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Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity

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Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure underpinning obesity

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SUPPLEMENTARY NOTE

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1. COMMON CODING VARIANTS ASSOCIATED WITH BMI

The main focus of our study was the analysis of the 215,917 rare and low frequency (R/LF) coding variants, which are more likely to disrupt protein function^{1,2}. However, besides R/LF coding variants, the ExomeChip also carries 13,786 common coding SNVs, which were also tested for association with BMI as part of the study.

We identified 41 novel loci that showed association with BMI (AWS: $P < 2.0 \times 10^{-7}$), independent from any previously identified loci (**Supplementary Table 4, Supplementary Figure 4**). The reasons why these 41 novel loci has not been reported by previous large-scale GWAS before are; the sample size of the current study is more than twice as large as the most recent GWAS³, thus providing greater statistical power for discovery, and/or SNPs may not have been tested in previous GWAS efforts because they were not available in HapMap, and thus not imputed, SNPs did not pass quality control, or are located on the X-chromosome, which has so far not been considered in GWAS.

We also identified common variants that clustered in 51 loci that had been identified before (< 1 Mb previous GWAS lead SNP) in large-scale GWAS efforts of adiposity traits (**Supplementary Table 4, Supplementary Figure 4**). Using conditional analyses (**Online Methods**), we were able to show that 38 of these 51 loci represent the same locus as the one identified before and one represents an independent secondary signal in the previously established locus. For the remaining 12 loci, we were not able to confirm whether the association represented secondary or the same signal within the established locus because the original SNP (or proxy) was not available on the ExomeChip to perform conditional analyses (**Supplementary Table 4, Supplementary Figure 4**).

Effect sizes of the 41 novel loci are smaller (on average 0.014 SD/allele, [range: 0.010 – 0.024 SD/allele]) than those of the 37 previously established loci (average 0.021 SD/allele, [range: 0.010 – 0.050 SD/allele]) (**Supplementary Figure 5**). This difference is likely due to the increased sample size ($N > 700,000$), and thus power, of our meta-analyses, compared to sample size of

previous GWAS efforts (N up to 340,000), allowing the identification of loci with smaller effects. Signals in established loci, for which conditional analyses could not convincingly determine whether it was a secondary observation, have effect sizes in between the novel and established loci (average 0.016 SD/allele, [range: 0.010 – 0.030 SD/allele]). The explained variance of the 41 novel loci ranges between 0.004% and 0.02%, and add up to a combined explained variance of 0.394%, as compared to the 2.7% of the variance explained by the 97 loci reported in our latest GWAS BMI effort³.

The novel common coding loci have features similar to those of previously established GWAS loci; i.e. they represent a cluster of variants in high LD with each other that require further fine-mapping efforts to identify the causal genes/variants in the locus. The common coding variants, including those that reached $P < 5 \times 10^{-4}$, were included in the EC-DEPICT analyses and results are described in the **Main text**.

2. COMPARISON OF NOVEL COMMON, LOW FREQUENCY AND RARE VARIANTS ACROSS ANCESTRIES

2.1. Low-frequency and rare coding SNVs

We observed no significant heterogeneity in effect sizes across ancestries, accounting for multiple testing across novel SNVs ($P_{\text{threshold}} = 9 \times 10^{-4} = 0.05/(14+41)$), which may in part be due to low statistical power in non-European ancestry populations (**Supplementary Table 7, Supplementary Figure 6**). Minor allele frequencies are general consistent across ancestries, with two exceptions. The minor allele of rs7636 (p.Pro477Pro) in *ACHE* is of low frequency in European ancestry populations (4.2%), but much more common in African (24.4%) and Hispanic (9.9%) ancestry populations and, similarly, that of rs12236219 in *ZNF169* is of low frequency in European ancestry populations, but common in all other ancestries studied.

Of interest are the two SNVs (p.His353Asn, p.Pro477Pro) in *ACHE*, which track together nearly perfectly in European ancestry populations ($r^2=0.98$; $D'=0.99$, MAFs=4.2%), whereas in African ancestry populations they are not correlated ($r^2=0.01$; $D'=0.95$). In the African ancestry

data, the non-synonymous SNV p.His353Asn is rare (0.60%) and has a similar estimated effect size (0.057 SD/allele, 95% CI [-0.050-0.164], $P=0.29$) to the effect seen in European ancestry individuals (0.034 SD/allele, 95% CI [0.023-0.044]), whereas the synonymous p.Pro477Pro is common (24.4%) and has no detectable effect on BMI (-0.006 SD/allele, $P=0.56$). Even though our sample size was relatively small, an effect of 0.023-0.044 SD/allele, as observed in European ancestry individuals, would have been detectable in our African-ancestry population (MAF=24.4%, $N\sim 24,000$, power $\sim 80\%$, at $\alpha=0.01$). The absence of such association suggests that p.Pro477Pro may not be driving the association at this locus and that p.His353Asn (or potentially a variant correlated with p.His353Asn, but not with p.Pro477Pro, in African-ancestry populations) is more likely to be the causal variant. This is consistent with functional role of many non-synonymous, as compared to synonymous variants.

2.2. Novel common SNVs

None of the 41 novel common SNVs showed evidence of heterogeneity across ancestries ($P_{\text{threshold}} = 9 \times 10^{-4}$). Generally, allele frequencies of the BMI-increasing allele in European ancestry populations were consistent with those of South Asian ($r^2 = 0.82$) and Hispanic ($r^2 = 0.86$) ancestry populations, and somewhat lower with African ($r^2 = 0.52$) and East Asian ($r^2 = 0.48$) ancestries (**Supplementary Table 7, Supplementary Figure 6**). Because of the relatively small sample sizes of non-European ancestry populations, statistical power for replication of associations observed in the total sample or European ancestry only meta-analyses was low. Nevertheless, of the 41 SNVs, associations were directionally consistent for 32 SNVs (78%), of which 7 reached nominal significance, in the African ancestry meta-analysis (**Supplementary Table 7, Supplementary Figure 6**). The directional consistency between European ancestry associations was similar for South Asian (34 SNVs (83%) of which 5 nominally significant) and Hispanic (34 SNVs (83%) of which 3 nominally significant) ancestry populations, and lower for East Asian ancestry populations (61 SNVs (61%) of which 6 nominally significant).

3. GENE SET ENRICHMENT ANALYSIS (EC-DEPICT)

DEPICT is a method for gene set enrichment analysis and gene prioritization of GWAS data⁴. Briefly, 14,462 gene sets from KEGG⁵, REACTOME⁶, Gene Ontology⁷, InWeb⁸ (protein-protein networks) and Mouse Phenotype⁹ databases were obtained and “reconstituted” using large-scale microarray data, based on the logic of guilt-by-association (genes with similar patterns of expression are more likely to be members of the same gene sets). We have adapted the gene set enrichment functionality of DEPICT for the ExomeChip (EC-DEPICT), with a few alterations: (1) instead of including all genes within a specified amount of linkage disequilibrium to each index SNP, we include only the gene containing the index SNV, (2) we include only nonsynonymous and splicing (coding) SNVs, discarding noncoding associations and (3) we use null ExomeChip data for p-value calculation (rather than null GWAS data). In this supplement, we provide a brief overview of the method and more detailed explanations of each analysis.

3.1. Method

The EC-DEPICT method has been described elsewhere¹⁰. We generated null ExomeChip data from the Malmö Diet and Cancer (MDC), All New Diabetics in Scania (ANDIS), and Scania Diabetes Registry (SDR) cohorts (a total of 11,899 samples with Swedish ancestry). After generating simulated normally-distributed phenotypes, we conducted 2,200 null ExomeChip association studies, filtering out all variants not present in the BMI association study. The variants in each null study were then sorted by ascending *P*-value and clumped (+/- 1 Mb on each side). Annotations from the CHARGE consortium were used to assign variants to genes (see URLs). For analyses of rare/low-frequency variants, a separate set of backgrounds was created that retained only loci where the index SNV had a minor allele frequency of <5%.

The method for gene set enrichment is as follows. A list of significant input variants from the ExomeChip is obtained (index SNVs for each locus, coding variants only) and filtered to remove variants not present in the null backgrounds or that are not marked as nonsynonymous/splice-site in the CHARGE consortium annotations. Then, we map the variants

to genes. For each gene set, we then calculate a test statistic: the sum of gene set membership z-scores from the reconstituted gene sets¹ for the input genes. We then take 2000 nulls and compute the average (null) test statistic and standard deviation for the given gene set (where the number of top genes we take from each null as “input genes” is matched to the observed number of input genes). A z-score for the gene set is then computed as the observed test statistic minus the null test statistic divided by the null standard deviation, which is converted to a p-value based on the normal distribution. False discovery rates (FDRs) were calculated using an additional 50 null permutations to generate a distribution of null p-values. The FDR was calculated as the average number of null p-values less than a given threshold divided by the number of observed p-values less than that threshold.

