



Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body-fat distribution

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1 **PROTEIN-CODING VARIANTS IMPLICATE NOVEL GENES RELATED TO LIPID HOMEOSTASIS**
2 **CONTRIBUTING TO BODY FAT DISTRIBUTION**

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426

427 **ABSTRACT**

428 Body fat distribution is a heritable risk factor for a range of adverse health consequences,
429 including hyperlipidemia and type 2 diabetes. To identify protein-coding variants associated with body fat
430 distribution, assessed by waist-to-hip ratio adjusted for body mass index, we analyzed 228,985 predicted
431 coding and splice site variants available on exome arrays in up to 344,369 individuals from five major
432 ancestries for discovery and 132,177 independent European-ancestry individuals for validation. We
433 identified 15 common (minor allele frequency, MAF \geq 5%) and 9 low frequency or rare (MAF < 5%) coding
434 variants that have not been reported previously. Pathway/gene set enrichment analyses of all associated
435 variants highlight lipid particle, adiponectin level, abnormal white adipose tissue physiology, and bone
436 development and morphology as processes affecting fat distribution and body shape. Furthermore, the
437 cross-trait associations and the analyses of variant and gene function highlight a strong connection to
438 lipids, cardiovascular traits, and type 2 diabetes. In functional follow-up analyses, specifically in *Drosophila*
439 RNAi-knockdown crosses, we observed a significant increase in the total body triglyceride levels for two
440 genes (*DNAH10* and *PLXND1*). By examining variants often poorly tagged or entirely missed by genome-
441 wide association studies, we implicate novel genes in fat distribution, stressing the importance of
442 interrogating low-frequency and protein-coding variants.

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449 Body fat distribution, as assessed by waist-to-hip ratio (WHR), is a heritable trait and a well-
450 established risk factor for adverse metabolic outcomes¹⁻⁶. A high WHR often indicates a large presence
451 of intra-abdominal fat whereas a low WHR is correlated with a greater accumulation of gluteofemoral
452 fat. Lower values of WHR have been consistently associated with lower risk of cardiometabolic diseases
453 like type 2 diabetes (T2D)^{7,8}, or differences in bone structure and gluteal muscle mass⁹. These
454 epidemiological associations are consistent with the results of our previously reported genome-wide
455 association study (GWAS) of 49 loci associated with WHR (after adjusting for body mass index,
456 WHRadjBMI)¹⁰. Notably, a genetic predisposition to higher WHRadjBMI is associated with increased risk
457 of T2D and coronary heart disease (CHD), and this association appears to be causal⁹.

458 More recently, large-scale genetic studies have identified ~125 common loci for central obesity,
459 primarily non-coding variants of relatively modest effect, for different measures of body fat distribution¹⁰⁻
460 ¹⁶. Large scale interrogation of both common (minor allele frequency [MAF]≥5%) and low frequency or
461 rare (MAF<5%) coding and splice site variation may lead to additional insights into the genetic and
462 biological etiology of central obesity by narrowing in on causal genes contributing to trait variance. Thus,
463 we set out to identify protein-coding and splice site variants associated with WHRadjBMI using exome
464 array data and to explore their contribution to variation in WHRadjBMI through multiple follow-up
465 analyses.

466 **RESULTS**

467 **Protein-coding and splice site variation associated with body fat distribution**

468 We conducted a 2-stage fixed-effects meta-analysis testing both additive and recessive models in
469 order to detect protein-coding genetic variants that influence WHRadjBMI (**Online Methods, Figure 1**).
470 Our stage 1 meta-analysis included up to 228,985 variants (218,195 with MAF<5%) in up to 344,369
471 individuals from 74 studies of European (N=288,492), South Asian (N=29,315), African (N=15,687), East

472 Asian (N=6,800) and Hispanic/Latino (N=4,075) descent, genotyped with an ExomeChip array
473 **(Supplementary Tables 1-3)**. For stage 2, we assessed 70 suggestively significant ($P < 2 \times 10^{-6}$) variants from
474 stage 1 in two independent cohorts from the United Kingdom [UK Biobank (UKBB), N=119,572] and
475 Iceland (deCODE, N=12,605) **(Online Methods, Supplementary Data 1-3)** for a total stage 1+2 sample size
476 of 476,546 (88% European). Variants were considered statistically significant in the total meta-analyzed
477 sample (stage 1+2) when they achieved a significance threshold of $P < 2 \times 10^{-7}$ after Bonferroni correction
478 for multiple testing (0.05/246,328 variants tested). Of the 70 variants brought forward, two common and
479 five rare variants were not available in either Stage 2 study **(Tables 1-2, Supplementary Data 1-3)**. Thus,
480 we require $P < 2 \times 10^{-7}$ in Stage 1 for significance. Variants are considered novel if they were greater than
481 one megabase (Mb) from a previously-identified WHRadjBMI lead SNP¹⁰⁻¹⁶.

482 In stages 1 and 2 combined all ancestry meta-analyses, we identified 48 coding variants (16 novel)
483 across 43 genes, 47 identified assuming an additive model, and one more variant under a recessive model
484 **(Table 1, Supplementary Figures 1-4)**. Due to the possible heterogeneity introduced by combining
485 multiple ancestries¹⁷, we also performed a European-only meta-analysis. Here, four additional coding
486 variants were significant (three novel) assuming an additive model **(Table 1, Supplementary Figures 5-8)**.
487 Of these 52 significant variants (48 from the all ancestry and 4 from the European-only analyses), eleven
488 were of low frequency, including seven novel variants in *RAPGEF3*, *FGFR2*, *R3HDML*, *HIST1H1T*, *PCNXL3*,
489 *ACVR1C*, and *DARS2*. These low frequency variants tended to display larger effect estimates than any of
490 the previously reported common variants **(Figure 2)**¹⁰. In general, variants with MAF < 1% had effect sizes
491 approximately three times greater than those of common variants (MAF > 5%). Although, we cannot rule
492 out the possibility that additional rare variants with smaller effects sizes exist that, despite our ample
493 sample size, we are still underpowered to detect (See estimated 80% power in **Figure 2**). However, in the
494 absence of common variants with similarly large effects, our results point to the importance of
495 investigating rare and low frequency variants to identify variants with large effects **(Figure 2)**.

496 Given the established differences in the genetic underpinnings between sexes for
497 WHRadjBMI^{10,11}, we also performed sex-stratified analyses and report variants that were array-wide
498 significant ($P < 2 \times 10^{-7}$) in at least one sex stratum and exhibit significant sex-specific effects ($P_{\text{sexhet}} < 7.14 \times 10^{-4}$, see **Online Methods**). We found four additional novel variants that were not identified in the sex-
499 combined meta-analyses (in *UGGT2* and *MMP14* for men only; and *DSTYK* and *ANGPTL4* for women only)
500 (**Table 2, Supplementary Figures 9-15**). Variants in *UGGT2* and *ANGPTL4* were of low frequency
501 (MAF_{men}=0.6% and MAF_{women}=1.9%, respectively). Additionally, 14 variants from the sex-combined meta-
502 analyses displayed stronger effects in women, including the novel, low frequency variant in *ACVR1C*
503 (rs55920843, MAF=1.1%, **Supplementary Figure 4**). Overall, 19 of the 56 variants (32%) identified across
504 all meta-analyses (48 from all ancestry, 4 from European-only and 4 from sex-stratified analyses) showed
505 significant sex-specific effects on WHRadjBMI (**Figure 1**): 16 variants with significantly stronger effects in
506 women, and three in men (**Figure 1**).

508 In summary, we identified 56 array-wide significant coding variants ($P < 2.0 \times 10^{-7}$); 43 common (14
509 novel) and 13 low frequency or rare variants (9 novel). For all 55 significant variants from the additive
510 model (47 from all ancestry, 4 from European-only, and 4 from sex-specific analyses), we examined
511 potential collider bias^{18,19}, i.e. potential bias in effect estimates caused by adjusting for a correlated and
512 heritable covariate like BMI, for the relevant sex stratum and ancestry. We corrected each of the variant
513 - WHRadjBMI associations for the correlation between WHR and BMI and the correlation between the
514 variant and BMI (**Online Methods, Supplementary Table 7, Supplementary Note 1**). Overall, 51 of the 55
515 additive model variants were robust against collider bias^{18,19} across all primary and secondary meta-
516 analyses. Of the 55, 25 of the WHRadjBMI variants from the additive model were nominally associated
517 with BMI ($P_{\text{BMI}} < 0.05$), yet effect sizes changed little after correction for potential biases (15% change in
518 effect estimate on average). For 4 of the 55 SNPs (rs141845046, rs1034405, rs3617, rs9469913, **Table 1**),
519 the association with WHRadjBMI appears to be attenuated following correction ($P_{\text{corrected}} > 9 \times 10^{-4}$,

520 0.05/55), including one novel variant, rs1034405 in *C3orf18*. Thus, these 4 variants warrant further
521 functional investigations to quantify their impact on WHR, as a true association may still exist, although
522 the effect may be slightly overestimated in the current analysis.

523 Using stage 1 meta-analysis results, we then aggregated low frequency variants across genes and
524 tested their joint effect with both SKAT and burden tests²⁰ (**Supplementary Table 8, Online Methods**). We
525 identified five genes that reached array-wide significance ($P < 2.5 \times 10^{-6}$, 0.05/16,222 genes tested),
526 *RAPGEF3*, *ACVR1C*, *ANGPTL4*, *DNAI1*, and *NOP2*. However, while all genes analyzed included more than
527 one variant, none remained significant after conditioning on the single variant with the most significant
528 p-value. We identified variants within *RAPGEF3*, *ACVR1C*, *ANGPTL4* that reached suggestive significance
529 in Stage 1 and chip-wide significance in stage 1+2 for one or more meta-analyses (**Tables 1 and 2**);
530 however, we did not identify any significant variants for *DNAI1* and *NOP2*. While neither of these genes
531 had a single variant that reached chip-wide significance, they each had variants with nearly significant
532 results (*NOP2*: $P = 3.69 \times 10^{-5}$, *DNAI1*: 4.64×10^{-5}). Combined effects with these single variants and others in
533 LD within the gene likely drove the association in our aggregate gene-based tests, but resulted in non-
534 significance following conditioning on the top variant. While our results suggest these associations are
535 driven by a single variant, each gene may warrant consideration in future investigations.

536

537 **Conditional analyses**

538 We next implemented conditional analyses to determine (1) the number of independent
539 association signals the 56 array-wide significant coding variants represent, and (2) whether the 33 variants
540 near known GWAS association signals (± 1 Mb) represent independent novel association signals. To
541 determine if these variants were independent association signals, we used approximate joint conditional
542 analyses to test for independence in stage 1 (**Online Methods; Supplementary Table 4**)²⁰. Only the *RSPO3*-
543 *KIAA0408* locus contains two independent variants 291 Kb apart, rs1892172 in *RSPO3* (MAF=46.1%,

544 $P_{\text{conditional}}=4.37 \times 10^{-23}$ in the combined sexes, and $P_{\text{conditional}}=2.4 \times 10^{-20}$ in women) and rs139745911 in
545 *KIAA0408* (MAF=0.9%, $P_{\text{conditional}}=3.68 \times 10^{-11}$ in the combined sexes, and $P_{\text{conditional}}=1.46 \times 10^{-11}$ in women;
546 **Figure 3A**).

547 Further, 33 of our significant variants are within one Mb of previously identified GWAS tag SNPs
548 for WHRadjBMI. We again used approximate joint conditional analysis to test for independence in the
549 stage 1 meta-analysis dataset and obtained further complementary evidence from the UKBB dataset
550 where necessary (**Online Methods**). We identified one coding variant representing a novel independent
551 signal in a known locus [*RREB1*; stage1 meta-analysis, rs1334576, EAF = 0.44, $P_{\text{conditional}}= 3.06 \times 10^{-7}$,
552 (**Supplementary Table 5, Figure 3 [B]**); UKBB analysis, rs1334576, *RREB1*, $P_{\text{conditional}}= 1.24 \times 10^{-8}$,
553 (**Supplementary Table 6**) in the sex-combined analysis.

554 In summary, we identified a total of 56 WHRadjBMI-associated coding variants in 41 independent
555 association signals. Of these 41 independent association signals, 24 are new or independent of known
556 GWAS-identified tag SNPs (either >1MB +/- or array-wide significant following conditional analyses)
557 (**Figure 1**). Thus, bringing our total to 15 common and 9 low-frequency or rare novel variants following
558 conditional analyses. The remaining non-GWAS-independent variants may assist in narrowing in on the
559 causal variant or gene underlying these established association signals.

