of this SNP is 0.03% in Europeans (Supplementary Table 7) and 0.02% in Asians (Table 1).

As shown in Table 1, the *FTO* SNP had the biggest effect on BMI and accounted for the largest proportion of the variance (0.18%) in our study population, as compared with 0.34% estimated from the GIANT consortium[8]. Together, the 10 BMI loci that reached the genome-wide significance level explained 0.87% of the inter-individual variation in BMI. In order to provide a comparison with data from the GIANT consortium, we also estimated the inter-individual variation in BMI explained by all 22 loci that were associated with BMI at $P<0.05$, including the above 10 SNPs with a genome-wide significant association (Supplementary Table 4). These 22 loci explained 1.18% of the inter-individual variation in BMI in our study population (see ONLINE METHODS). These explained variances are lower than those reported by the GIANT consortium (1.45% for overall and 0.34% for FTO)[8]. Even after excluding SNPs within these 22 loci associated with BMI at $P<0.05$, the number of SNPs with small observed *P* values for an association with BMI still appeared to exceed the expected number (Figure 2), suggesting that additional BMI-related loci remain to be uncovered in these East Asian populations.

As shown in Supplementary Table 6, the associations with BMI for the SNPs in the four new loci at or near the *CDKAL1*, *PCSK1*, *PAX6*, and *GP2* genes were consistent across studies. Stratified analyses by sex and population showed that associations for all four loci were similar between men and women (*P* for homogeneity test ≥0.0837) and across Chinese, Japanese, Korean, and Malay populations (*P* for homogeneity test ≥0.185). Meta-analyses performed after excluding 23,093 subjects with chronic disease (cancer or diabetes), found similar associations, although with less significant *P* values due to the decreased sample size. Meta-analyses of obesity as a dichotomous outcome (BMI≥27.5)[14] also showed similar associations with odds ratios per allele ranging from 1.05 to 1.10, although the statistical power for this analysis was lower (Supplementary Table 8). Of the studies participating in our analyses, one stage II study (SCORM) was based on children (aged 9 years). Analysis of data from the SCROM study showed that all the four loci had an association with BMI consistent with the meta-analysis, and SNP rs652722 near the *PAX6* gene was nominally significant ($P=0.0335$) (Supplementary Table 6). Additional analysis excluding the SCORM study showed little change in the results.

The consistency of the findings across studies and populations suggests that population structure alone cannot account for the significant associations we identified. In addition, multiple SNPs in LD with each other showed similar associations in the combined stage I and II data at each locus (Figure 3, Supplementary Table 9). This plus the finding of similar associations in the *de novo* replication suggest that our results are unlikely to have been caused by genotyping or imputation errors.

The locus represented by SNP rs9356744 (6p22.3) contains the *CDKAL1* gene, which has been reported to affect type 2 diabetes risk in a number of studies[15–17]. A recent study reported an association between a *CDKAL1* SNP, rs4712526, and BMI at age 8 years[18]. SNP rs4712526 was not included in our stage II replication set, but our stage I data for this SNP showed results consistent with the previous report (the minor allele *A* was associated

with lower BMI, $P=1.75\times10^{-4}$, Supplementary Table 10). The SNP we identified, rs9356744, is in strong LD with rs4712526 ($r^2=0.87$) in Asians. To date, no study has reported an association between *CDKAL1* variants and adult BMI. Given the strong link between type 2 diabetes and obesity, we carried out additional analyses and reevaluated the association with BMI after excluding participants with type 2 diabetes. A similar association was observed, although the *P* value ($P=4.01\times10^{-8}$) was less significant (Supplementary Table 6). These results indicate that the association of rs9356744 with BMI cannot be explained by the inclusion of subjects with diabetes. Additionally, two SNPs in the *CDKAL1* gene (rs9356744 and rs9368222, Supplementary Table 9) are cis-expression quantitative trait loci (eQTLs) for the nearby *E2F3* gene, a transcription factor and tumor suppressor[19]. Okada et al[20] identified another SNP (rs2206734) in the *CDKAL1* gene. While the data obtained from the GIANT consortium showed no significant association of our identified SNP rs9356744 with BMI ($P=0.186$, Supplementary Table 7), a nominally significant association ($P=0.0049$, Table 1 in Okada et al[20]) between rs2206734 and BMI was observed in the GIANT consortium data. This discrepancy could be explained by differences in genetic architecture between East Asians and Europeans. SNPs rs9356744 and rs2206734 are in strong LD in Asians ($r^2=0.932$) and in weaker LD in Europeans ($r^2=0.396$). Taken together, the findings of our study and those of Okada et al, suggest that the functional SNP encoding risk for obesity is in LD with both rs9356744 and rs2206734 in East Asians but only with rs2206734 in populations of European ancestry. These differences in patterns of LD may facilitate further fine mapping to identify the functional variant by combining data across ethnic groups.