Our null data (MDC, ANDIS, and SDR cohorts) was also used for the ExomeChip analysis of height¹⁰. As in the height analysis, before gene set enrichment analysis of BMI-associated variants, we removed variants absent in this null ExomeChip data. This resulted in exclusion of about 30% of the BMI-associated variants at suggestive of array-wide significance. Most of the excluded variants were in the very rarest allele frequency bins, and mostly reached suggestive rather than array-wide significance. The exclusion of the rarest variants is expected due to the much smaller sample size of the null cohorts relative to the BMI data. To try to include more variants in the analysis, we also generated null ExomeChip data based on the UK Biobank, which resulted in the exclusion of fewer BMI-associated variants (due to the much larger sample size of the UK Biobank data). However, we observed that use of these null data, despite including more of the rarest BMI-associated variants in the gene set enrichment analysis, dampened the signal and resulted in fewer significantly enriched gene sets. This result suggests that 1) the rarest variants are more likely to have a lower true positive rate and/or 2) the heterogeneity of the underlying biology increases with the inclusion of very rare variants.

Although some variants were excluded from the EC-DEPICT analysis, we have included them in the heatmap figures (Figure 2, Supplementary Figure 10). This is because we assume

that if the genes containing those variants have strong predicted membership in gene sets found to be significantly enriched, they are still good candidates for prioritization (and one of the main purposes of the heatmap strategy is to visually prioritize the best candidate genes). In fact, this is arguably even stronger evidence for prioritization of these genes, because they had no opportunity to influence the gene sets that are identified as enriched and, as such, independently support the biology implicated by these gene sets.

We have observed that extreme non-normality of gene set membership z-scores can, in certain situations, cause minor inflation of Type I error. To address this issue, we repeated the original EC-DEPICT analysis with an inverse-normal-transformed version of the reconstituted gene sets, in which every gene set is forced to have a normal z-score distribution for pathway membership. We then compared the rank of each significant gene set in the original results with the rank in the inverse normal transform and flagged “outliers” with respect to the change in rank ($> 1.5 \times$ the interquartile range). In visualizing the results with heat maps and in supplementary tables, outlier gene sets were excluded.

3.2. Analyses

We performed four different analyses of the BMI-associated variants. In each case, for each locus, we included the best coding variant, including secondary signals if present. “GWAS-independent” analyses were performed by excluding EC loci conditionally dependent on or <1 Mb away from a known GWAS locus (see below for details). For this purpose, “known loci” consisted of a list of all variants used as input in the original DEPICT analysis in Locke et al.³ ($P < 5 \times 10^{-4}$). This was necessary to confirm true independence from the original DEPICT findings (i.e. gene set enrichment results for EC that come from a completely non-overlapping set of genes relative to the original DEPICT analysis).

The breakdown of included variants is as follows. Array-wide significant variants ($P < 2 \times 10^{-7}$) came from the final meta-analysis of Discovery, deCODE, and UK Biobank results across all analysis strata. For these variants (“stringent”), independence from genome-wide significant

GWAS loci was determined by conditional analysis. Additional variants with p-values between 5×10^{-4} and 2×10^{-7} (“relaxed”) were based on Discovery in the all-ancestries sex-combined additive model. For these variants, independence from genome-wide significant GWAS loci was based on a distance of >1 Mb. For both stringent and relaxed variants, independence from marginally significant GWAS loci was also based on a distance of > 1 Mb. All loci were clumped ± 1 Mb.

For the first analysis, we included all EC loci with $p < 5 \times 10^{-4}$. After filtering, this left 244 variants in 242 genes; we discovered 67 gene sets (24 meta-gene sets) at FDR < 0.05 . After removing inverse normal transform outliers (see description above), that left 62 gene sets (still in 24 meta-gene sets). The second analysis included EC loci with 5×10^{-4} “independent” of a known GWAS locus³ (110 variants in 110 genes after filtering). We found no significant gene sets in this analysis.

The third and fourth analyses included rare and low-frequency (RLF; $< 5\%$ MAF) variants only. The third analyses included all RLF variants with $P < 5 \times 10^{-4}$, representing a total of 50 variants in 50 genes after filtering. We found 512 significant gene sets at FDR < 0.05 (107 meta-gene sets). After applying the inverse normal transform filter, this was reduced to 471 significant gene sets in 106 meta-gene sets. Finally, the last analysis included RLF variants with $P < 5 \times 10^{-4}$ “independent” of a known GWAS locus³ (after filtering, 30 variants in 30 genes). This recovered 31 significant gene sets in 12 meta-gene sets at FDR < 0.05 . After the inverse normal transform, we retained 29 significant gene sets, still in 12 meta-gene sets.

3.3. Affinity propagation clustering

To collapse the most highly correlated gene sets, affinity propagation clustering was performed as described in Marouli et al. (2017)¹⁰. Briefly, “meta-gene sets” were generated by affinity propagation clustering³ of all pairs of 14,462 gene sets, using SciKit-Learn.clustering.AffinityPropagation version 0.17¹¹, with a maximum iteration of 10,000 and a convergence iteration of 1,000. For each meta-gene set, *P*-values were assigned based on the most significant member gene set (considered the “best representative gene set”). In heat maps,

z-scores for meta-gene set membership represent the z-score of the best representative gene set. Heat maps were generated with the ComplexHeatmap package in R¹². For Online Mendelian Inheritance in Man (OMIM) annotations, a manual curation of obesity-related terms in the OMIM database was performed.

3.4. URLs

CHARGE Consortium ExomeChip annotation file:

<http://www.chargeconsortium.com/main/exomechip/>

EC-DEPICT: <https://github.com/RebeccaFine/obesity-ec-depict>

EC-DEPICT meta-gene sets: https://github.com/RebeccaFine/obesity-ec-depict/blob/master/data/metacluster_labels.txt