560 **Gene set and pathway enrichment analysis**

561 To determine if the significant coding variants highlight novel biological pathways and/or provide
562 additional support for previously identified biological pathways, we applied two complementary pathway
563 analysis methods using the EC-DEPICT (ExomeChip Data-driven Expression Prioritized Integration for
564 Complex Traits) pathway analysis tool,^{21,22} and PASCAL²³ (**Online Methods**). While for PASCAL all variants
565 were used, in the case of EC-DEPICT, we examined 361 variants with suggestive significance ($P < 5 \times 10^{-4}$)^{10,17}
566 from the combined ancestries and combined sexes analysis (which after clumping and filtering became

567 101 lead variants in 101 genes). We separately analyzed variants that exhibited significant sex-specific
568 effects ($P_{\text{sexhet}} < 5 \times 10^{-4}$).

569 The sex-combined analyses identified 49 significantly enriched gene sets ($\text{FDR} < 0.05$) that grouped
570 into 25 meta-gene sets (**Supplementary Note 2, Supplementary Data 4-5**). We noted a cluster of meta-
571 gene sets with direct relevance to metabolic aspects of obesity (“enhanced lipolysis,” “abnormal glucose
572 homeostasis,” “increased circulating insulin level,” and “decreased susceptibility to diet-induced
573 obesity”); we observed two significant adiponectin-related gene sets within these meta-gene sets. While
574 these pathway groups had previously been identified in the GWAS DEPICT analysis (**Figure 4**), many of the
575 individual gene sets within these meta-gene sets were not significant in the previous GWAS analysis, such
576 as “insulin resistance,” “abnormal white adipose tissue physiology,” and “abnormal fat cell morphology”
577 (**Supplementary Data 4, Figure 4, Supplementary Figure 16a**), but represent similar biological
578 underpinnings implied by the shared meta-gene sets. Despite their overlap with the GWAS results, these
579 analyses highlight novel genes that fall outside known GWAS loci, based on their strong contribution to
580 the significantly enriched gene sets related to adipocyte and insulin biology (e.g. *MLXIPL*, *ACVR1C*, and
581 *ITIH5*) (**Figure 4**).

582 To focus on novel findings, we conducted pathway analyses after excluding variants from previous
583 WHRadjBMI analyses¹⁰ (**Supplemental Note 2**). Seventy-five loci/genes were included in the EC-DEPICT
584 analysis, and we identified 26 significantly enriched gene sets (13 meta-gene sets). Here, all but one gene
585 set, “lipid particle size”, were related to skeletal biology. This result likely reflects an effect on the pelvic
586 skeleton (hip circumference), shared signaling pathways between bone and fat (such as TGF-beta) and
587 shared developmental origin²⁴ (**Supplementary Data 5, Supplementary Figure 16b**). Many of these
588 pathways were previously found to be significant in the GWAS DEPICT analysis; these findings provide a
589 fully independent replication of their biological relevance for WHRadjBMI.

590 We used PASCAL (**Online Methods**) to further distinguish between enrichment based on *coding-*
591 *only* variant associations (this study) and *regulatory-only* variant associations (up to 20 kb upstream of the
592 gene from a previous GIANT study¹⁰). For completeness, we also compared the coding pathways to those
593 that could be identified in the total previous GWAS effort (using both *coding and regulatory* variants) by
594 PASCAL. The analysis revealed 116 significantly enriched coding pathways (FDR<0.05; **Supplementary**
595 **Table 9**). In contrast, a total of 158 gene sets were identified in the coding+regulatory analysis that
596 included data from the previous GIANT waist GWAS study. Forty-two gene sets were enriched in both
597 analyses. Thus, while we observed high concordance in the $-\log_{10}$ (p-values) between ExomeChip and
598 GWAS gene set enrichment (Pearson's r (coding vs regulatory only) = 0.38, $P < 10^{-300}$; Pearson's r (coding vs
599 coding+regulatory) = 0.51, $P < 10^{-300}$), there are gene sets that seem to be enriched *specifically* for variants
600 in coding regions (e.g., decreased susceptibility to diet-induced obesity, abnormal skeletal morphology)
601 or unique to variants in regulatory regions (e.g. transcriptional regulation of white adipocytes)
602 (**Supplementary Figure 17**).

603 The EC-DEPICT and PASCAL results showed a moderate but strongly significant correlation (for EC-
604 DEPICT and the PASCAL max statistic, $r = .277$ with $p = 9.8 \times 10^{-253}$; for EC-DEPICT and the PASCAL sum
605 statistic, $r = .287$ with $p = 5.42 \times 10^{-272}$). Gene sets highlighted by both methods strongly implicated a role
606 for pathways involved in skeletal biology, glucose homeostasis/insulin signaling, and adipocyte biology.
607 Indeed, we are even more confident in the importance of this core overlapping group of pathways due to
608 their discovery by both methods (**Supplementary Figure 18**).

609 **Cross-trait associations**

610 To assess the relevance of our identified variants with cardiometabolic, anthropometric, and
611 reproductive traits, we conducted association lookups from existing ExomeChip studies of 15 traits
612 (**Supplementary Data 6, Supplementary Figure 19**). Indeed, the clinical relevance of central adiposity is
613 likely to be found in the cascade of impacts such variants have on downstream cardiometabolic

614 disease.^{22,25-29} We found that variants in *STAB1* and *PLCB3* display the greatest number of significant cross-
615 trait associations, each associating with seven different traits ($P < 9.8 \times 10^{-4}$, 0.05/51 variants tested). Of
616 note, these two genes cluster together with *RSPO3*, *DNAH10*, *MNS1*, *COBLL1*, *CCDC92*, and *ITIH3*
617 (**Supplementary Data 6, Supplementary Figure 19**). The WHR-increasing alleles in this cluster of variants
618 exhibit a pattern of increased cardiometabolic risk (e.g. increased fasting insulin [FI], two-hour glucose
619 [TwoHGlu], and triglycerides [TG]; and decreased high-density lipoprotein cholesterol [HDL]), but also
620 decreased BMI. This phenomenon, where variants associated with lower BMI are also associated with
621 increased cardiometabolic risk, has been previously reported.³⁰⁻³⁶ A recent Mendelian Randomization
622 (MR) analysis of the relationship between central adiposity (measured as WHRadjBMI) and
623 cardiometabolic risk factors found central adiposity to be causal.⁹ Using 48 WHR-increasing variants
624 reported in the recent GIANT analysis¹⁰ to calculate a polygenic risk score, Emdin *et al.* found that a 1 SD
625 increase in genetic risk of central adiposity was associated with higher total cholesterol, triglyceride levels,
626 fasting insulin and two-hour glucose, and lower HDL – all indicators of cardiometabolic disease, and also
627 associated with a 1 unit decrease in BMI⁹.

628 We conducted a search in the NHGRI-EBI GWAS Catalog^{37,38} to determine if any of our significant
629 ExomeChip variants are in high LD ($R^2 > 0.7$) with variants associated with traits or diseases not covered by
630 our cross trait lookups (**Supplementary Data 7**). We identified several cardiometabolic traits (adiponectin,
631 coronary heart disease *etc.*) and behavioral traits potentially related to obesity (carbohydrate, fat intake
632 *etc.*) with GWAS associations that were not among those included in cross-trait analyses and nearby one
633 or more of our WHRadjBMI- associated coding variants. Additionally, many of our ExomeChip variants are
634 in LD with GWAS variants associated with other behavioral and neurological traits (schizophrenia, bipolar
635 disorder *etc.*), and inflammatory or autoimmune diseases (Crohn's Disease, multiple sclerosis *etc.*)
636 (**Supplementary Data 7**).

637 Given the established correlation between total body fat percentage and WHR ($R= 0.052$ to
638 0.483)³⁹⁻⁴¹, we examined the association of our top exome variants with both total body fat percentage
639 (BF%) and truncal fat percentage (TF%) available in a sub-sample of up to 118,160 participants of UKBB
640 (**Supplementary Tables 10-11**). Seven of the common novel variants were significantly associated
641 ($P<0.001$, 0.05/48 variants examined) with both BF% and TF% in the sexes-combined analysis (*COBLL1*,
642 *UHRF1BP1*, *WSCD2*, *CCDC92*, *IFI30*, *MPV17L2*, *IZUMO1*). Only one of our tag SNPs, rs7607980 in *COBLL1*,
643 is nearby a known total body fat percentage BF% GWAS locus (rs6738627; $R^2=0.1989$, distance=6751 bp,
644 with our tag SNP)⁴². Two additional variants, rs62266958 in *EFCAB12* and rs224331 in *GDF5*, were
645 significantly associated with TF% in the women-only analysis. Of the nine SNPs associated with at least
646 one of these two traits, all variants displayed much greater magnitude of effect on TF% compared to BF%
647 (**Supplementary Figure 20**).

648 Previous studies have demonstrated the importance of examining common and rare variants
649 within genes with mutations known to cause monogenic diseases^{43,44}. We assessed enrichment of our
650 WHRadjBMI within genes that cause monogenic forms of lipodystrophy) and/or insulin resistance
651 (**Supplementary Data 8**). No significant enrichment was observed (**Supplementary Figure 21**). For
652 lipodystrophy, the lack of significant findings may be due in part to the small number of implicated genes
653 and the relatively small number of variants in monogenic disease-causing genes, reflecting their
654 intolerance of variation.

655 **Genetic architecture of WHRadjBMI coding variants**

656 We used summary statistics from our stage 1 results to estimate the phenotypic variance
657 explained by ExomeChip coding variants. We calculated the variance explained by subsets of SNPs across
658 various significance thresholds ($P< 2\times 10^{-7}$ to 0.2) and conservatively estimated using only independent tag
659 SNPs (**Supplementary Table 12, Online Methods, and Supplementary Figure 22**). The 22 independent
660 significant coding SNPs in stage 1 account for 0.28% of phenotypic variance in WHRadjBMI. For

661 independent variants that reached suggestive significance in stage 1 ($P < 2 \times 10^{-6}$), 33 SNPs explain 0.38% of
662 the variation; however, the 1,786 independent SNPs with a liberal threshold of $P < 0.02$ explain 13 times
663 more variation (5.12%). While these large effect estimates may be subject to winner's curse, for array-
664 wide significant variants, we detected a consistent relationship between effect magnitude and MAF in our
665 stage 2 analyses in UK Biobank and deCODE (**Supplementary Data 1-3**). Notably, the Exomechip coding
666 variants explained less of the phenotypic variance than in our previous GIANT investigation, wherein 49
667 significant SNPs explained 1.4% of the variance in WHRadjBMI. When considering all coding variants on
668 the ExomeChip in men and women together, 46 SNPs with a $P < 2 \times 10^{-6}$ and 5,917 SNPs with a $P < 0.02$ explain
669 0.51% and 13.75% of the variance in WHRadjBMI, respectively. As expected given the design of the
670 ExomeChip, the majority of the variance explained is attributable to rare and low frequency coding
671 variants (independent SNPs with $MAF < 1\%$ and $MAF < 5\%$ explain 5.18% and 5.58%, respectively). However,
672 for rare and low frequency variants, those that passed significance in stage 1 explain only 0.10% of the
673 variance in WHRadjBMI. As in **Figure 2**, these results also indicate that there are additional coding variants
674 associated with WHRadjBMI that remain to be discovered, particularly rare and low frequency variants
675 with larger effects than common variants. Due to observed differences in association strength between
676 women and men, we estimated variance explained for the same set of SNPs in women and men
677 separately. As observed in previous studies¹⁰, there was significantly ($P_{RsqDiff} < 0.002 = 0.05/21$, Bonferroni-
678 corrected threshold) more variance explained in women compared to men at each significance threshold
679 considered (differences ranged from 0.24% to 0.91%).