At the chromosome 5 locus (5q15), the top SNP, rs261967, along with 13 other SNPs that are in strong LD ($r^2=1.0$) with it, all reached the genome-wide significance threshold in the combined stage I and II data (Supplementary Table 9). The nearest gene to this locus is *PCSK1* (81.3kb away). A study using the candidate-gene approach reported two common non-synonymous coding variants (rs6234, rs6235) in the *PCSK1* gene that were associated with obesity[21]. However, these two SNPs showed no association with BMI in our study (Supplementary Table 10). None of the 14 SNPs identified at this locus by our study are in LD with the previously reported *PCSK1* SNPs ($r^2=0$) according to HapMap Asian data. Although SNP rs261967 was not statistically significant in the stage III replication, it showed an association with BMI ($P=0.00158$, Supplementary Table 7) in the data provided by the GIANT consortium[8]. Therefore, we believe that 5q15 represents a novel genetic locus for BMI and the association is unlikely to be a false positive finding.

The nearest genes flanking the chromosome 16 locus (16p12.3) are *GPR139* and *GP2*. Although only one SNP at this locus, rs12597579, reached the significance threshold of 1×10^{-4} for stage I screening and was therefore included in our stage II replication, multiple SNPs in this region showed an association with BMI that nearly met this significance threshold (Figure 3d). One of those SNPs, rs12598578 ($P=1.63\times10^{-4}$, Supplementary Table 10), which is in LD ($r^2=0.968$ in Asians) with the identified SNP rs12597579, is highly conserved across species according to the TRANSFAC database[22] and the common G allele creates a Ying-Yang transcription factor binding site (CONSITE http://www.phylogood.org/consite).

The top SNP at the chromosome 11 locus (11p13), rs652722, is approximately 66.0kb from the nearest gene, *PAX6*. However, SNP rs652722 exhibits no significant LD with SNPs in the *PAX6* gene or its 5′ region according to HapMap and 1000 Genomes Project data. Nevertheless, rs652722 is in LD with several SNPs that are predicted to be eQTLs, according to the SCAN database[23], for a number of genes potentially important in the regulation of body weight. Among them is expression of the *MIF* gene based on HapMap lymphoblastoid cell lines. High plasma levels of MIF are related to higher BMI[24]. Another gene associated with this eQTL is the *PFKP* gene, which, along with the *FTO* gene, has been associated with increased BMI, hip circumference, and weight[2]. The association of BMI with rs652722 did not reach the conventional genome-wide significance level; thus, additional replication is needed.

Among the multiple hits at the *ADCY3/RBJ* locus (Supplementary Table 4), SNP rs11676272 (P=5.88×10^{-10}) is a predicted missense mutation and causes a Ser107Pro change in the *ADCY3* gene. This change is predicted to be potentially deleterious by Polyphen (http://genetics.bwh.harvard.edu/pph/). This locus is also associated with expression of the *POMC* gene, which regulates energy balance, thus, the susceptibility to obesity[8]. In addition, SNPs rs11676272 and rs6545814 at this locus (r^2 =0.98 for LD between the two SNPs in Asians) are both eQTLs for the *ADCY3* gene[25].