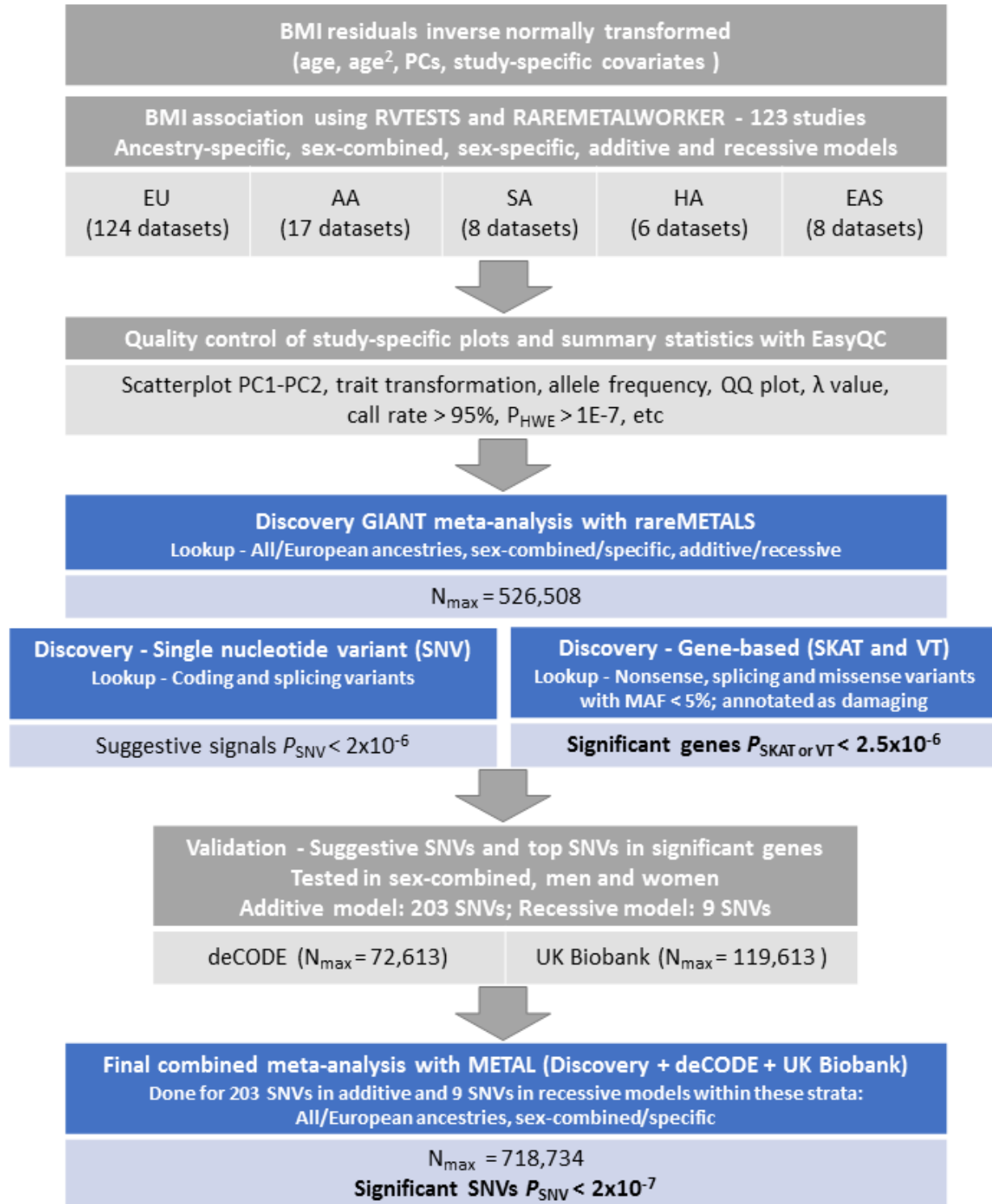
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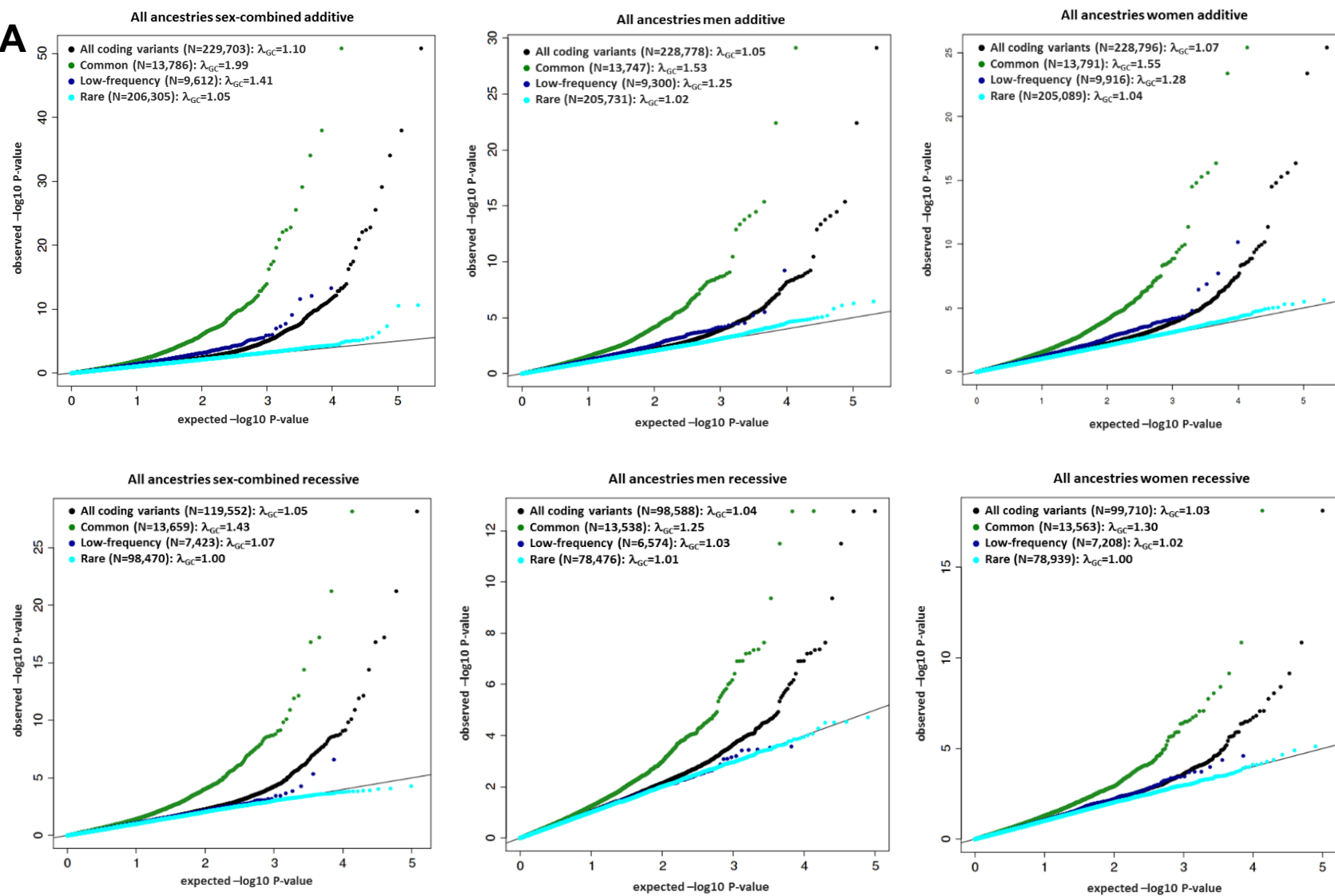
4. SUPPLEMENTARY FIGURES

Supplementary Figure 1 | Flowchart of the GIANT ExomeChip BMI study design.