680 To better understand the potential clinical impact of WHRadjBMI associated variants, we
681 conducted penetrance analysis using the UKBB population (both sexes combined, and men- and women-
682 only). We compared the number of carriers and non-carriers of the minor allele for each of our significant
683 variants in centrally obese and non-obese individuals to determine if there is a significant accumulation
684 of the minor allele in either the centrally obese or non-obese groups (**Online Methods**). Three rare and

685 low frequency variants (MAF \leq 1%) with larger effect sizes (effect size $>$ 0.90) were included in the
686 penetrance analysis using World Health Organization (WHO- obese women WHR $>$ 0.85 and obese men
687 WHR $>$ 0.90) WHR cut-offs for central obesity. Of these, one SNV (rs55920843-ACVR1C; $P_{\text{sex-combined}}=9.25 \times 10^{-5}$;
688 $P_{\text{women}}=4.85 \times 10^{-5}$) showed a statistically significant difference in the number of carriers and non-carriers
689 of the minor allele when the two strata were compared (sex-combined obese carriers=2.2%; non-obese
690 carriers=2.6%; women obese carriers=2.1%; non-obese women carriers=2.6% (**Supplementary Table 13**,
691 **Supplementary Figure 23**). These differences were significant in women, but not in men ($P_{\text{men}} < 5.5 \times 10^{-3}$
692 after Bonferroni correction for 9 tests) and agree with our overall meta-analysis results, where the minor
693 allele (G) was significantly associated with lower WHRadjBMI in women only (**Tables 1 and 2**).

694 **Evidence for functional role of significant variants**

695 ***Drosophila* Knockdown**

696 Considering the genetic evidence of adipose and insulin biology in determining body fat
697 distribution¹⁰, and the lipid signature of the variants described here, we examined whole-body
698 triglycerides levels in adult *Drosophila*, a model organism in which the fat body is an organ functionally
699 analogous to mammalian liver and adipose tissue and triglycerides are the major source of fat storage⁴⁵.
700 Of the 51 genes harboring our 56 significantly associated variants, we identified 27 with *Drosophila*
701 orthologues for functional follow-up analyses. In order to prioritize genes for follow-up, we selected genes
702 with large changes in triglyceride storage levels ($>$ 20% increase or $>$ 40% decrease, as chance alone is
703 unlikely to cause changes of this magnitude, although some decrease is expected) after considering each
704 corresponding orthologue in an existing large-scale screen for adipose with \leq 2 replicates per knockdown
705 strain.⁴⁵ Two orthologues, for *PLXND1* and *DNAH10*, from two separate loci met these criteria. For these
706 two genes, we conducted additional knockdown experiments with \geq 5 replicates using tissue-specific
707 drivers (fat body [cg-Gal4] and neuronal [elav-Gal4] specific RNAi-knockdowns) (**Supplementary Table**
708 **14**). A significant ($P < 0.025$, 0.05/2 orthologues) increase in the total body triglyceride levels was observed

709 in *DNAH10* orthologue knockdown strains for both the fat body and neuronal drivers. However, only the
710 neuronal driver knockdown for *PLXND1* produced a significant change in triglyceride storage. *DNAH10*
711 and *PLXND1* both lie within previous GWAS identified regions. Adjacent genes have been highlighted as
712 likely candidates for the *DNAH10* association region, including *CCDC92* and *ZNF664* based on eQTL
713 evidence. However, our fly knockdown results support *DNAH10* as the causal genes underlying this
714 association. Of note, rs11057353 in *DNAH10* showed suggestive significance after conditioning on the
715 known GWAS variants in nearby *CCDC92* (sex-combined $P_{\text{conditional}}=7.56 \times 10^{-7}$; women-only rs11057353
716 $P_{\text{conditional}}= 5.86 \times 10^{-7}$, **Supplementary Table 6**; thus providing some evidence of multiple causal
717 variants/genes underlying this association signal. Further analyses are needed to determine whether the
718 implicated coding variants from the current analysis are the putatively functional variants, specifically how
719 these variants affect transcription in and around these loci, and exactly how those effects alter biology of
720 relevant human metabolic tissues.

721 ***eQTL Lookups***

722 To gain a better understanding of the potential functionality of novel and low frequency variants,
723 we examined the *cis*-association of the identified variants with expression level of nearby genes in
724 subcutaneous adipose tissue, visceral omental adipose tissue, skeletal muscle and pancreas from GTEx⁴⁶,
725 and assessed whether the exome and eQTL associations implicated the same signal (**Online Methods**,
726 **Supplementary Data 9, Supplementary Table 15**). The lead exome variant was associated with expression
727 level of the coding gene itself for *DAGLB*, *MLXIPL*, *CCDC92*, *MAPKBP1*, *LRRC36* and *UQCC1*. However, at
728 three of these loci (*MLXIPL*, *MAPKBP1*, and *LRRC36*), the lead exome variant is also associated with
729 expression level of additional nearby genes, and at three additional loci, the lead exome variant is only
730 associated with expression level of nearby genes (*HEMK1* at *C3orf18*; *NT5DC2*, *SMIM4* and *TMEM110* at
731 *STAB1/ITIH3*; and *C6orf106* at *UHRF1BP1*). Although detected with a missense variant, these loci are also

732 consistent with a regulatory mechanism of effect as they are significantly associated with expression levels
733 of genes, and the association signal may well be due to LD with nearby regulatory variants.

734 Some of the coding genes implicated by eQTL analyses are known to be involved in adipocyte
735 differentiation or insulin sensitivity: e. g. for *MLXIPL*, the encoded carbohydrate responsive element
736 binding protein is a transcription factor, regulating glucose-mediated induction of *de novo* lipogenesis in
737 adipose tissue, and expression of its *beta*-isoform in adipose tissue is positively correlated with adipose
738 insulin sensitivity^{47,48}. For *CCDC92*, the reduced adipocyte lipid accumulation upon knockdown confirmed
739 the involvement of its encoded protein in adipose differentiation⁴⁹.

740 ***Biological Curation***

741 To gain further insight into the possible functional role of the identified variants, we conducted
742 thorough searches of the literature and publicly available bioinformatics databases (**Supplementary Data**
743 **10-11, Box 1, Online Methods**). Many of our novel low frequency variants are in genes that are intolerant
744 of nonsynonymous mutations (e.g. *ACVR1C*, *DARS2*, *FGFR2*; ExAC Constraint Scores >0.5). Like previously
745 identified GWAS variants, several of our novel coding variants lie within genes that are involved in glucose
746 homeostasis (e.g. *ACVR1C*, *UGGT2*, *ANGPTL4*), angiogenesis (*RASIP1*), adipogenesis (*RAPGEF3*), and lipid
747 biology (*ANGPTL4*, *DAGLB*) (**Supplementary Data 10, Box 1**).

748

749 **DISCUSSION**

750 Our two-staged approach to analysis of coding variants from ExomeChip data in up to 476,546
751 individuals identified a total of 56 array-wide significant variants in 41 independent association signals,
752 including 24 newly identified (23 novel and one independent of known GWAS signals) that influence
753 WHRadjBMI. Nine of these variants were low frequency or rare, indicating an important role for low
754 frequency variants in the polygenic architecture of fat distribution and providing further insights into its

755 underlying etiology. While, due to their rarity, these coding variants only explain a small proportion of the
756 trait variance at a population level, they may, given their predicted role, be more functionally tractable
757 than non-coding variants and have a critical impact at the individual and clinical level. For instance, the
758 association between a low frequency variant (rs11209026; R381Q; MAF<5% in ExAC) located in the *IL23R*
759 gene and multiple inflammatory diseases (such as psoriasis⁵⁰, rheumatoid arthritis⁵¹, ankylosing
760 spondylitis⁵², and inflammatory bowel diseases⁵³) led to the development of new therapies, targeting *IL23*
761 and *IL12* in the same pathway (reviewed in ⁵⁴⁻⁵⁶). Thus, we are encouraged that our associated low
762 frequency coding variants displayed large effect sizes; all but one of the nine novel low frequency variants
763 had an effect size larger than the 49 SNPs reported in Shungin *et al.* 2015, and some of these effect sizes
764 were up to 7-fold larger than those previously reported for GWAS. This finding mirrors results for other
765 cardiometabolic traits⁵⁷, and suggests variants of possible clinical significance with even larger effect and
766 lower frequency variants will likely be detected through larger additional genome-wide scans of many
767 more individuals.

768 We continue to observe sexual dimorphism in the genetic architecture of WHRadjBMI¹¹. Overall,
769 we identified 19 coding variants that display significant sex differences, of which 16 (84%) display larger
770 effects in women compared to men. Of the variants outside of GWAS loci, we reported three (two with
771 MAF<5%) that show a significantly stronger effect in women and two (one with MAF<5%) that show a
772 stronger effect in men. Additionally, genetic variants continue to explain a higher proportion of the
773 phenotypic variation in body fat distribution in women compared to men^{10,11}. Of the novel female (*DSTYK*
774 and *ANGPTL4*) and male (*UGGT2* and *MMP14*) specific signals, only *ANGPTL4* implicated fat distribution
775 related biology associated with both lipid biology and cardiovascular traits (**Box 1**). Sexual dimorphism in
776 fat distribution is apparent from childhood and throughout adult life⁵⁸⁻⁶⁰, and at sexually dimorphic loci,
777 hormones with different levels in men and women may interact with genomic and epigenomic factors to
778 regulate gene activity, though this remains to be experimentally documented. Dissecting the underlying

779 molecular mechanisms of the sexual dimorphism in body fat distribution, and also how it is correlated
780 with – and causing – important comorbidities like T2D and cardiovascular diseases will be crucial for
781 improved understanding of disease risk and pathogenesis.

782 Overall, we observe fewer significant associations between WHRadjBMI and coding variants on
783 the ExomeChip than Turcot *et al.*²⁵ examining the association of low frequency and rare coding variants
784 with BMI. In line with these observations, we identify fewer pathways and cross-trait associations. One
785 reason for fewer WHRadjBMI implicated variants and pathways may be smaller sample size ($N_{\text{WHRadjBMI}} =$
786 $476,546$, $N_{\text{BMI}} = 718,639$), and thus, lower statistical power. Power, however, is likely not the only
787 contributing factor. For example, Turcot *et al.*²⁵ have comparative sample sizes between BMI and that of
788 Marouli *et al.*²² studying height ($N_{\text{height}} = 711,428$). However, greater than seven times the number of
789 coding variants are identified for height than for BMI, indicating that perhaps a number of other factors,
790 including trait architecture, heritability (possibly overestimated in some phenotypes), and phenotype
791 precision, likely all contribute to our study's capacity to identify low frequency and rare variants with large
792 effects. Further, it is possible that the comparative lack of significant findings for WHRadjBMI and BMI
793 compared to height may be a result of higher selective pressure against genetic predisposition to
794 cardiometabolic phenotypes, such as BMI and WHR. As evolutionary theory predicts that harmful alleles
795 will be low frequency⁶¹, we may need larger sample sizes to detect rare variants that have so far escaped
796 selective pressures. Lastly, the ExomeChip is limited by the variants that are present on the chip, which
797 was largely dictated by sequencing studies in European-ancestry populations and a MAF detection criteria
798 of $\sim 0.012\%$. It is likely that through an increased sample size, use of chips designed to detect variation
799 across a range of continental ancestries, high quality, deep imputation with large reference samples (e.g.
800 HRC), and/or alternative study designs, future studies will detect additional variation from the entire allele
801 frequency spectrum that contributes to fat distribution phenotypes.

802 The collected genetic and epidemiologic evidence has now demonstrated that fat distribution (as
803 measured by increased WHRadjBMI) is correlated with increased risk of T2D and CVD, and that this
804 association is likely causal with potential mediation through blood pressure, triglyceride-rich lipoproteins,
805 glucose, and insulin⁹. This observation yields an immediate follow-up question: Which mechanisms
806 regulate depot-specific fat accumulation and are risks for disease, driven by increased visceral or
807 decreased subcutaneous adipose tissue mass (or both)? Pathway analysis identified several novel
808 pathways and gene sets related to metabolism and adipose regulation, bone growth and development
809 we also observed a possible role for adiponectin, a hormone which has been linked to “healthy” expansion
810 of adipose tissue and insulin sensitivity⁶². Similarly, expression/eQTL results support the function and
811 relevance of adipogenesis, adipocyte biology, and insulin signaling, supporting our previous findings for
812 WHRadjBMI¹⁰. We also provide evidence suggesting known biological functions and pathways
813 contributing to body fat distribution (e.g., diet-induced obesity, angiogenesis, bone growth and
814 morphology, and enhanced lipolysis).