In conclusion, our study identified 10 BMI-associated loci at the genome-wide significance level (P<5.0×10^{-8}), including seven loci previously identified by studies conducted among European-ancestry populations (*FTO, SEC16B, MC4R, GIPR/QPCTL, ADCY3/RBJ, BDNF*, and *MAP2K5*) and three novel loci in or near the *CDKAL1,PCSK1*, and *GP2* genes. Three additional loci nearly reached the genome-wide significance threshold, including two previously identified loci in the *GNPDA2* and *TFAP2B* genes and a new locus near *PAX6*, which all had P<5.0×10^{-7}.Of the three previously reported loci at *GIPR/QPCTL, ADCY3/RBJ*, and *MAP2K5*), conditional analyses with both SNPs at the same locus included in the same models showed that only the SNPs identified by our study were associated with BMI in East Asian populations. The representative SNP (rs261967) near the newly identified *PCSK1* gene exhibited a significant association (P=0.00158) with BMI in a European population. As expected, the explained variances of the previously reported loci were generally lower in East Asians compared with those in Europeans, while the explained variances for the newly identified loci from this study were generally larger in East Asians than in Europeans. Although the specific mechanisms through which these loci affect BMI and obesity require further study, the identification of new loci may shed light on new pathways involved in obesity. In addition, fine mapping of multi-ethnic populations could lead to identification of causal links.

Supplementary Material

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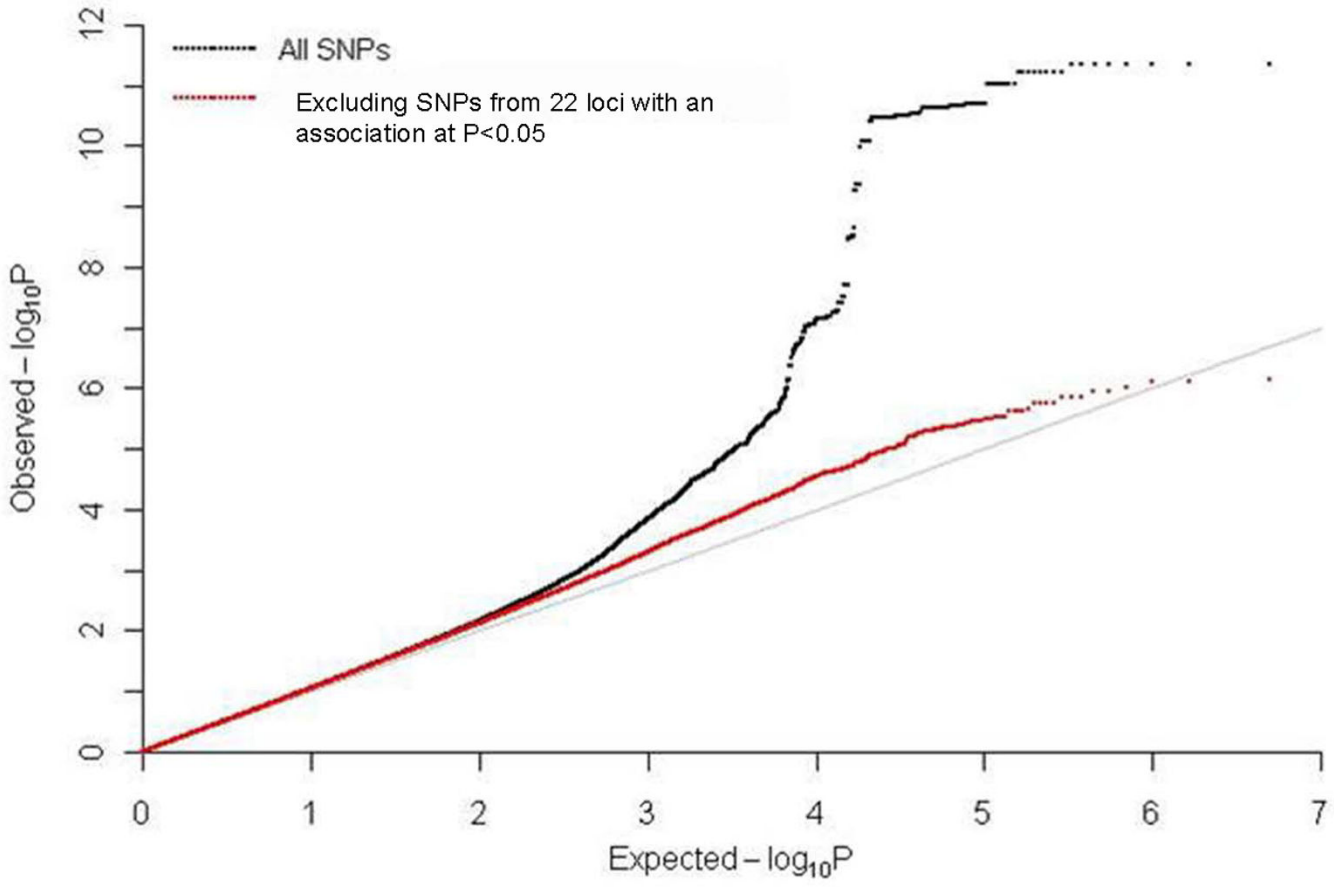