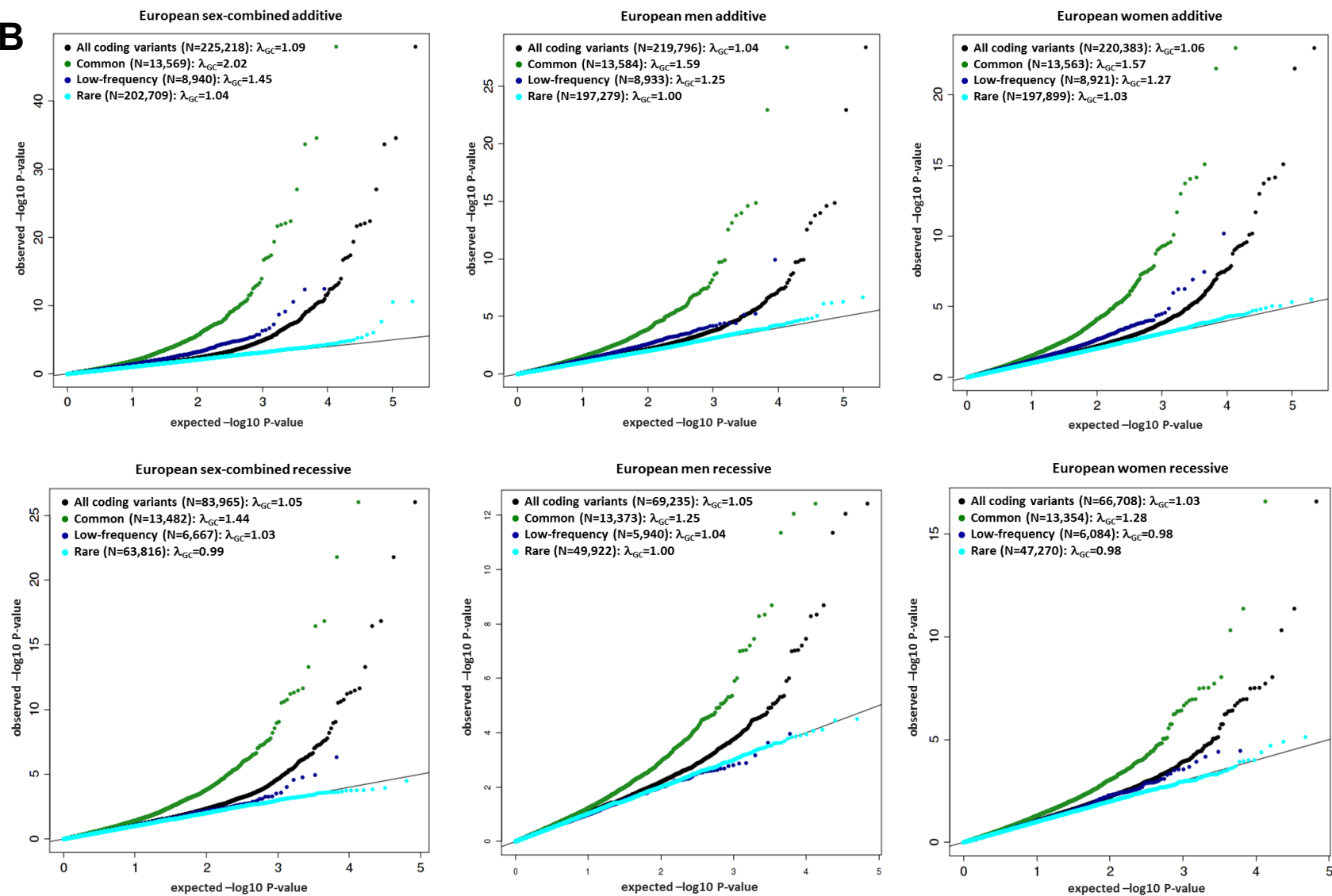


Supplementary Figure 2 | Quantile-quantile plots of BMI associations for coding SNVs tested in the Discovery GIANT meta-analyses. A-B. Quantile-quantile plots of BMI associations tested in all-ancestries (**A**) and European ancestry (**B**) strata for all coding (exonic and splicing) SNVs in black, and stratified by minor allele frequency (MAF) cut-offs; common variants ($MAF \geq 5\%$) in green, rare and low-frequency variants ($MAF < 5\%$) in dark blue, and rare variants ($MAF < 1\%$) in light blue. **C-D**. Quantile-quantile plots of BMI associations tested in all-ancestries (C) and European ancestry (D) strata for all coding (exonic and splicing) SNVs in black, and after excluding ($\pm 1\text{Mb}$) known and novel loci identified in previous BMI GWAS and in the ExomeChip meta-analysis (pink).

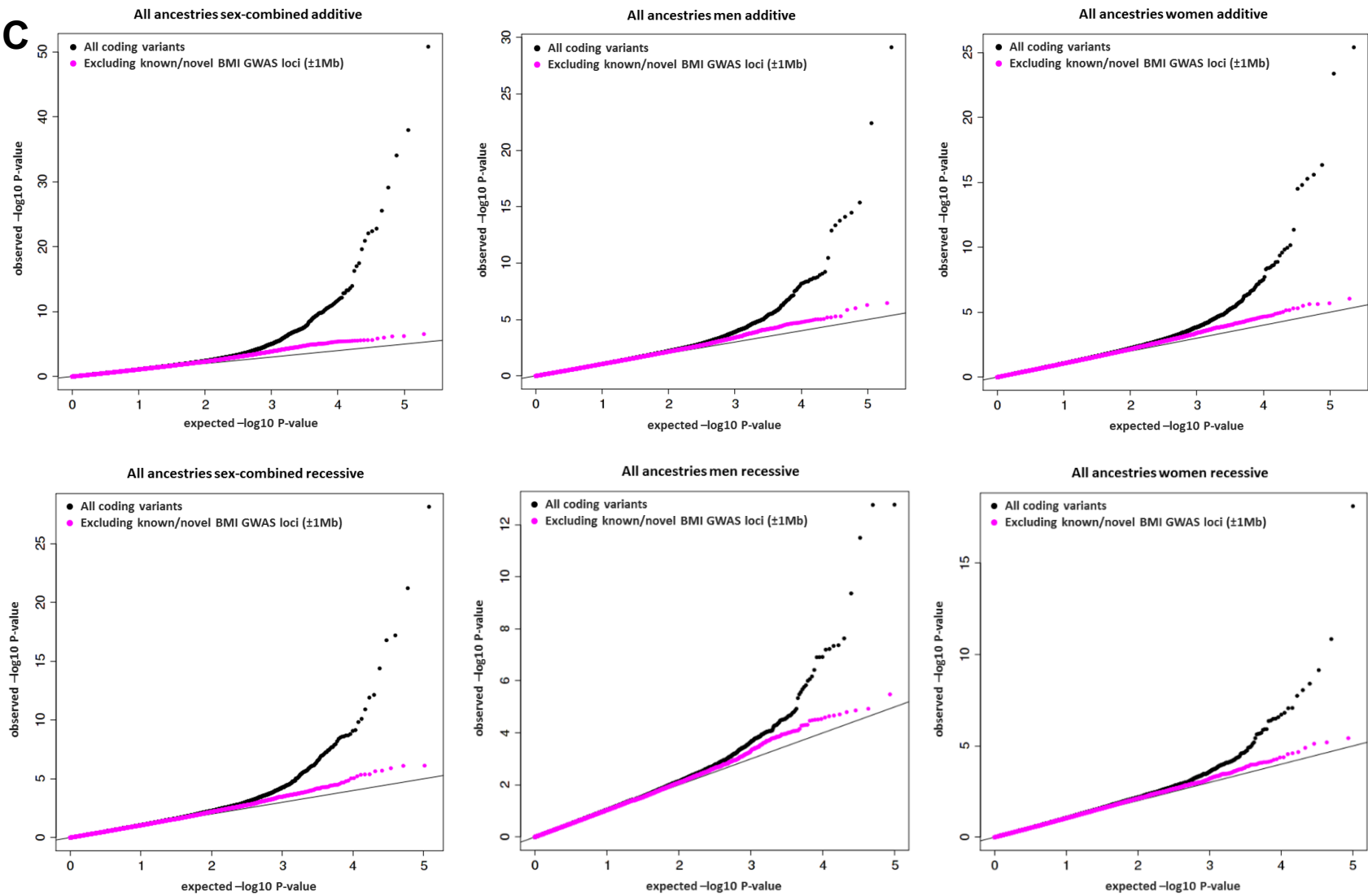
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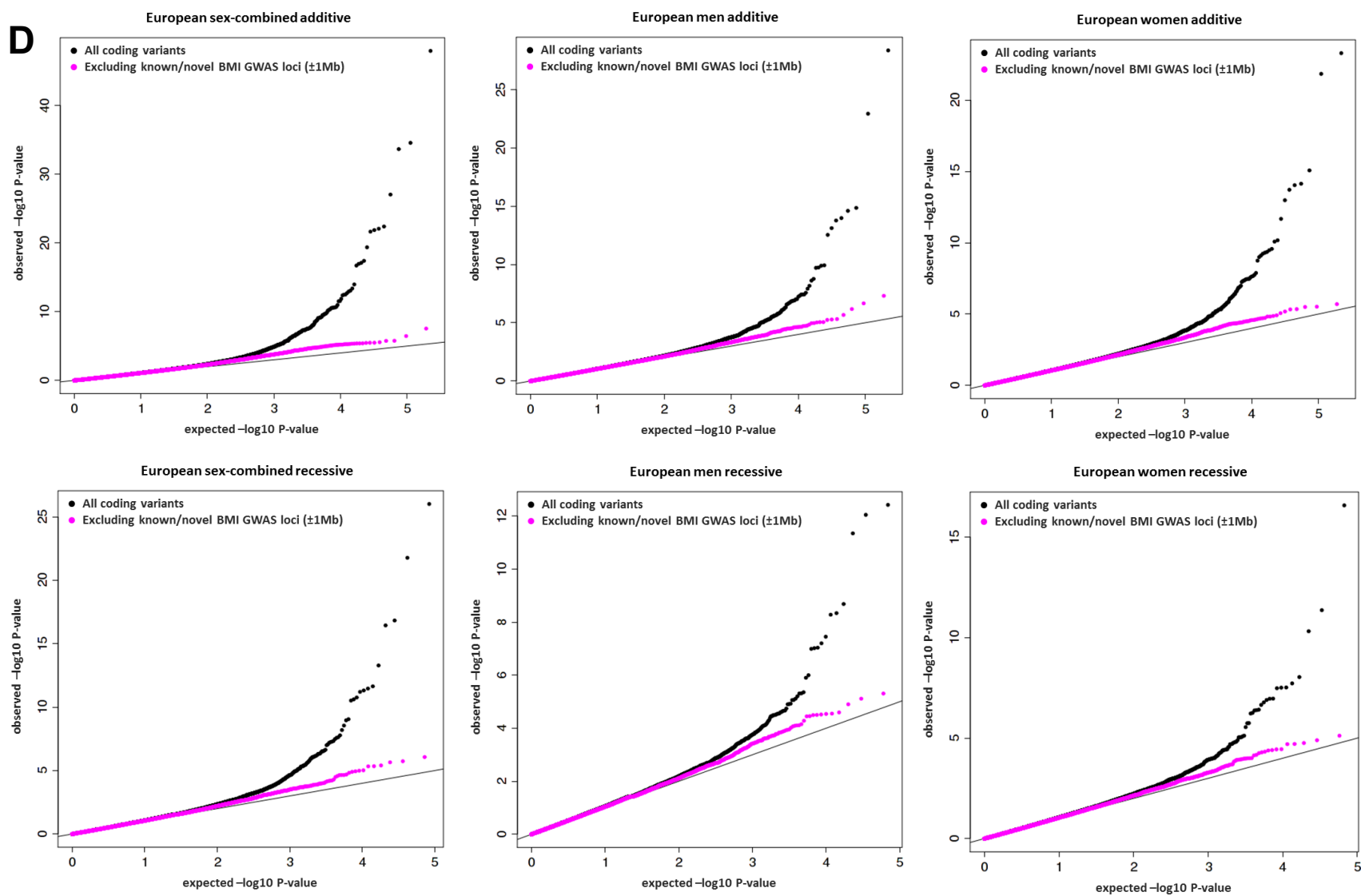
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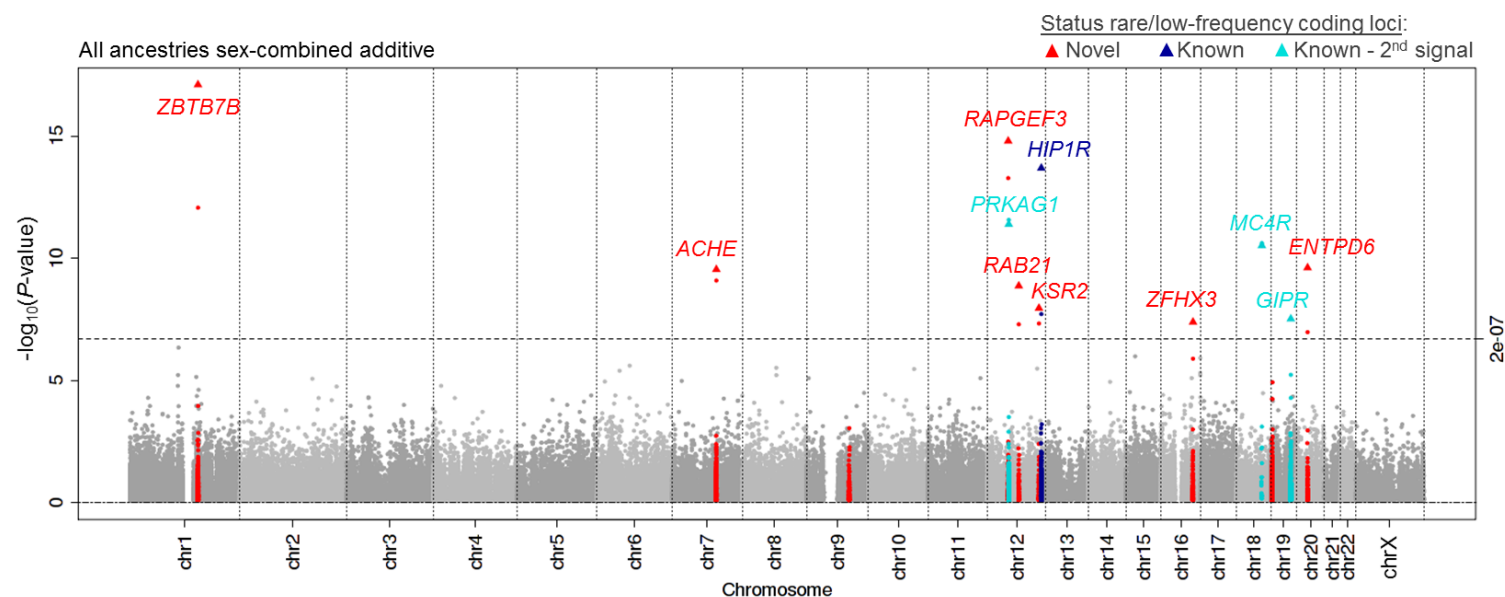