815 The ultimate aim of genetic investigations of obesity-related traits, like those presented here, is
816 to identify genomic pathways that are dysregulated leading to obesity pathogenesis, and may result in a
817 myriad of downstream illnesses. Thus, our findings may enhance the understanding of central obesity and
818 identify new molecular targets to avert its negative health consequences. Significant cross-trait
819 associations and additional associations observed in the GWAS Catalog are consistent with expected
820 direction of effect for several traits, i.e. the WHR-increasing allele is associated with higher values of TG,
821 DBP, fasting insulin, TC, LDL and T2D across many significant variants. However, it is worth noting that
822 there are some exceptions. For example, rs9469913-A in *UHRF1BP1* is associated with both increased
823 WHRadjBMI and increased HDL. Also, we identified two variants in *MLXIPL* (rs3812316 and rs35332062),
824 a well-known lipids-associated locus, in which the WHRadjBMI-increasing allele also increases all lipid
825 levels, risk for hypertriglyceridemia, SBP and DBP. However, our findings show a significant and negative

826 association with HbA1C, and nominally significant and negative associations with two-hour glucose,
827 fasting glucose, and Type 2 diabetes, and potential negative associations with biomarkers for liver disease
828 (e.g. gamma glutamyl transpeptidase). Other notable exceptions include *ITIH3* (negatively associated with
829 BMI, HbA1C, LDL and SBP), *DAGLB* (positively associated with HDL), and *STAB1* (negatively associated with
830 TC, LDL, and SBP in cross-trait associations). Therefore, caution in selecting pathways for therapeutic
831 targets is warranted; one must look beyond the effects on central adiposity, but also at the potential
832 cascading effects of related diseases.

833 A seminal finding from this study is the importance of lipid metabolism for body fat distribution.
834 In fact, pathway analyses that highlight enhanced lipolysis, cross-trait associations with circulating lipid
835 levels, existing biological evidence from the literature, and knockdown experiments in *Drosophila*
836 examining triglyceride storage point to novel candidate genes (*ANGPTL4*, *ACVR1C*, *DAGLB*, *MGA*, *RASIP1*,
837 and *IZUMO1*) and new candidates in known regions (*DNAH10*¹⁰ and *MLXIPL*¹⁴) related to lipid biology and
838 its role in fat storage. Newly implicated genes of interest include *ACVR1C*, *MLXIPL*, and *ANGPTL4*, all of
839 which are involved in lipid homeostasis; all are excellent candidate genes for central adiposity. Carriers of
840 inactivating mutations in *ANGPTL4* (*Angiopoietin Like 4*), for example, display low triglyceride levels and
841 low risk of coronary artery disease⁶³. *ACVR1C* encodes the activin receptor-like kinase 7 protein (ALK7), a
842 receptor for the transcription factor TGFB-1, well known for its central role in growth and development in
843 general⁶⁴⁻⁶⁸, and adipocyte development in particular⁶⁸. *ACVR1C* exhibits the highest expression in adipose
844 tissue, but is also highly expressed in the brain⁶⁹⁻⁷¹. In mice, decreased activity of *ACVR1C* upregulates
845 PPAR γ and C/EBP α pathways and increases lipolysis in adipocytes, thus decreasing weight and diabetes in
846 mice^{69,72,73}. Such activity is suggestive of a role for ALK7 in adipose tissue signaling and therefore for
847 therapeutic targets for human obesity. *MLXIPL*, also important for lipid metabolism and postnatal cellular
848 growth, is a transcription factor which activates triglyceride synthesis genes in a glucose-dependent
849 manner^{74,75}. The lead exome variant in this gene is highly conserved, most likely damaging, and is

850 associated with reduced *MLXIPL* expression in adipose tissue. Furthermore, in a recent longitudinal, *in*
851 *vitro* transcriptome analysis of adipogenesis in human adipose-derived stromal cells, gene expression of
852 *MLXIPL* was up-regulated during the maturation of adipocytes, suggesting a critical role in the regulation
853 of adipocyte size and accumulation⁷⁶. However, given our observations on cross-trait associations with
854 variants in *MLXIPL* and diabetes-related traits, development of therapeutic targets must be approached
855 cautiously.

856 Taken together, our 24 novel variants for WHRadjBMI offer new biology, highlighting the
857 importance of lipid metabolism in the genetic underpinnings of body fat distribution. We continue to
858 demonstrate the critical role of adipocyte biology and insulin resistance for central obesity and offer
859 support for potentially causal genes underlying previously identified fat distribution GWAS loci. Notably,
860 our findings offer potential new therapeutic targets for intervention in the risks associated with abdominal
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863
864

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1103 **COMPETING INTERESTS**

1104 The authors declare the following competing interests: ASB holds interest in AstraZeneca, Biogen,
1105 Bioverativ, Merck, Novartis and Pfizer. ASC and CSF are current employees of Merck.
1106 Authors affiliated with deCODE (VSt, GT, UT and KS) are employed by deCODE Genetics/Amgen, I
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1108 Sanofi Aventis; Eli Lilly; NIH; Omthera Pharmaceuticals, Pfizer, Elsal Inc. AstraZeneca; DalCor and Services;
1109 Lecture fees: Sanofi Aventis; Advisory Boards: Acetelion, Sirtex, CSL Boehringer. JD has received grants from
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1111 GlaxoSmithKline. MPD received honoraria and holds minor equity in Dalcor. VS has participated in a
1112 conference trip sponsored by Novo Nordisk.

1113 **METHODS**

1114 **Studies**

1115 Stage 1 consisted of 74 studies (12 case/control studies, 59 population-based studies, and five
1116 family studies) comprising 344,369 adult individuals of the following ancestries: 1) European descent (N=
1117 288,492), 2) African (N= 15,687), 3) South Asian (N= 29,315), 4) East Asian (N=6,800), and 5) Hispanic
1118 (N=4,075). Stage 1 meta-analyses were carried out in each ancestry separately and in the all ancestries
1119 group, for both sex-combined and sex-specific analyses. Follow-up analyses were undertaken in 132,177
1120 individuals of European ancestry from the deCODE anthropometric study and UK Biobank (**Supplementary**
1121 **Tables 1-3**). Conditional analyses were performed in the all ancestries and European descent groups.
1122 Informed consent was obtained for participants by the parent study and protocols approved by each
1123 study's institutional review boards.

1124 **Phenotypes**

1125 For each study, WHR (waist circumference divided by hip circumference) was corrected for age,
1126 BMI, and the genomic principal components (derived from GWAS data, the variants with MAF >1% on the
1127 ExomeChip, and ancestry informative markers available on the ExomeChip), as well as any additional
1128 study-specific covariates (e.g. recruiting center), in a linear regression model. For studies with non-related
1129 individuals, residuals were calculated separately by sex, whereas for family-based studies sex was included
1130 as a covariate in models with both men and women. Additionally, residuals for case/control studies were
1131 calculated separately. Finally, residuals were inverse normal transformed and used as the outcome in
1132 association analyses. Phenotype descriptives by study are shown in **Supplementary Table 3**.

1133 **Genotypes and QC**

1134 The majority of studies followed a standardized protocol and performed genotype calling using
1135 the algorithms indicated in **Supplementary Table 2**, which typically included zCall³. For 10 studies
1136 participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium,
1137 the raw intensity data for the samples from seven genotyping centers were assembled into a single project
1138 for joint calling⁴. Study-specific quality control (QC) measures of the genotyped variants were
1139 implemented before association analysis (**Supplementary Tables 1-2**). Furthermore, to assess the
1140 possibility that any significant associations with rare and low-frequency variants could be due to allele
1141 calling in the smaller studies, we performed a sensitivity meta-analysis including all large studies (>5,000
1142 participants) and compared to all studies. We found very high concordance for effect sizes, suggesting
1143 that smaller studies do not bias our results (**Supplementary Fig. 24**).

1144 **Study-level statistical analyses**

1145 Individual cohorts were analyzed for each ancestry separately, in sex-combined and sex-specific
1146 groups, with either RAREMETALWORKER (<http://genome.sph.umich.edu/wiki/RAREMETALWORKER>) or
1147 RVTESTs (<http://zhanxw.github.io/rvtests/>), to associate inverse normal transformed WHRadjBMI with
1148 genotype accounting for cryptic relatedness (kinship matrix) in a linear mixed model. These software
1149 programs are designed to perform score-statistic based rare-variant association analysis, can
1150 accommodate both unrelated and related individuals, and provide single-variant results and variance-
1151 covariance matrices. The covariance matrix captures linkage disequilibrium (LD) relationships between
1152 markers within 1 Mb, which is used for gene-level meta-analyses and conditional analyses^{77,78}. Single-
1153 variant analyses were performed for both additive and recessive models.

1154 **Centralized quality-control**

1155 Individual cohorts identified ancestry population outliers based on 1000 Genome Project phase 1
1156 ancestry reference populations. A centralized quality-control procedure implemented in EasyQC⁷⁹ was

1157 applied to individual cohort association summary statistics to identify cohort-specific problems: (1)
1158 assessment of possible errors in phenotype residual transformation; (2) comparison of allele frequency
1159 alignment against 1000 Genomes Project phase 1 reference data to pinpoint any potential strand issues,
1160 and (3) examination of quantile-quantile (QQ) plots per study to identify any inflation arising from
1161 population stratification, cryptic relatedness and genotype biases.

1162 **Meta-analyses**

1163 Meta-analyses were carried out in parallel by two different analysts at two sites using
1164 RAREMETAL⁷⁷. During the meta-analyses, we excluded variants if they had call rate <95%, Hardy-Weinberg
1165 equilibrium P-value < 1×10^{-7} , or large allele frequency deviations from reference populations (>0.6 for all
1166 ancestries analyses and >0.3 for ancestry-specific population analyses). We also excluded from
1167 downstream analyses markers not present on the Illumina ExomeChip array 1.0, variants on the Y-
1168 chromosome or the mitochondrial genome, indels, multiallelic variants, and problematic variants based
1169 on the Blat-based sequence alignment analyses. Significance for single-variant analyses was defined at an
1170 array-wide level ($P < 2 \times 10^{-7}$). For all suggestive significant variants from Stage 1, we tested for significant
1171 sex differences. We calculated P_{sexhet} for each SNP, testing for difference between women-specific and
1172 men-specific beta estimates and standard errors using EasyStrata^{11,80}. Each SNP that reached
1173 $P_{\text{sexhet}} < 0.05/\#$ of variants tested (70 variants brought forward from Stage 1, $P_{\text{sexhet}} < 7.14 \times 10^{-4}$) was
1174 considered significant. Additionally, while each individual study was asked to perform association analyses
1175 stratified by race/ethnicity, and adjust for population stratification, all study-specific summary statistics
1176 were meta-analyzed together for our all ancestry meta-analyses. To investigate potential heterogeneity
1177 across ancestries, we did examine ancestry-specific meta-analysis results for our top 70 variants from
1178 stage 1, and found no evidence of significant across-ancestry heterogeneity observed for any of our top
1179 variants (I^2 values noted in **Supplementary Data 1-3**).

1180 For the gene-based analyses, we applied two sets of criteria to select variants with a MAF<5%
1181 within each ancestry based on coding variant annotation from five prediction algorithms (PolyPhen2,
1182 HumDiv and HumVar, LRT, MutationTaster, and SIFT)^{80,81}. Our broad gene-based tests included nonsense,
1183 stop-loss, splice site, and missense variants annotated as damaging by at least one algorithm mentioned
1184 above. Our strict gene-based tests included only nonsense, stop-loss, splice site, and missense variants
1185 annotated as damaging by all five algorithms. These analyses were performed using the sequence kernel
1186 association test (SKAT) and variable threshold (VT) methods. Statistical significance for gene-based tests
1187 was set at a Bonferroni-corrected threshold of $P < 2.5 \times 10^{-6}$ (0.05/~20,000 genes). All gene-based tests were
1188 performed in RAREMETAL⁷⁷.

1189 **Genomic inflation**

1190 We observed a marked genomic inflation of the test statistics even after controlling for population
1191 stratification (linear mixed model) arising mainly from common markers; λ_{GC} in the primary meta-analysis
1192 (combined ancestries and combined sexes) was 1.06 and 1.37 for all and only common coding and splice
1193 site markers considered herein, respectively (**Supplementary Figures 3, 7 and 13, Supplementary Table**
1194 **16**). Such inflation is expected for a highly polygenic trait like WHRadjBMI, for studies using a non-random
1195 set of variants across the genome, and is consistent with our very large sample size^{79,82,83}.

1196 **Conditional analyses**

1197 The RAREMETAL R-package⁷⁷ was used to identify independent WHRadjBMI association signals
1198 across all ancestries and European meta-analysis results. RAREMETAL performs conditional analyses by
1199 using covariance matrices to distinguish true signals from the shadows of adjacent significant variants in
1200 LD. First, we identified the lead variants ($P < 2 \times 10^{-7}$) based on a 1Mb window centered on the most
1201 significantly associated variant. We then conditioned on the lead variants in RAREMETAL and kept new

1202 lead signals at $P < 2 \times 10^{-7}$ for conditioning in a second round of analysis. The process was repeated until no
1203 additional signal emerged below the pre-specified P-value threshold ($P < 2 \times 10^{-7}$).