Figure 1.

Manhattan plot showing the significance of associations between BMI and SNPs in the stage I data. The SNPs in previously reported genes showing significant associations with BMI are highlighted in red. The SNPs in newly identified loci are highlighted in blue.

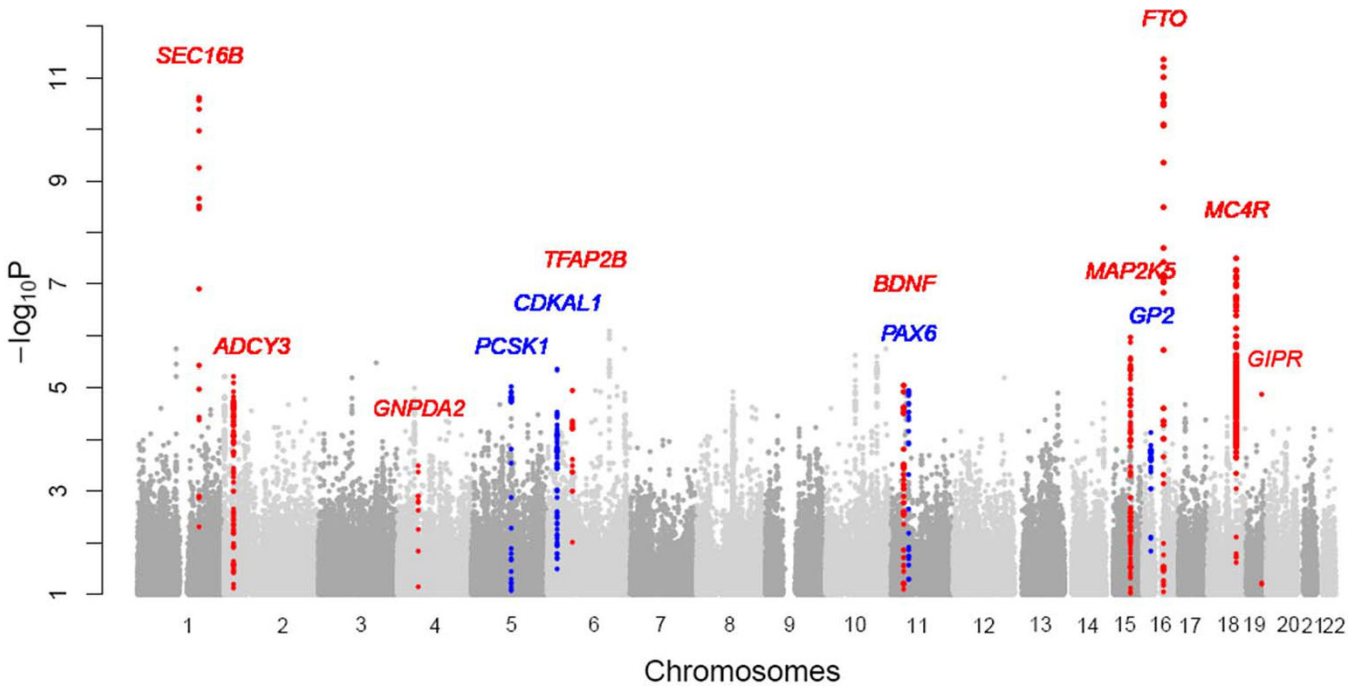

Figure 2.

Quantile-quantile plot for the association of BMI with SNPs in all stage I data (black) and after excluding SNPs in the 22 loci (red) with an association at P<0.05 as shown in Supplementary Table 4.