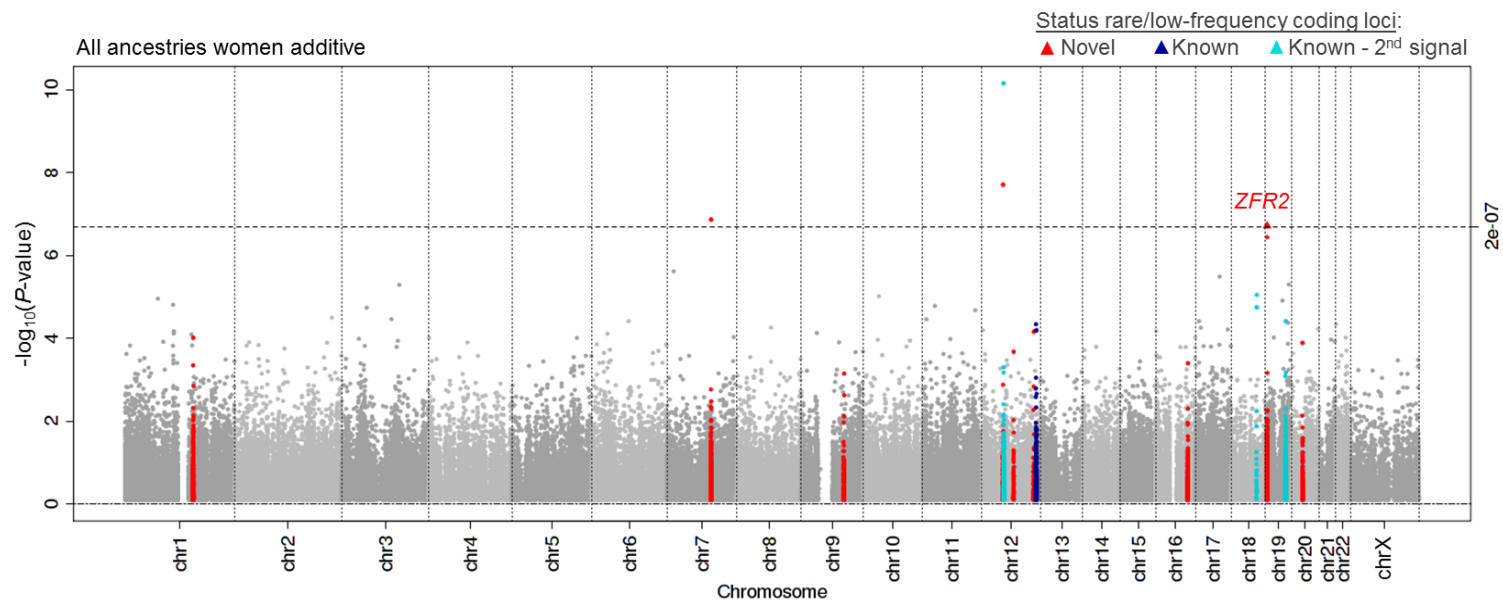
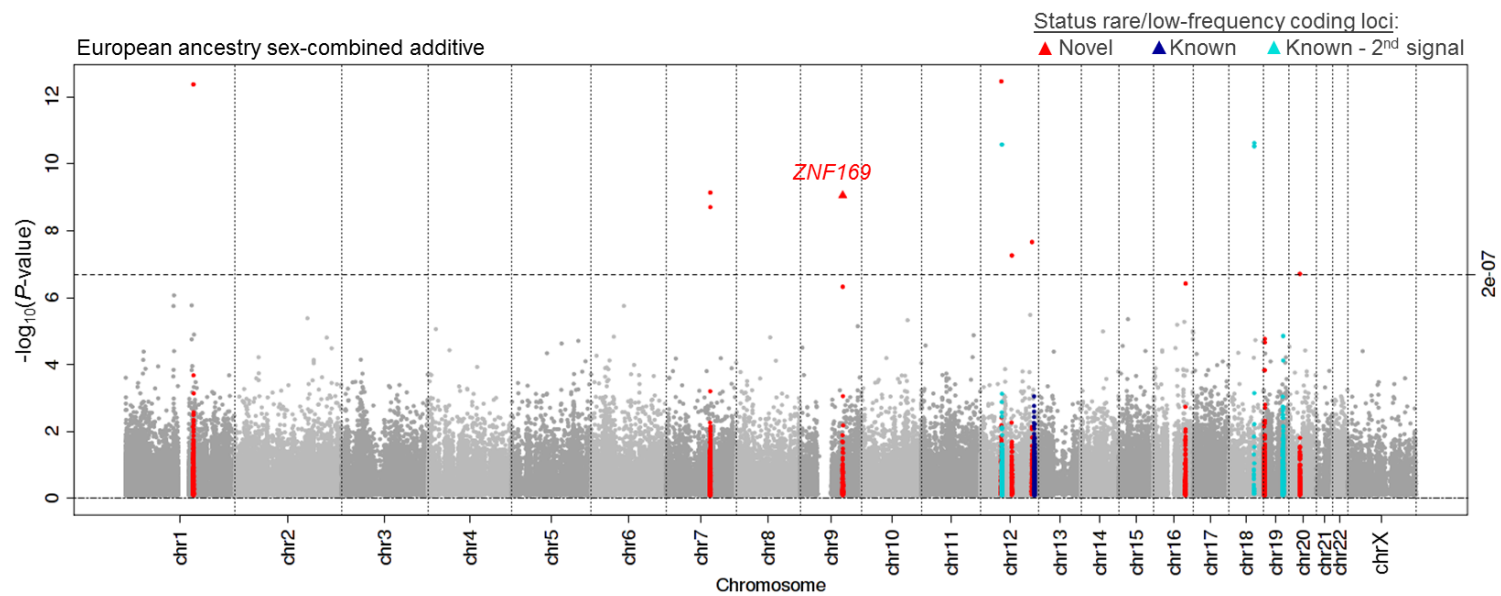
D