1204 To test if the associations detected were independent of the previously published WHRadjBMI
1205 variants^{10,14,16}, we performed conditional analyses in the stage 1 discovery set if the GWAS variant or its
1206 proxy ($r^2 \geq 0.8$) was present on the ExomeChip using RAREMETAL⁷⁷. All variants identified in our meta-
1207 analysis and the previously published variants were also present in the UK Biobank dataset⁸⁴. This dataset
1208 was used as a replacement dataset if a good proxy was not present on the ExomeChip as well as a
1209 replication dataset for the variants present on the ExomeChip. All conditional analyses in the UK Biobank
1210 dataset were performed using SNPTTEST⁸⁵⁻⁸⁷. The conditional analyses were carried out reciprocally,
1211 conditioning on the ExomeChip variant and then the previously published variant. An association was
1212 considered independent of the previously published association if there was a statistically significant
1213 association detected prior to the conditional analysis ($P < 2 \times 10^{-7}$) with both the exome chip variant and the
1214 previously published variant, and the observed association with both or either of the variants disappeared
1215 upon conditional analysis ($P > 0.05$). A conditional p-value between 9×10^{-6} and 0.05 was considered
1216 inconclusive. However, a conditional p-value $< 9 \times 10^{-6}$ was also considered suggestive.

1217

1218 **Stage 2 meta-analyses**

1219 In our Stage 2, we sought to validate a total of 70 variants from Stage 1 that met $P < 2 \times 10^{-6}$ in two
1220 independent studies, the UK Biobank (Release 1⁸⁴) and Iceland (deCODE), comprising 119,572 and 12,605
1221 individuals, respectively (Supplementary Tables 1-3). The same QC and analytical methodology were used
1222 for these studies. Genotyping, study descriptions and phenotype descriptives are provided in
1223 **Supplementary Tables 1-3**. For the combined analysis of Stage 1 plus 2, we used the inverse-variance
1224 weighted fixed effects meta-analysis method. Significant associations were defined as those nominally

1225 significant ($P < 0.05$) in the Stage 2 study and for the combined meta-analysis (Stage 1 plus Stage 2)
1226 significance was set at $P < 2 \times 10^{-7}$ ($0.05 / \sim 250,000$ variants).

1227 **Pathway enrichment analyses: EC-DEPICT**

1228 We adapted DEPICT, a gene set enrichment analysis method for GWAS data, for use with the
1229 ExomeChip ('EC-DEPICT'); this method is also described in a companion manuscript²². DEPICT's primary
1230 innovation is the use of "reconstituted" gene sets, where many different types of gene sets (e.g. canonical
1231 pathways, protein-protein interaction networks, and mouse phenotypes) were extended through the use
1232 of large-scale microarray data (see Pers et al.²¹ for details). EC-DEPICT computes p-values based on
1233 Swedish ExomeChip data (Malmö Diet and Cancer (MDC), All New Diabetics in Scania (ANDIS), and Scania
1234 Diabetes Registry (SDR) cohorts, $N = 11,899$) and, unlike DEPICT, takes as input only the genes directly
1235 containing the significant (coding) variants rather than all genes within a specified amount of linkage
1236 disequilibrium (see **Supplementary Note 2**).

1237 Two analyses were performed for WHRadjBMI ExomeChip: one with all variants $p < 5 \times 10^{-4}$ (49
1238 significant gene sets in 25 meta-gene sets, $FDR < 0.05$) and one with all variants > 1 Mb from known GWAS
1239 loci¹⁰ (26 significant gene sets in 13 meta-gene sets, $FDR < 0.05$). Affinity propagation clustering⁸⁸ was
1240 used to group highly correlated gene sets into "meta-gene sets"; for each meta-gene set, the member
1241 gene set with the best p-value was used as representative for purposes of visualization (see
1242 Supplementary Note). DEPICT for ExomeChip was written using the Python programming language, and
1243 the code can be found at <https://github.com/RebeccaFine/obesity-ec-depict>.

1244 **Pathway enrichment analyses: PASCAL**

1245 We also applied the PASCAL pathway analysis tool²³ to exome-wide association summary statistics
1246 from Stage 1 for all coding variants. The method derives gene-based scores (both SUM and MAX statistics)
1247 and subsequently tests for over-representation of high gene scores in predefined biological pathways. We

1248 used standard pathway libraries from KEGG, REACTOME and BIOCARTA, and also added dichotomized (Z-
1249 score>3) reconstituted gene sets from DEPICT²¹. To accurately estimate SNP-by-SNP correlations even for
1250 rare variants, we used the UK10K data (TwinsUK⁸⁹ and ALSPAC⁹⁰ studies , N=3781). In order to separate
1251 the contribution of regulatory variants from the coding variants, we also applied PASCAL to association
1252 summary statistics of only regulatory variants (20 kb upstream) and regulatory+coding variants from the
1253 Shungin et al¹⁰ study. In this way, we could comment on what is gained by analyzing coding variants
1254 available on ExomeChip arrays. We performed both MAX and SUM estimations for pathway enrichment.
1255 MAX is more sensitive to genesets driven primarily by a single signal, while SUM is better when there are
1256 multiple variant associations in the same gene.

1257 **Monogenic obesity enrichment analyses**

1258 We compiled two lists consisting of 31 genes with strong evidence that disruption causes
1259 monogenic forms of insulin resistance or diabetes; and 8 genes with evidence that disruption causes
1260 monogenic forms of lipodystrophy. To test for enrichment of association, we conducted simulations by
1261 matching each gene with others based on gene length and number of variants tested, to create a matched
1262 set of genes. We generated 1,000 matched gene sets from our data, and assessed how often the number
1263 of variants exceeding set significance thresholds was greater than in our monogenic obesity gene set.

1264 **Variance explained**

1265 We estimated the phenotypic variance explained by the association signals in Stage 1 all
1266 ancestries analyses for men, women, and combined sexes⁹¹. For each associated region, we pruned
1267 subsets of SNPs within 500 kb, as this threshold was comparable with previous studies, of the SNPs with
1268 the lowest P-value and used varying P value thresholds (ranging from 2×10^{-7} to 0.02) from the combined
1269 sexes results. Additionally, we examined all variants and independent variants across a range of MAF
1270 thresholds. The variance explained by each subset of SNPs in each strata was estimated by summing the

1271 variance explained by the individual top coding variants. For the comparison of variance explained
1272 between men and women, we tested for the significance of the differences assuming that the weighted
1273 sum of chi-squared distributed variables tend to a Gaussian distribution ensured by Lyapunov's central
1274 limit theorem.^{91,92}

1275 **Cross-trait lookups**

1276 To carefully explore the relationship between WHRadjBMI and related cardiometabolic,
1277 anthropometric, and reproductive traits, association results for the 51 WHRadjBMI coding SNPs were
1278 requested from existing or on-going meta-analyses from 7 consortia, including ExomeChip data from
1279 GIANT (BMI, height), Global Lipids Genetics Consortium Results (GLGC) (total cholesterol, triglycerides,
1280 HDL-cholesterol, LDL-cholesterol), International Consortium for Blood Pressure (IBPC)⁹³ (systolic and
1281 diastolic blood pressure), Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)
1282 (glycemic traits), and DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium (type 2
1283 diabetes).^{22,25-29} For coronary artery disease, we accessed 1000 Genomes Project-imputed GWAS data
1284 released by CARDIoGRAMplusC4D⁹⁴ and for the ReproGen consortium (age at menarche and menopause)
1285 we used a combination of ExomeChip and 1000 Genomes Project-Imputed GWAS data. Heatmaps were
1286 generated in R v3.3.2 using gplots (<https://CRAN.R-project.org/package=gplots>). We used Euclidean
1287 distance based on p-value and direction of effect and complete linkage clustering for the dendrograms.

1288 **GWAS Catalog Lookups**

1289 In order to determine if significant coding variants were associated with any related
1290 cardiometabolic and anthropometric traits, we also searched the NHGRI-EBI GWAS Catalog for previous
1291 variant-trait associations near our lead SNPs (+/- 500 kb). We used PLINK to calculate LD for variants using
1292 ARIC study European participants. All SNVs within the specified regions with an r^2 value > 0.7 were retained
1293 from NHGRI-EBI GWAS Catalog for further evaluation³⁷. Consistent direction of effect was based on WHR-

1294 increasing allele, LD, and allele frequency. Therefore, when a GWAS Catalog variant was not identical or
1295 in high LD ($r^2 > 0.9$) with the WHR variant, and MAF > 0.45 , we do not comment on direction of effect.

1296 **Body-fat percentage associations**

1297 We performed body fat percent and truncal fat percent look-up of 48 of the 56 identified variants
1298 (tables 1 and 2) that were available in the UK Biobank, Release 1⁸⁴, data (notably some of the rare variants
1299 in table 1 and 2 were not available) to further characterize their effects on WHRadjBMI. Genome-wide
1300 association analyses for body fat percent and truncal fat percent were carried out in the UK Biobank. Prior
1301 to analysis, phenotype data were filtered to exclude pregnant or possibly pregnant women, individuals
1302 with body mass index < 15 , and without genetically confirmed European ancestry, resulting in a sample
1303 size of 120,286. Estimated measures of body fat percent and truncal fat percent were obtained using the
1304 Tanita BC418MA body composition analyzer (Tanita, Tokyo, Japan). Individuals were not required to fast
1305 and did not follow any specific instructions prior to the bioimpedance measurements. SNPTTEST was used
1306 to perform the analyses based on residuals adjusted for age, 15 principle components, assessment center
1307 and the genotyping chip⁸⁵.

1308 **Collider bias**

1309 In order to evaluate SNPs for possible collider bias¹⁸, we used results from a recent association
1310 analysis from GIANT on BMI²⁵. For each significant SNP identified in our additive models, WHRadjBMI
1311 associations were corrected for potential bias due to associations between each variant and BMI (See
1312 **Supplementary Note 1** for additional details). Variants were considered robust against collider bias if they
1313 met Bonferroni-corrected significance following correction ($P_{\text{corrected}} < 9.09 \times 10^{-4}$, $0.05/55$ variants
1314 examined).

1315 **Drosophila RNAi knockdown experiments**

1316 For each gene in which coding variants were associated with WHRadjBMI in the final combined
1317 meta-analysis ($P < 2 \times 10^{-7}$), its corresponding *Drosophila* orthologues were identified in the Ensembl
1318 ortholog database (www.ensembl.org), when available. *Drosophila* triglyceride content values were
1319 mined from a publicly available genome-wide fat screen data set⁴⁵ to identify potential genes for follow-
1320 up knockdowns. Estimated values represent fractional changes in triglyceride content in adult male flies.
1321 Data are from male progeny resulting from crosses of male UAS-RNAi flies from the Vienna *Drosophila*
1322 Resource Center (VDRC) and Hsp70-GAL4; Tub-GAL8ts virgin females. Two-to-five-day-old males were
1323 sorted into groups of 20 and subjected to two one-hour wet heatshocks four days apart. On the seventh
1324 day, flies were picked in groups of eight, manually crushed and sonicated, and the lysates heat-inactivated
1325 for 10 min in a thermocycler at 95 °C. Centrifuge-cleared supernatants were then used for triglyceride
1326 (GPO Trinder, Sigma) and protein (Pierce) determination. Triglyceride values from these adult-induced
1327 ubiquitous RNAi knockdown individuals were normalized to those obtained in parallel from non-
1328 heatshocked progeny from the very same crosses. The screen comprised one to three biological replicates.
1329 We followed up each gene with a >0.2 increase or >0.4 decrease in triglyceride content.

1330 Orthologues for two genes were brought forward for follow-up, *DNAH10* and *PLXND1*. For both
1331 genes, we generated adipose tissue (*cg-Gal4*) and neuronal (*elav-Gal4*) specific RNAi-knockdown crosses
1332 to knockdown transcripts in a tissue specific manner, leveraging upstream activation sequence (UAS)-
1333 inducible short-hairpin knockdown lines, available through the VDRC (Vienna *Drosophila* Resource
1334 Center). Specifically, *elav-Gal4*, which drives expression of the RNAi construct in post mitotic neurons
1335 starting at embryonic stages all the way to adulthood, was used. *Cg* drives expression in the fat body and
1336 hemocytes starting at embryonic stage 12, all the way to adulthood. We crossed male UAS-RNAi flies and
1337 *elav-GAL4* or *CG-GAL4* virgin female flies. All fly experiments were carried out at 25°C. Five-to-seven-day-
1338 old males were sorted into groups of 20, weighed and homogenated in PBS with 0.05% Tween with Lysing
1339 Matrix D in a beadshaker. The homogenate was heat-inactivated for 10 min in a thermocycler at 70°C.