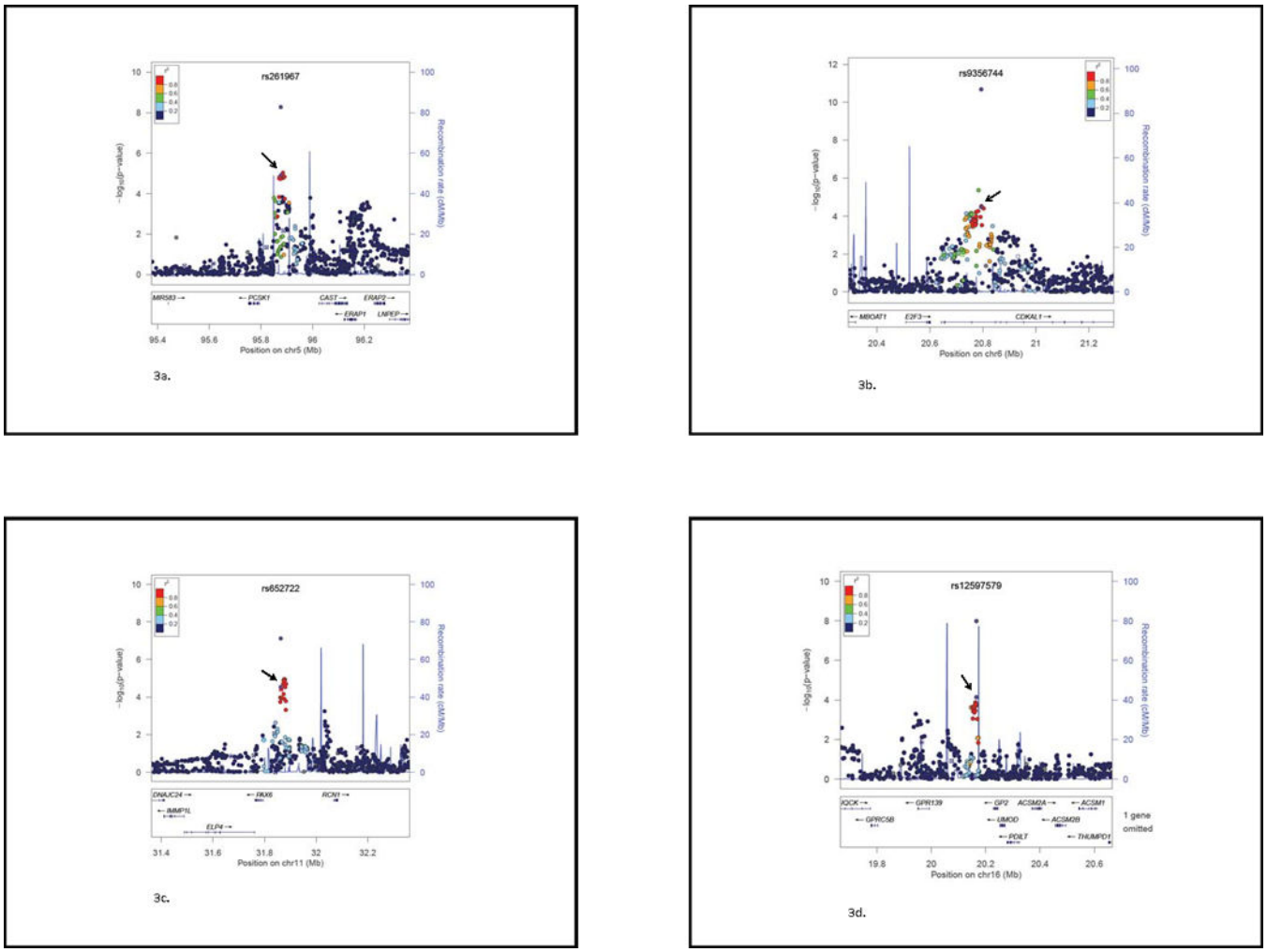

Figure 3.

Regional plots of four novel loci identified in this study. SNPs are plotted by their position on the chromosome against their association (-log10 *P* value) with BMI using stage 1 (GWAS meta-analysis) data. The name and *P* value for the top SNP shown on the plots is based on all combined data with full genomic control adjustment (Table 1). The *P* value in stage I for the same SNP is denoted by a purple circle and indicated with an arrow. Estimated recombination rates (from HapMap) are plotted in cyan to reflect the local LD structure. The SNPs surrounding the top SNP are color-coded (see inset) to reflect their LD with the top SNP (using pair-wise r^2 values from HapMap CHB + JPT). Genes and positions of exons, as well as directions of transcription, are shown below the plots (using data from the UCSC Genome Browser, genome.ucsc.edu). Plots were generated using LocusZoom.

Table 1

Identified loci associated with BMI variation in East Asian populations

Gene	Chr	SNP	Genotype[a]	EAF[b]	β (SE)[c]	P value by stages[d]				Explained Variance[f]
						I	II	III	Final[e]	
Previously identified BMI loci										
FTO	16	rs17817449	G/T	0.17	7.92(1.06)	6.13E-12	8.18E-14		4.60E-27	0.18%