Supplementary Figure 3 | Manhattan plots of coding rare and low-frequency SNV associations in the Discovery GIANT dataset appended with the significant SNVs from the final combined meta-analysis. Manhattan plot of associations in all-ancestries sex-combined additive (A), all-ancestries women additive (B) and European ancestry sex-combined additive (C) strata. Each locus was defined using a 1Mb window on each side of the lead coding variant. Dots correspond to the Discovery GIANT meta-analysis results, while the final combined meta-analysis results were appended to the plots using triangles. Only significant loci in the final combined meta-analysis were colored; novel loci, secondary signals (in known GWAS loci, but independent from GWAS hit/proxy) and known loci were highlighted in red, light blue and dark blue, respectively.

A



B**C**

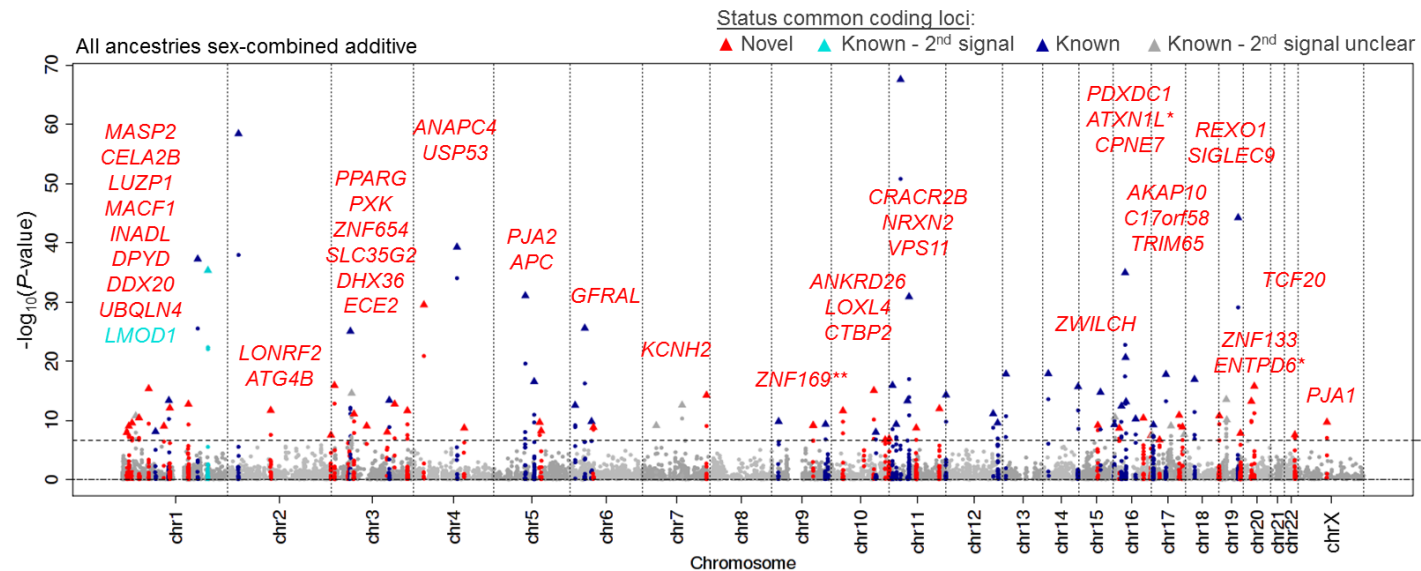
Supplementary Figure 4 | Manhattan plots of coding common SNV associations obtained in the Discovery GIANT dataset appended with the significant SNVs from the final combined meta-analysis See also Supplementary Table 4 for detailed results.

Each locus was defined using a 1Mb window on each side of the lead coding variant. Dots correspond to the Discovery GIANT meta-analysis results, while the final combined meta-analysis results were appended to the plots using triangles.

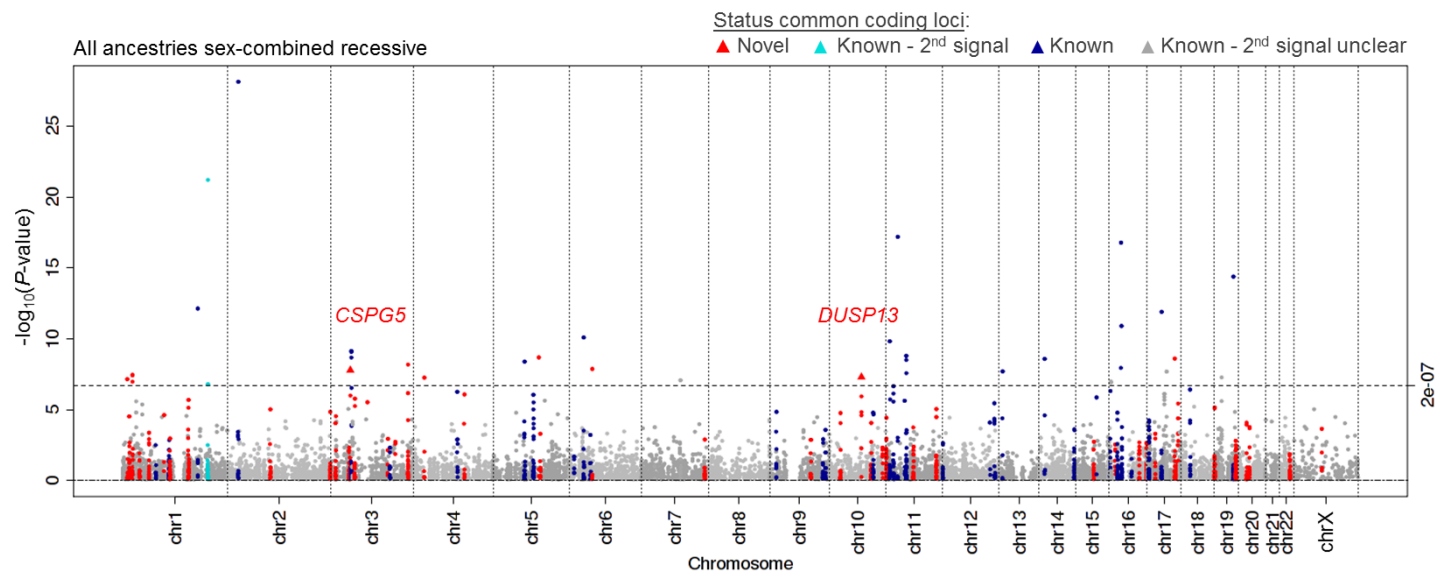
Panels A, B & C: Results from novel loci and novel secondary signals. Manhattan plot of associations in all-ancestries sex-combined additive (A), all-ancestries sex-combined recessive (B) and European ancestry sex-combined additive (C) strata. Only novel loci (in red) and novel secondary signals in known loci (in cyan) are shown in panels A, B & C.

Panels D & E: Results from known loci, some of which with potential secondary signals. Manhattan plot of associations in all-ancestries sex-combined additive (D) and all-ancestries women additive (E) strata. Loci that were previously established (in blue), and signals in previously known loci, but for which conditional analyses could not convincingly determine whether the signal was secondary or the same locus (in grey) are shown in panels D & E.