1340 10 μ l of the homogenate was subsequently used in a triglyceride assay (Sigma, Serum Triglyceride
1341 Determination Kit) which was carried out in duplicate according to protocol, with one alteration: the
1342 samples were cleared of residual particulate debris by centrifugation before absorbance reading.
1343 Resulting triglyceride values were normalized to fly weight and larval/population density. We used the
1344 non-parametric Kruskal-Wallis test to compare wild type with knockdown lines.

1345 **Expression quantitative trait loci (eQTLs) analysis**

1346 We queried the significant variant (Exome coding SNPs)-gene pairs associated with eGenes across
1347 five metabolically relevant tissues (skeletal muscle, subcutaneous adipose, visceral adipose, liver and
1348 pancreas) with at least 70 samples in the GTEx database⁴⁶. For each tissue, variants were selected based
1349 on the following thresholds: the minor allele was observed in at least 10 samples, and the minor allele
1350 frequency was ≥ 0.01 . eGenes, genes with a significant eQTL, are defined on a false discovery rate (FDR)⁹⁵
1351 threshold of ≤ 0.05 of beta distribution-adjusted empirical p-value from FastQTL. Nominal p-values were
1352 generated for each variant-gene pair by testing the alternative hypothesis that the slope of a linear
1353 regression model between genotype and expression deviates from 0. To identify the list of all significant
1354 variant-gene pairs associated with eGenes, a genome-wide empirical p-value threshold⁶⁴, p_t , was defined
1355 as the empirical p-value of the gene closest to the 0.05 FDR threshold. p_t was then used to calculate a
1356 nominal p-value threshold for each gene based on the beta distribution model (from FastQTL) of the
1357 minimum p-value distribution $f(p_{min})$ obtained from the permutations for the gene. For each gene,
1358 variants with a nominal p-value below the gene-level threshold were considered significant and included
1359 in the final list of variant-gene pairs⁶⁴. For each eGene, we also listed the most significantly associated
1360 variants (eSNP). Only these exome SNPs with $r^2 > 0.8$ with eSNPs were considered for the biological
1361 interpretation (Supplementary eQTL GTEx).

1362 We also performed cis-eQTL analysis in 770 METSIM subcutaneous adipose tissue samples as
1363 described in Civelek, et al.⁹⁶ A false discovery rate (FDR) was calculated using all p-values from the cis-

1364 eQTL detection in the q-value package in R. Variants associated with nearby genes at an FDR less than 1%
1365 were considered to be significant (equivalent p-value $< 2.46 \times 10^{-4}$).

1366 For loci with more than one microarray probeset of the same gene associated with the
1367 exome variant, we selected the probeset that provided the strongest LD r^2 between the exome variant
1368 and the eSNP. In reciprocal conditional analysis, we conditioned on the lead exome variant by
1369 including it as a covariate in the cis-eQTL detection and reporting the p-value of the eSNP and vice
1370 versa. We considered the signals to be coincident if both the lead exome variant and the eSNP were no
1371 longer significant after conditioning on the other and the variants were in high pairwise LD ($r^2 > 0.80$).

1372 For loci that also harbored reported GWAS variants, we performed reciprocal conditional analysis
1373 between the GWAS lead variant and the lead eSNP. For loci with more than one reported GWAS variant,
1374 the GWAS lead variant with the strongest LD r^2 with the lead eSNP was reported.

1375 **Penetrance analysis**

1376 Phenotype and genotype data from the UK Biobank (UKBB) were used for the penetrance analysis.
1377 Three of 16 rare and low frequency variants ($MAF \leq 1\%$) detected in the final Stage 1 plus 2 meta-analysis
1378 were available in the UKBB and had relatively larger effect sizes (>0.90). The phenotype data for these
1379 three variants were stratified with respect to waist-to-hip ratio (WHR) using the World Health
1380 Organization (WHO) guidelines. These guidelines consider women and men with WHR greater than 0.85
1381 and 0.90 as obese, respectively. Genotype and allele counts were obtained for the available variants and
1382 these were used to calculate the number of carriers of the minor allele. The number of carriers for women,
1383 men and all combined was then compared between two strata (obese vs. non-obese) using a χ^2 test. The
1384 significance threshold was determined by using a Bonferroni correction for the number of tests performed
1385 ($0.05/9=5.5 \times 10^{-3}$).

1386 **DATA AVAILABILITY**

1387 Summary statistics of all analyses are available at <https://www.broadinstitute.org/collaboration/giant/>.

1388

Box 1. Genes of biological interest harboring WHR-associated variants

PLXND1- (3:129284818, rs2625973, known locus) The major allele of a common non-synonymous variant in Plexin D1 (L1412V, MAF=26.7%) is associated with increased WHRadjBMI (β (SE)= 0.0156 (0.0024), P-value=9.16x10⁻¹¹). *PLXND1* is a semaphorin class 3 and 4 receptor gene, and therefore, is involved in cell to cell signaling and regulation of growth in development for a number of different cell and tissue types, including those in the cardiovascular system, skeleton, kidneys, and the central nervous system⁹⁷⁻¹⁰¹. Mutations in this gene are associated with Moebius syndrome¹⁰²⁻¹⁰⁵, and persistent truncus arteriosus^{99,106}. *PLXND1* is involved in angiogenesis as part of the SEMA and VEGF signalling pathways¹⁰⁷⁻¹¹⁰. *PLXND1* was implicated in the development of T2D through its interaction with *SEMA3E* in mice. *SEMA3E* and *PLXND1* are upregulated in adipose tissue in response to diet-induced obesity, creating a cascade of adipose inflammation, insulin resistance, and diabetes mellitus¹⁰¹. *PLXND1* is highly expressed in adipose (both subcutaneous and visceral) (GTEx). *PLXND1* is highly intolerant of mutations and therefore highly conserved (**Supplementary Data 10**). Last, our lead variant is predicted as damaging or possibly damaging for all algorithms examined (SIFT, Polyphen2/HDIV, Polyphen2/HVAR, LRT, MutationTaster).

ACVR1C- (2:158412701, rs55920843, novel locus) The major allele of a low frequency non-synonymous variant in activin A receptor type 1C (rs55920843, N150H, MAF=1.1%) is associated with increased WHRadjBMI (β (SE)= 0.0652 (0.0105), P-value= 4.81x10⁻¹⁰). *ACVR1C*, also called Activin receptor-like kinase 7 (*ALK7*), is a type I receptor for TGFB (Transforming Growth Factor, Beta-1), and is integral for the activation of SMAD transcription factors; therefore, *ACVR1C* plays an important role in cellular growth and differentiation⁶⁴⁻⁶⁸, including adipocytes⁶⁸. Mouse *Acvr1c* decreases secretion of insulin and

is involved in lipid storage^{69,72,73,69,72,73,111}. *ACVR1C* exhibits the highest expression in adipose tissue, but is also highly expressed in the brain (GTEx)⁶⁹⁻⁷¹. Expression is associated with body fat, carbohydrate metabolism and lipids in both obese and lean individuals⁷⁰. *ACVR1C* is moderately tolerant of mutations (EXAC Constraint Scores: synonymous= -0.86, nonsynonymous = 1.25, LoF = 0.04, **Supplementary Data 10**). Last, our lead variant is predicted as damaging for two of five algorithms examined (LRT and MutationTaster).

FGFR2– (10:123279643, rs138315382, novel locus) The minor allele of a rare synonymous variant in Fibroblast Growth Factor Receptor 2 (rs138315382, MAF=0.09%) is associated with increased WHRadjBMI (β (SE) = 0.258 (0.049), P-value= 1.38×10^{-07}). The extracellular portion of the FGFR2 protein binds with fibroblast growth factors, influencing mitogenesis and differentiation. Mutations in this gene have been associated with many rare monogenic disorders, including skeletal deformities, craniosynostosis, eye abnormalities, and LADD syndrome, as well as several cancers including breast, lung, and gastric cancer. Methylation of *FGFR2* is associated with high birth weight percentile¹¹². *FGFR2* is tolerant of synonymous mutations, but highly intolerant of missense and loss-of-function mutations (ExAC Constraint scores: synonymous=-0.9, missense=2.74, LoF=1.0, **Supplementary Data 10**). Last, this variant is not predicted to be damaging based on any of the 5 algorithms tested.

ANGPTL4 – (19:8429323, rs116843064, novel locus) The major allele of a nonsynonymous low frequency variant in Angiopoietin Like 4 (rs116843064, E40K, EAF=98.1%) is associated with increased WHRadjBMI (β (SE) = 0.064 (0.011) P-value= 1.20×10^{-09}). *ANGPTL4* encodes a glycosylated, secreted protein containing a C-terminal fibrinogen domain. The encoded protein is induced by peroxisome proliferation activators and functions as a serum hormone that regulates glucose homeostasis, triglyceride metabolism^{113,114}, and insulin sensitivity¹¹⁵. *Angptl4*-deficient mice have

hypotriglyceridemia and increased lipoprotein lipase (LPL) activity, while transgenic mice overexpressing *Angptl4* in the liver have higher plasma triglyceride levels and decreased LPL activity¹¹⁶. The major allele of rs116843064 has been previously associated with increased risk of coronary heart disease and increased TG⁶³. *ANGPTL4* is moderately tolerant of mutations (ExAC constraint scores synonymous=1.18, missense=0.21, LoF=0.0, **Supplementary Data 10**). Last, our lead variant is predicted damaging for four of five algorithms (SIFT, Polyphen 2/HDIV, Polyphen2/HVAR, and MutationTaster).

RREB1 – (6:7211818, rs1334576, novel association signal) The major allele of a common non-synonymous variant in the Ras responsive element binding protein 1 (rs1334576, G195R, EAF=56%) is associated with increased WHRadjBMI (β (SE)=0.017 (0.002), P-value=3.9x10⁻¹⁵). This variant is independent of the previously reported GWAS signal in the *RREB1* region (rs1294410; 6:6738752¹⁰). The protein encoded by this gene is a zinc finger transcription factor that binds to RAS-responsive elements (RREs) of gene promoters. It has been shown that the calcitonin gene promoter contains an RRE and that the encoded protein binds there and increases expression of calcitonin, which may be involved in Ras/Raf-mediated cell differentiation¹¹⁷⁻¹¹⁹. The ras responsive transcription factor *RREB1* is a candidate gene for type 2 diabetes associated end-stage kidney disease¹¹⁸. This variant is highly intolerant to loss of function (ExAC constraint score LoF = 1, **Supplementary Data 10**).

DAGLB – (7:6449496, rs2303361, novel locus) The minor allele of a common non-synonymous variant (rs2303361, Q664R, MAF=22%) in *DAGLB* (Diacylglycerol lipase beta) is associated with increased WHRadjBMI (β (SE)= 0.0136 (0.0025), P-value=6.24x10⁻⁸). *DAGLB* is a diacylglycerol (DAG) lipase that catalyzes the hydrolysis of DAG to 2-arachidonoyl-glycerol, the most abundant endocannabinoid in tissues. In the brain, DAGL activity is required for axonal growth during development and for retrograde synaptic signaling at mature synapses (2-AG)¹²⁰. The *DAGLB* variant, rs702485 (7:6449272, r²= 0.306

and $D'=1$ with rs2303361) has been previously associated with high-density lipoprotein cholesterol (HDL) previously. Pathway analysis indicate a role in the triglyceride lipase activity pathway¹²¹. *DAGLB* is tolerant of synonymous mutations, but intolerant of missense and loss of function mutations (ExAC Constraint scores: synonymous=-0.76, missense=1.07, LoF=0.94, **Supplementary Data 10**). Last, this variant is not predicted to be damaging by any of the algorithms tested.