SEC16B	1	rs574367	T/G	0.20	5.93(0.92)	2.38E-11	1.28E-10		9.47E-20	0.11%
MC4R	18	rs6567160	C/T	0.21	5.51(0.93)	6.92E-08	3.35E-09		2.76E-15	0.10%
GIPR/QPCTL	19	rs11671664	G/A	0.50	4.22(0.76)	1.29E-05	2.57E-08	3.57E-03	5.93E-14	0.09%
ADCY3/RBJ	2	rs6545814	G/A	0.45	3.26(0.76)	1.20E-05	1.62E-05	1.05E-05	1.35E-13	0.05%
BDNF	11	rs6265	C/T	0.44	4.97(0.83)	1.18E-05	2.72E-09		3.56E-13	0.12%
MAP2K5	15	rs4776970	A/T	0.22	2.55(0.90)	1.10E-06	4.63E-03	2.90E-03	2.33E-09	0.02%
Newly identified BMI loci										
CDKAL1	6	rs9356744	T/C	0.58	3.39(0.76)	3.21E-05	7.67E-06	3.02E-03	2.00E-11	0.06%
PCSK1	5	rs261967	C/A	0.41	3.77(0.77)	1.22E-05	9.36E-07	8.46E-01	5.13E-09	0.07%
GP2	16	rs12597579	C/T	0.80	4.09(0.96)	7.13E-05	2.07E-05	1.45E-01	1.02E-08	0.05%

[a] Shown as effect allele/other allele.

[b] Effect allele frequency in Asians, estimated from stages I and II studies.

[c] Per allele effect of SNPs (in percentage) on BMI, obtained from stage II data only.

[d] Derived from meta-analysis. The p values for the combined data were adjusted for both study-specific inflation factors and the estimated inflation factor for the stage I meta-analysis statistic.

[e] Combined all available data from three stages.

[f] The effect sizes obtained from stage II data were used to estimate the explained variance.