MLXIPL (7:73012042, rs35332062 and 7:73020337, rs3812316, known locus) The major alleles of two common non-synonymous variants (A358V, MAF=12%; Q241H, MAF=12%) in *MLXIPL* (MLX interacting protein like) are associated with increased WHRadjBMI (β (SE)= 0.02 (0.0033), P-value= 1.78×10^{-9} ; β (SE)= 0.0213 (0.0034), P-value= 1.98×10^{-10}). These variants are in strong linkage disequilibrium ($r^2=1.00$, $D'=1.00$, 1000 Genomes CEU). This gene encodes a basic helix-loop-helix leucine zipper transcription factor of the Myc/Max/Mad superfamily. This protein forms a heterodimeric complex and binds and activates carbohydrate response element (ChoRE) motifs in the promoters of triglyceride synthesis genes in a glucose-dependent manner^{74,75}. This gene is possibly involved in the growth hormone signaling pathway and lipid metabolism. The WHRadjBMI-associated variant rs3812316 in this gene has been associated with the risk of non-alcoholic fatty liver disease and coronary artery disease^{74,122,123}. Furthermore, Williams-Beuren syndrome (an autosomal dominant disorder characterized by short stature, abnormal weight gain, various cardiovascular defects, and mental retardation) is caused by a deletion of about 26 genes from the long arm of chromosome 7 including *MLXIPL*. *MLXIPL* is generally intolerant to variation, and therefore conserved (ExAC Constraint scores: synonymous = 0.48, missense=1.16, LoF=0.68, **Supplementary Data 10**). Last, both variants reported here are predicted as possible or probably damaging by one of the algorithms tested (PolyPhen).

RAPGEF3 (12:48143315, rs145878042, novel locus) The major allele of a low frequency non-synonymous variant in Rap Guanine-Nucleotide-Exchange Factor (GEF) 3 (rs145878042, L300P, MAF=1.1%) is associated with increased WHRadjBMI (β (SE)=0.085 (0.010), P-value = $7.15E^{-17}$). *RAPGEF3* codes for an intracellular cAMP sensor, also known as Epac (the Exchange Protein directly Activated by Cyclic AMP). Among its many known functions, *RAPGEF3* regulates the ATP sensitivity of the KATP channel involved in insulin secretion¹²⁴, may be important in regulating adipocyte differentiation¹²⁵⁻¹²⁷, plays an important role in regulating adiposity and energy balance¹²⁸. *RAPGEF3* is tolerant of mutations (ExAC Constraint Scores: synonymous = -0.47, nonsynonymous = 0.32, LoF = 0, **Supplementary Data 10**). Last, our lead variant is predicted as damaging or possibly damaging for all five algorithms examined (SIFT, Polyphen2/HDIV, Polyphen2/HVAR, LRT, MutationTaster).

TBX15 (1:119427467, rs61730011, known locus) The major allele of a low frequency non-synonymous variant in T-box 15 (rs61730011, M460R, MAF=4.3%) is associated with increased WHRadjBMI (β (SE)=0.041(0.005)). T-box 15 (*TBX15*) is a developmental transcription factor expressed in adipose tissue, but with higher expression in visceral adipose tissue than in subcutaneous adipose tissue, and is strongly downregulated in overweight and obese individuals¹²⁹. *TBX15* negatively controls depot-specific adipocyte differentiation and function¹³⁰ and regulates glycolytic myofiber identity and muscle metabolism¹³¹. *TBX15* is moderately intolerant of mutations and therefore conserved (ExAC Constraint Scores: synonymous = 0.42, nonsynonymous = 0.65, LoF = 0.88, **Supplementary Data 10**). Last, our lead variant is predicted as damaging or possibly damaging for four of five algorithms (Polyphen2/HDIV, Polyphen2/HVAR, LRT, MutationTaster).

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1676 **FIGURES**

1677 **Figure 1. Summary of meta-analysis study design and workflow.** Abbreviations:

1678 EUR- European, AFR- African, SAS- South Asian, EAS- East Asian, and HIS- Hispanic/Latino ancestry.

1679 **Figure 2.** Minor allele frequency compared to estimated effect. This scatter plot displays the relationship
1680 between minor allele frequency (MAF) and the estimated effect (β) for each significant coding variant in
1681 our meta-analyses. All novel WHRadjBMI variants are highlighted in orange, and variants identified only
1682 in models that assume recessive inheritance are denoted by diamonds and only in sex-specific analyses
1683 by triangles. Eighty percent power was calculated based on the total sample size in the Stage 1+2 meta-
1684 analysis and $P=2 \times 10^{-7}$. Estimated effects are shown in original units (cm/cm) calculated by using effect
1685 sizes in standard deviation (SD) units times SD of WHR in the ARIC study (sexes combined=0.067,
1686 men=0.052, women=0.080).

1687 **Figure 3.** Regional association plots for known loci with novel coding signals. Point color reflects r^2
1688 calculated from the ARIC dataset. In a) there are two independent variants in *RSPO3* and *KIAA0408*, as
1689 shown by conditional analysis. In b) we have a variant in *RREB1* that is independent of the GWAS variant
1690 rs1294421.

1691 **Figure 4.** Heat maps showing DEPICT gene set enrichment results. For any given square, the color indicates
1692 how strongly the corresponding gene (shown on the x-axis) is predicted to belong to the reconstituted
1693 gene set (y-axis). This value is based on the gene's z-score for gene set inclusion in DEPICT's reconstituted
1694 gene sets, where red indicates a higher and blue a lower z-score. To visually reduce redundancy and
1695 increase clarity, we chose one representative "meta-gene set" for each group of highly correlated gene
1696 sets based on affinity propagation clustering (**Online Methods, Supplementary Note 2**). Heatmap
1697 intensity and DEPICT P-values (see P-values in **Supplementary Data 4-5**) correspond to the most
1698 significantly enriched gene set within the meta-gene set. Annotations for the genes indicate (1) the minor

1699 allele frequency of the significant ExomeChip (EC) variant (shades of blue; if multiple variants, the lowest-
1700 frequency variant was kept), (2) whether the variant's P-value reached array-wide significance ($<2 \times 10^{-7}$)
1701 or suggestive significance ($<5 \times 10^{-4}$) (shades of purple), (3) whether the variant was novel, overlapping
1702 "relaxed" GWAS signals from Shungin et al.¹⁰ (GWAS $P < 5 \times 10^{-4}$), or overlapping "stringent" GWAS signals
1703 (GWAS $P < 5 \times 10^{-8}$) (shades of pink), and (4) whether the gene was included in the gene set enrichment
1704 analysis or excluded by filters (shades of brown/orange) (Online Methods and Supplementary
1705 Information). Annotations for the gene sets indicate if the meta-gene set was found significant (shades of
1706 green; FDR < 0.01 , < 0.05 , or not significant) in the DEPICT analysis of GWAS results from Shungin et al.

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1709 TABLES

1710 **Table 1. Association results for Combined Sexes.** Association results based on an additive or recessive model for coding variants that met array-wide significance ($P < 2 \times 10^{-7}$) in the sex-combined
 1711 meta-analyses.

Locus (+/-1Mb of a given variant)	Chr:Position (GRCh37) ^b	rsID	EA	OA	Gene ^c	Amino Acid Change ^c	If locus is known, nearby (< 1 MB) published variant(s) ^d	N	EAF	β^e	SE	P-value	P-value for Sex- heterogeneity ^f	Other Criteria For Sig ^h
Variants in Novel Loci														
All Ancestry Additive model Sex-combined analyses														
1	2:158412701	rs55920843	T	G	<i>ACVR1C</i>	N150H	-	455,526	0.989	0.065	0.011	4.8E-10	1.7E-07	
2	3:50597092	rs1034405	G	A	<i>C3orf18</i>	A162V	-	455,424	0.135	0.016	0.003	1.9E-07	8.8E-01	G,C
3	4:120528327	rs3733526	G	A	<i>PDE5A</i>	A41V	-	461,521	0.187	0.015	0.003	2.6E-08	5.2E-03	
4	6:26108117	rs146860658	T	C	<i>HIST1H1T</i>	A69T	-	217,995	0.001	0.229	0.042	4.3E-08	6.3E-01	S
5	7:6449496	rs2303361	C	T	<i>DAGLB</i>	Q664R	-	475,748	0.221	0.014	0.003	6.2E-08	3.4E-03	G
6	10:123279643	rs138315382	T	C	<i>FGFR2</i>	synonymous	-	236,962	0.001	0.258	0.049	1.4E-07	1.1E-01	G,S
7	11:65403651	rs7114037	C	A	<i>PCNXL3</i>	H1822Q	-	448,861	0.954	0.029	0.005	1.8E-08	4.4E-01	
8	12:48143315	rs145878042	A	G	<i>RAPGEF3</i>	L300P	-	470,513	0.990	0.085	0.010	7.2E-17	7.3E-03	
9	12:108618630	rs3764002	C	T	<i>WSCD2</i>	T266I	-	474,637	0.737	0.014	0.002	9.8E-10	5.5E-01	
10	15:42032383	rs17677991	G	C	<i>MGA</i>	P1523A	-	469,874	0.345	0.015	0.002	3.5E-11	9.1E-01	
11	16:4432029	rs3810818	A	C	<i>VASN</i>	E384A	-	424,163	0.231	0.016	0.003	2.0E-09	3.3E-01	
	16:4445327	rs3747579	C	T	<i>CORO7</i>	R193Q	-	453,078	0.299	0.018	0.002	2.2E-13	4.3E-02	
	16:4484396	rs1139653	A	T	<i>DNAJA3</i>	N75Y	-	434,331	0.284	0.015	0.002	4.3E-10	1.4E-01	
12	19:49232226	rs2287922	A	G	<i>RASIP1</i>	R601C	-	430,272	0.494	0.014	0.002	1.6E-09	3.7E-02	
	19:49244220	rs2307019	G	A	<i>IZUMO1</i>	A333V	-	476,147	0.558	0.012	0.002	4.7E-08	3.9E-02	
13	20:42965811	rs144098855	T	C	<i>R3HDML</i>	P5L	-	428,768	0.001	0.172	0.032	9.7E-08	1.0E+00	G

European Ancestry Additive model Sex-combined analyses														
14	1:173802608	rs35515638	G	A	<i>DARS2</i>	K196R	-	352,646	0.001	0.201	0.038	1.4E-07	6.0E-02	G
15	14:58838668	rs1051860	A	G	<i>ARID4A</i>	synonymous	-	367,079	0.411	0.013	0.002	2.2E-08	1.3E-01	
16	15:42115747	rs3959569	C	G	<i>MAPKBP1</i>	R1240H	-	253,703	0.349	0.017	0.003	2.0E-08	6.3E-01	

Variants in Previously Identified Loci

All Ancestry Additive model Sex-combined analyses														
1	1:119427467	rs61730011	A	C	<i>TBX15</i>	M566R	rs2645294, rs12731372, rs12143789, rs1106529	441,461	0.957	0.041	0.005	2.2E-14	6.7E-01	
	1:119469188	rs10494217	T	G		H156N		472,259	0.174	0.018	0.003	1.4E-10	6.0E-01	
2	1:154987704	rs141845046	C	T	<i>ZBTB7B</i>	P190S	rs905938	476,440	0.976	0.037	0.007	3.8E-08	7.9E-07	C
3	2:165551201	rs7607980	T	C	<i>COBLL1</i>	N941D	rs1128249, rs10195252, rs12692737, rs12692738, rs17185198	389,883	0.879	0.026	0.004	1.6E-13	3.0E-30	
4	2:188343497	rs7586970	T	C	<i>TFPI</i>	N221S	rs1569135	452,638	0.697	0.016	0.002	3.0E-12	6.3E-01	
5	3:52558008	rs13303	T	C	<i>STAB1</i>	M113T	rs2276824	470,111	0.445	0.019	0.002	5.5E-18	6.7E-02	
	3:52833805	rs3617	C	A	<i>ITIH3</i>	Q315K		452,150	0.541	0.015	0.002	1.6E-12	4.0E-01	C
6	3:129137188	rs62266958	C	T	<i>EFCAB12</i>	R197H	rs10804591	476,382	0.936	0.036	0.004	8.3E-17	9.3E-05	
	3:129284818	rs2625973	A	C	<i>PLXND1</i>	L1412V		476,338	0.733	0.016	0.002	9.2E-11	1.6E-05	
7	4:89625427	rs1804080	G	C	<i>HERC3</i>	E946Q	rs9991328	446,080	0.838	0.021	0.003	1.5E-12	4.1E-06	
	4:89668859	rs7657817	C	T	<i>FAM13A</i>	V443I		476,383	0.815	0.016	0.003	5.0E-09	9.6E-05	
8	5:176516631	rs1966265	A	G	<i>FGFR4</i>	V10I	rs6556301	455,246	0.236	0.023	0.003	1.7E-19	2.1E-01	
9	6:7211818	rs1334576^g	G	A	<i>RREB1</i>	G195R	rs1294410	451,044	0.565	0.017	0.002	3.9E-15	1.5E-01	
10	6:34827085	rs9469913	A	T	<i>UHRF1BP1</i>	Q984H	rs1776897	309,684	0.847	0.021	0.004	1.2E-08	2.7E-01	C
11	6:127476516	rs1892172	A	G	<i>RSPO3</i>	synonymous	rs11961815, rs72959041, rs1936805	476,358	0.543	0.031	0.002	2.6E-47	7.7E-09	
	6:127767954	rs139745911^g	A	G	<i>KIAA0408</i>	P504S		391,469	0.010	0.103	0.012	6.8E-19	2.0E-04	
12	7:73012042	rs35332062	G	A	<i>MLXIPL</i>	A358V	rs6976930	451,158	0.880	0.020	0.003	1.8E-09	1.5E-01	
	7:73020337	rs3812316	C	G		Q241H		454,738	0.881	0.021	0.003	2.0E-10	5.8E-02	

13	10:95931087	rs17417407	T	G	<i>PLCE1</i>	R240L	rs10786152	476,475	0.173	0.018	0.003	2.5E-11	5.9E-01	
14	11:64031241	rs35169799	T	C	<i>PLCB3</i>	S778L	rs11231693	476,457	0.061	0.034	0.004	9.1E-15	1.3E-04	
15	12:123444507	rs58843120	G	T	<i>DNAAH10</i>	F92L	rs4765219, rs863750	466,498	0.987	0.053	0.009	1.3E-08	3.5E-01	
	12:124265687	rs11057353	T	C		S228P		476,360	0.373	0.018	0.002	2.1E-16	2.7E-08	
	12:124330311	rs34934281	C	T	T1785M	476,395		0.889	0.025	0.003	2.9E-14	3.1E-08		
	12:124427306	rs11057401	T	A	<i>CCDC92</i>	S53C		467,649	0.695	0.029	0.002	7.3E-37	5.5E-11	
16	15:56756285	rs1715919	G	T	<i>MNS1</i>	Q55P	rs8030605	476,274	0.096	0.023	0.004	8.8E-11	2.7E-02	
17	16:67397580	rs9922085	G	C	<i>LRRC36</i>	R101P	rs6499129	469,474	0.938	0.034	0.005	3.8E-13	5.9E-01	
	16:67409180	rs8052655	G	A		G388S		474,035	0.939	0.034	0.005	5.5E-13	4.0E-01	
18	19:18285944	rs11554159	A	G	<i>IFI30</i>	R76Q	rs12608504	476,389	0.257	0.015	0.002	3.5E-10	3.1E-03	
	19:18304700	rs874628	G	A	<i>MPV17L2</i>	M72V		476,388	0.271	0.015	0.002	1.2E-10	2.5E-03	
19	20:33971914	rs4911494	T	C	<i>UQCC1</i>	R51Q	rs224333	451,064	0.602	0.018	0.002	2.5E-16	1.5E-03	
	20:34022387	rs224331	A	C	<i>GDF5</i>	S276A		345,805	0.644	0.017	0.003	1.8E-11	3.2E-03	

All Ancestry Recessive model Sex-combined analyses

20	17:17425631	rs897453	C	T	<i>PEMT</i>	V58L	rs4646404	476,546	0.569	0.025	0.004	4.1E-11	8.2E-01	
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European Ancestry Additive model Sex-combined analyses

6	3:129293256	rs2255703	T	C	<i>PLXND1</i>	M870V	rs10804591	420,520	0.620	0.014	0.002	3.1E-09	1.6E-04	
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1712 Abbreviations: GRCh37=human genome assembly build37;rsID=based on dbSNP; VEP=Ensembl Variant Effect Predictor toolset; GTEx=Genotype-Tissue Expression project;SD=standard deviation; SE=standard error;N=sample size;

1713 EAF=effect allele frequency; EA=effect allele; OA=other allele.

1714 a Coding variants refer to variants located in the exons and splicing junction regions.

1715 b Variant positions are reported according to Human assembly build 37 and their alleles are coded based on the positive strand.

1716 c The gene the variant falls in and amino acid change from the most abundant coding transcript is shown (protein annotation is based on VEP toolset and transcript abundance from GTEx database).

1717 d Previously published variants within +/-1Mb are from Shungin et al.¹⁰, except for rs6976930 and rs10786152 from Graff et al.¹⁴ and rs6499129 from Ng. et al.¹⁶.

1718 e Effect size is based on standard deviation (SD) per effect allele

1719 f P-value for sex heterogeneity, testing for difference between women-specific and men-specific beta estimates and standard errors, was calculated using EasyStrata: Winkler, T.W. et al. EasyStrata: evaluation and visualization of

1720 stratified genome-wide association meta-analysis data. Bioinformatics 2015; 31, 259-61.PMID: 25260699. Bolded P-values met significance threshold after bonferonni correction (P-value<7.14E-04; i.e. 0.05/70 variants).

1721 g **rs1334576 in *RREB1*** is a new signal in a known locus that is independent from the known signal, rs1294410; **rs139745911 in *KIAA0408*** is a new signal in a known locus that is independent from all known signals rs11961815, rs72959041,

1722 rs1936805, in a known locus (see Supplementary 8A/B).

1723 h Each flag indicates a that a secondary criteria for significance may not be met, G- P-value $> 5 \times 10^{-8}$ (GWAS significant), C- Association Signal was not robust against collider bias; S- variant was not available in stage 2 studies for validation
1724 of Stage 1 association.
1725

1726 **Table 2. Association results for Sex-stratified analyses.** Association results based on an additive or recessive model for coding variants that met array-wide significance ($P < 2 \times 10^{-7}$) in the sex-
 1727 specific meta-analyses and reach bonferonni corrected P-value for sex heterogeneity ($P_{\text{sexhet}} < 7.14 \times 10^{-4}$).

Locus (+/-1Mb of a given variant)	Chr:Position (GRCh37) ^c	rsID	EA	OA	Gene ^d	Amino Acid Change ^d	In sex-combined analyses ^e	If locus is known, nearby (< 1 MB) published variant(s) ^f	P-value for Sex-heterogeneity ^g	Men					Women					Other Criteria For Sig ^j	
										N	EA	β^h	SE	P	N	EA	β^h	SE	P		
Variants in Novel Loci																					
All Ancestry Additive model Men only analyses																					
1	13:96665697	rs148108950	A	G	<i>UGGT2</i>	P175L	No	-	1.5E-06	203,009	0.006	0.130	0.024	6.1E-08	221,390	0.004	-0.044	0.027	1.1E-01	G	
2	14:23312594	rs1042704	A	G	<i>MMP14</i>	D273N	No	-	2.6E-04	226,646	0.202	0.021	0.004	2.6E-08	250,018	0.197	0.002	0.004	6.1E-01		
All Ancestry Additive model Women only analyses																					
3	1:205130413	rs3851294	G	A	<i>DSTYK</i>	C641R	No	-	9.8E-08	225,803	0.914	-0.005	0.005	3.4E-01	249,471	0.912	0.034	0.005	4.5E-11		
4	2:158412701	rs55920843	T	G	<i>ACVR1C</i>	N150H	Yes	-	1.7E-07	210,071	0.989	0.006	0.015	7.2E-01	245,808	0.989	0.113	0.014	1.7E-15		
5	19:8429323	rs116843064	G	A	<i>ANGPTL4</i>	E40K	No	-	1.3E-07	203,098	0.981	-0.017	0.011	1.4E-01	243,351	0.981	0.064	0.011	1.2E-09		
Variants in Previously Identified Loci																					
All Ancestry Additive model Women only analyses																					
1	1:154987704	rs141845046	C	T	<i>ZBTB7B</i>	P190S	Yes	rs905938	7.9E-07	226,709	0.975	0.004	0.010	6.9E-01	250,084	0.977	0.070	0.010	2.3E-13		
2	2:165551201	rs7607980	T	C	<i>COBLL1</i>	N941D	Yes	rs1128249, rs10195252, rs12692737, rs12692738, rs17185198	3.0E-30	173,600	0.880	-0.018	0.005	5.8E-04	216,636	0.878	0.062	0.005	6.7E-39		
3	3:129137188	rs62266958	C	T	<i>EFCAB12</i>	R197H	Yes	rs10804591	9.3E-05	226,690	0.937	0.018	0.006	3.1E-03	250,045	0.936	0.051	0.006	8.1E-18		
	3:129284818	rs2625973	A	C	<i>PLXND1</i>	L1412V	Yes		1.6E-05	226,650	0.736	0.005	0.003	1.9E-01	250,023	0.730	0.025	0.003	8.2E-14		
	3:129293256	rs2255703	T	C		M870V	Yes		5.0E-04	226,681	0.609	0.003	0.003	3.1E-01	250,069	0.602	0.018	0.003	1.9E-09		
4	4:89625427	rs1804080	G	C	<i>HERC3</i>	E946Q	Yes	rs9991328	4.1E-06	222,556	0.839	0.008	0.004	6.6E-02	223,877	0.837	0.034	0.004	2.1E-16		

	4:89668859	rs7657817	C	T	<i>FAM13A</i>	V443I	Yes		9.6E-05	226,680	0.816	0.006	0.004	1.5E-01	242,970	0.815	0.026	0.004	5.9E-12
5	6:127476516	rs1892172	A	G	<i>RSPO3</i>	synonymous	Yes	rs11961815, rs72959041, rs1936805	7.7E-09	226,677	0.541	0.018	0.003	5.6E-10	250,034	0.545	0.042	0.003	3.4E-48
	6:127767954	rs139745911	A	G	<i>KIAA0408</i>	P504S	Yes		2.0E-04	188,079	0.010	0.057	0.017	6.8E-04	205,203	0.010	0.143	0.016	5.9E-19
6	11:64031241	rs35169799	T	C	<i>PLCB3</i>	S778L	Yes	rs11231693	1.3E-04	226,713	0.061	0.016	0.006	9.6E-03	250,097	0.061	0.049	0.006	6.7E-16
7	12:124265687	rs11057353	T	C	<i>DNAH10</i>	S228P	Yes	rs4765219, rs863750	2.7E-08	226,659	0.370	0.005	0.003	8.3E-02	250,054	0.376	0.029	0.003	3.1E-22
	12:124330311	rs34934281	C	T		T1785M	Yes		3.1E-08	226,682	0.891	0.006	0.005	1.9E-01	250,066	0.887	0.043	0.005	1.4E-20
	12:124427306	rs11057401	T	A	<i>CCDC92</i>	S53C	Yes		5.5E-11	223,324	0.701	0.013	0.003	4.3E-05	244,678	0.689	0.043	0.003	1.0E-41

1728 Abbreviations: GRCh37=human genome assembly build 37;rsID=based on dbSNP; VEP=Ensembl Variant Effect Predictor toolset; GTEx=Genotype-Tissue Expression project; SD=standard deviation; SE=standard error;N=sample size; EA=effect

1729 allele; OA=other allele; EAF=effect allele frequency.

1730 a Coding variants refer to variants located in the exons and splicing junction regions.

1731 b Bonferonni corrected Pvalue for the number of SNPs tested for sex-heterogeneity is <7.14E-04 i.e. 0.05/70 variants.

1732 c Variant positions are reported according to Human assembly build 37 and their alleles are coded based on the positive strand.

1733 d The gene the variant falls in and amino acid change from the most abundant coding transcript is shown (protein annotation is based on VEP toolset and transcript abundance from GTEx database).

1734 e Variant was also identified as array-wide significant in the sex-combined analyses.

1735 f Previously published variants within +/-1Mb are from Shungin D et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015; 518, 187–196 doi:10.1038/nature14132 (PMID 25673412).

1736 g P-value for sex heterogeneity, testing for difference between women-specific and men-specific beta estimates and standard errors, was calculated using EasyStrata: Winkler, T.W. et al. EasyStrata: evaluation and visualization of stratified
1737 genome-wide association meta-analysis data. Bioinformatics 2015: 31, 259-61. PMID: 25260699.

1738 h Effect size is based on standard deviation (SD) per effect allele

1739 i rs139745911 in KIAA0408 is a new signal in a known locus that is independent from all known signals rs11961815, rs72959041, rs1936805, in a known locus (see Supplementary 8A/B).

1740 j Each flag indicates a that a secondary criteria for significance may not be met, G- P-value > 5x10-8 (GWAS significant), C- Association Signal was not robust against collider bias; S- variant was not available in Stage 2 studies for validation
1741 of Stage 1 association.

1742