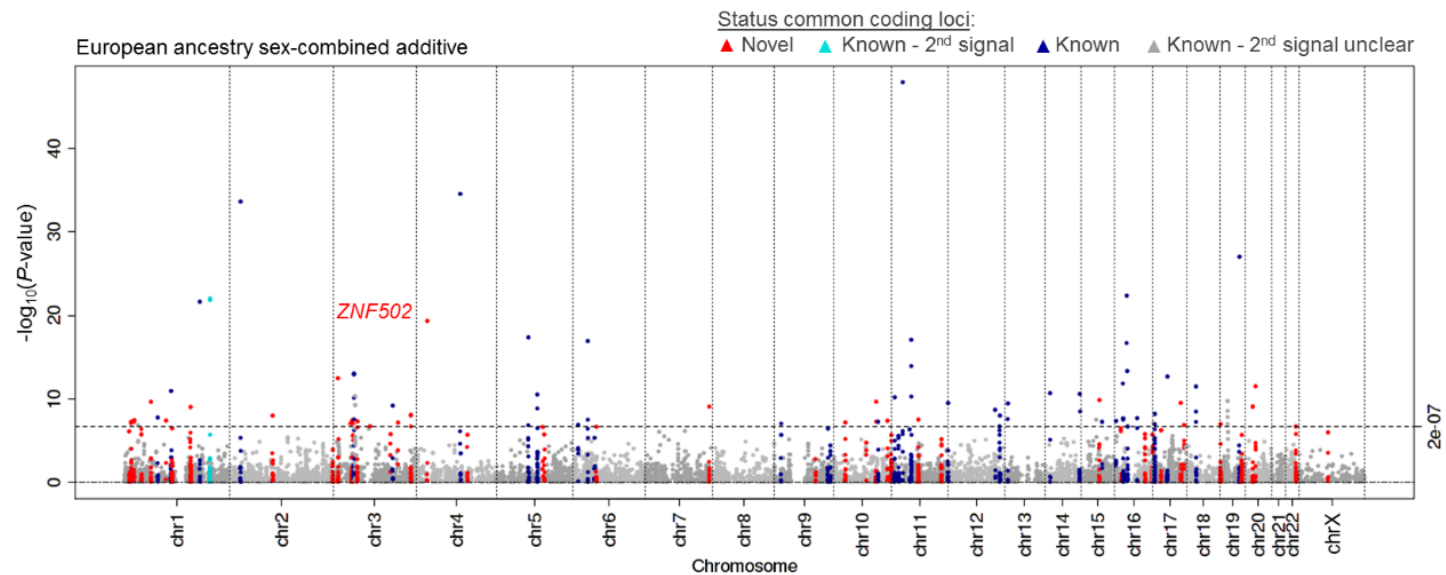
A



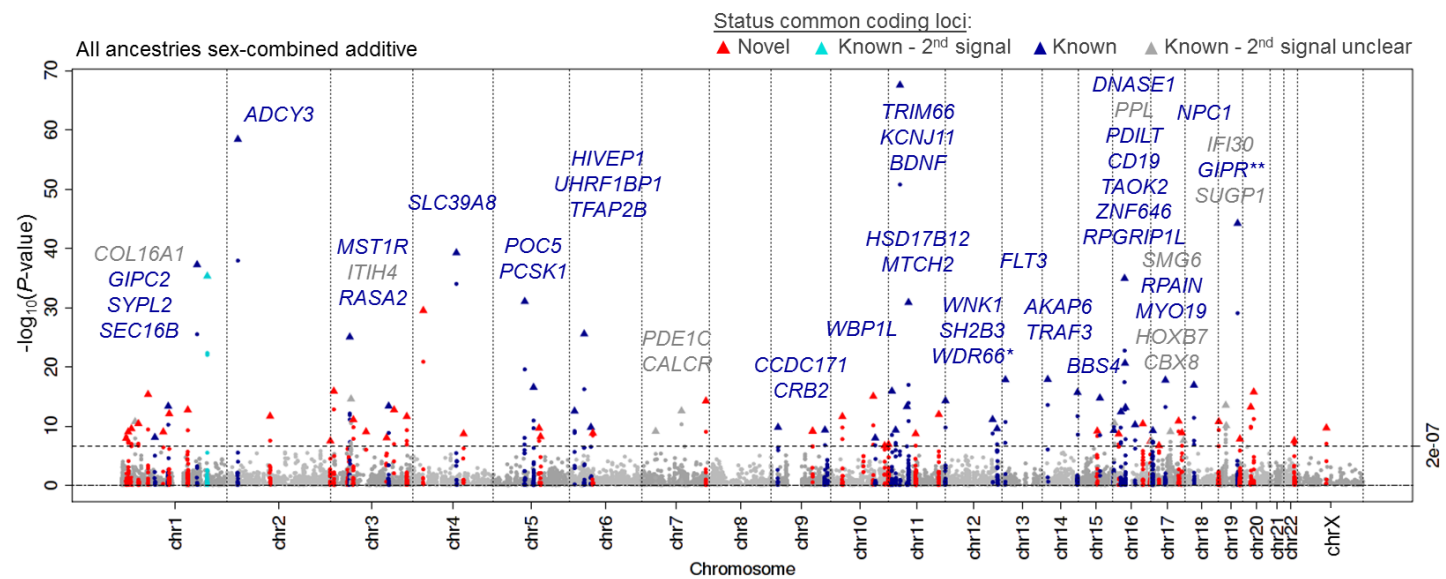
B

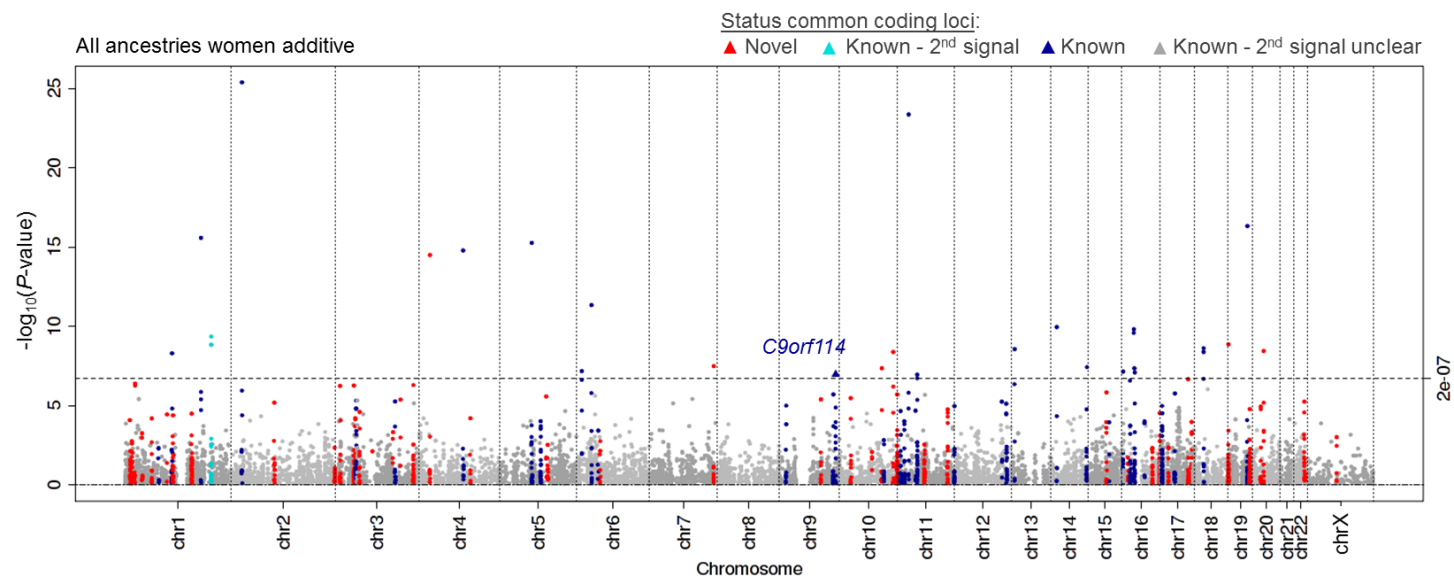


C



D

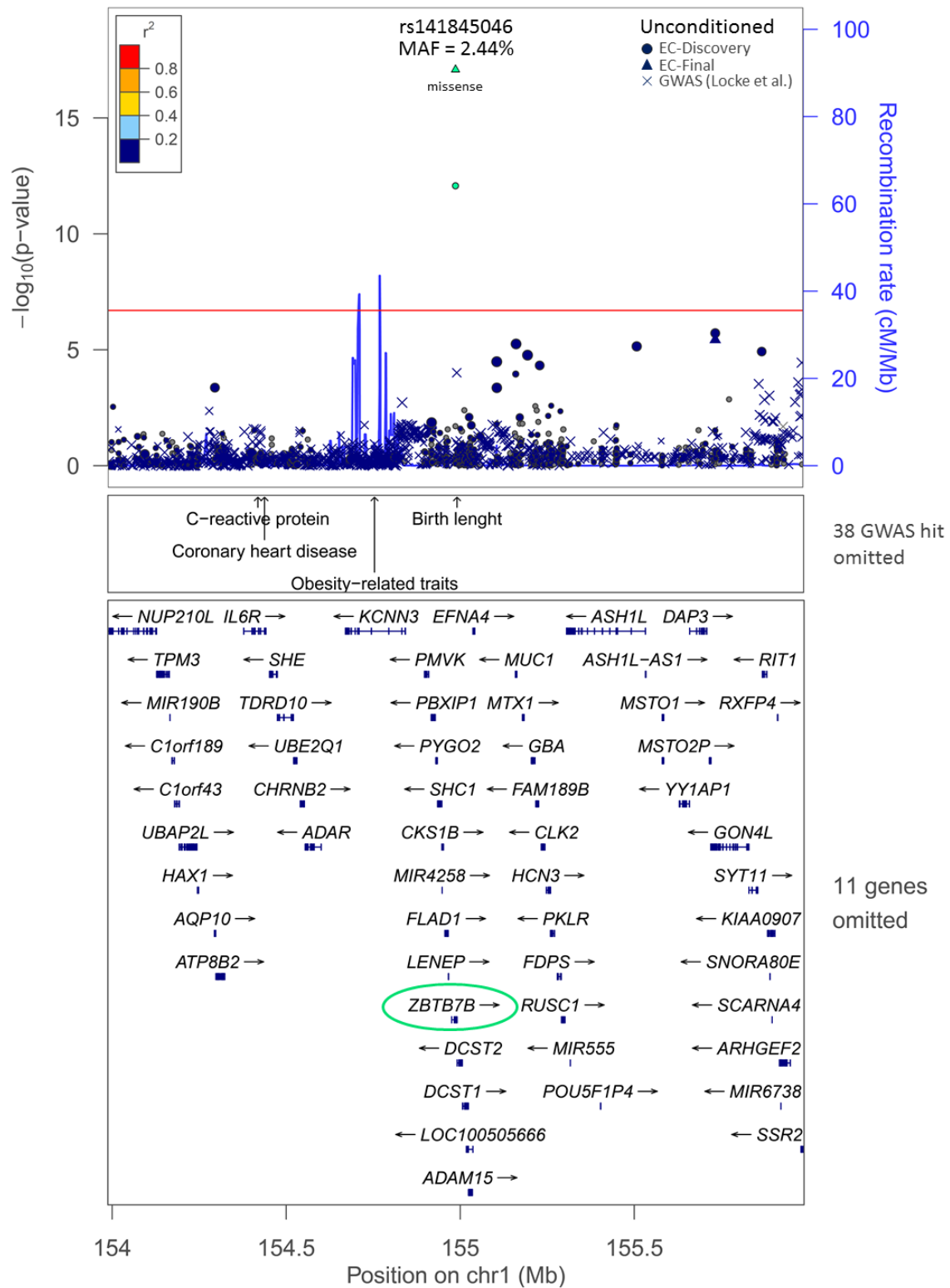


E

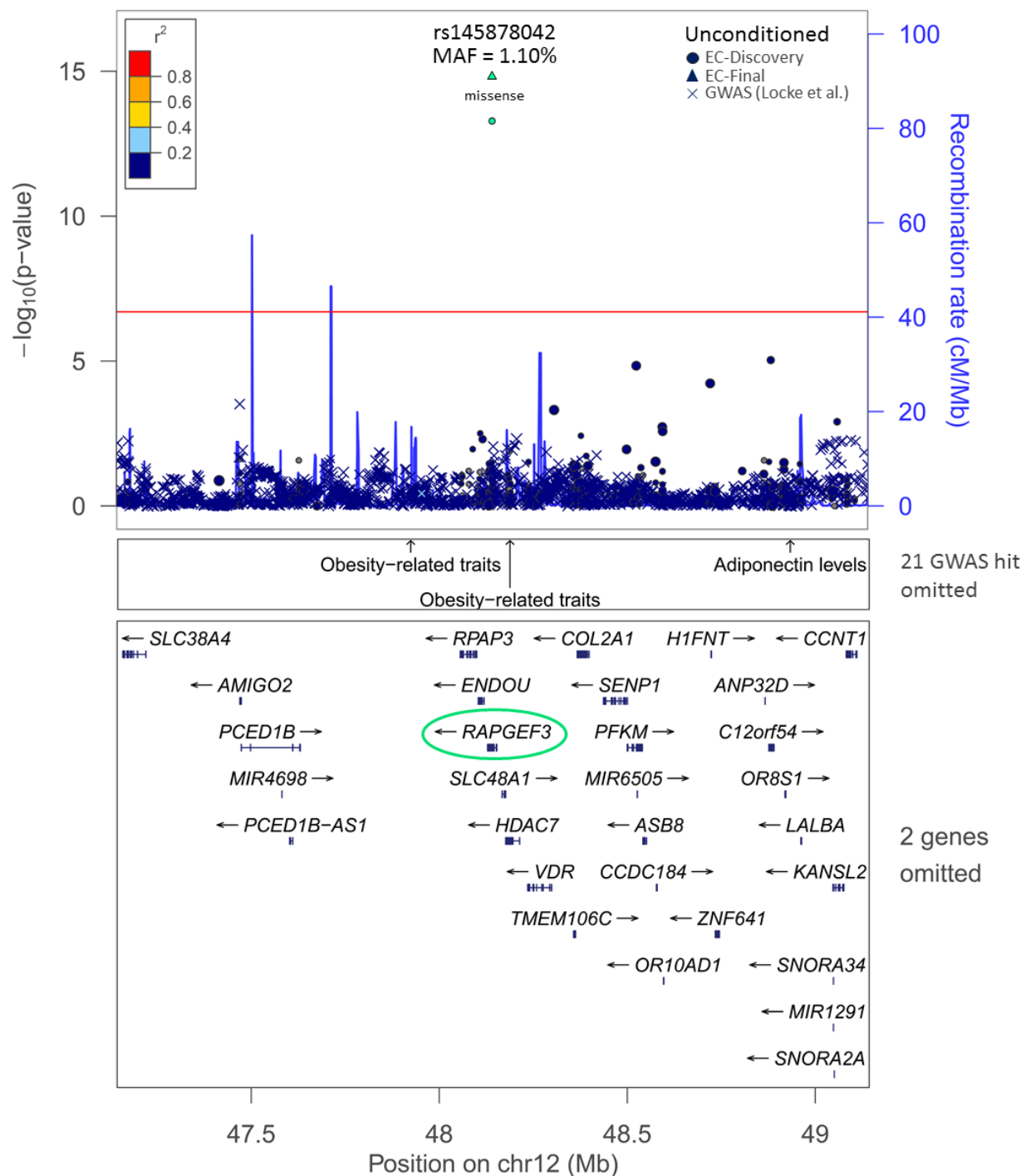
Supplementary Figure 5 | Regional association plots for the significant rare and low-frequency coding loci identified in the final combined meta-analysis among all analysis strata. The association results shown in these plots are from the Discovery GIANT meta-analysis in the specified analysis strata for all ExomeChip SNVs (dots) and appended with the previous BMI GWAS results (European ancestry) from Locke et al. (crosses; Locke et al. Nature 518, 197-206). The size of the dots and crosses are weighted on the minor allele frequency. We have used the UK Biobank dataset (European ancestry; N=136,727) to calculate the linkage disequilibrium between the SNVs in the window and the reference coding SNV shown in turquoise. Only GWAS traits related with body weight are shown in the plots. (A) Regional plots for loci with only one significant coding SNV in the region (only unconditioned results shown). (B) Regional plots for loci with more than one significant coding SNVs or with a GWAS hit or proxy ($r^2 > 0.80$ in EUR 1000G phase 3) in the region ($\pm 1\text{MB}$). Both unconditioned and conditioned results are shown.

A

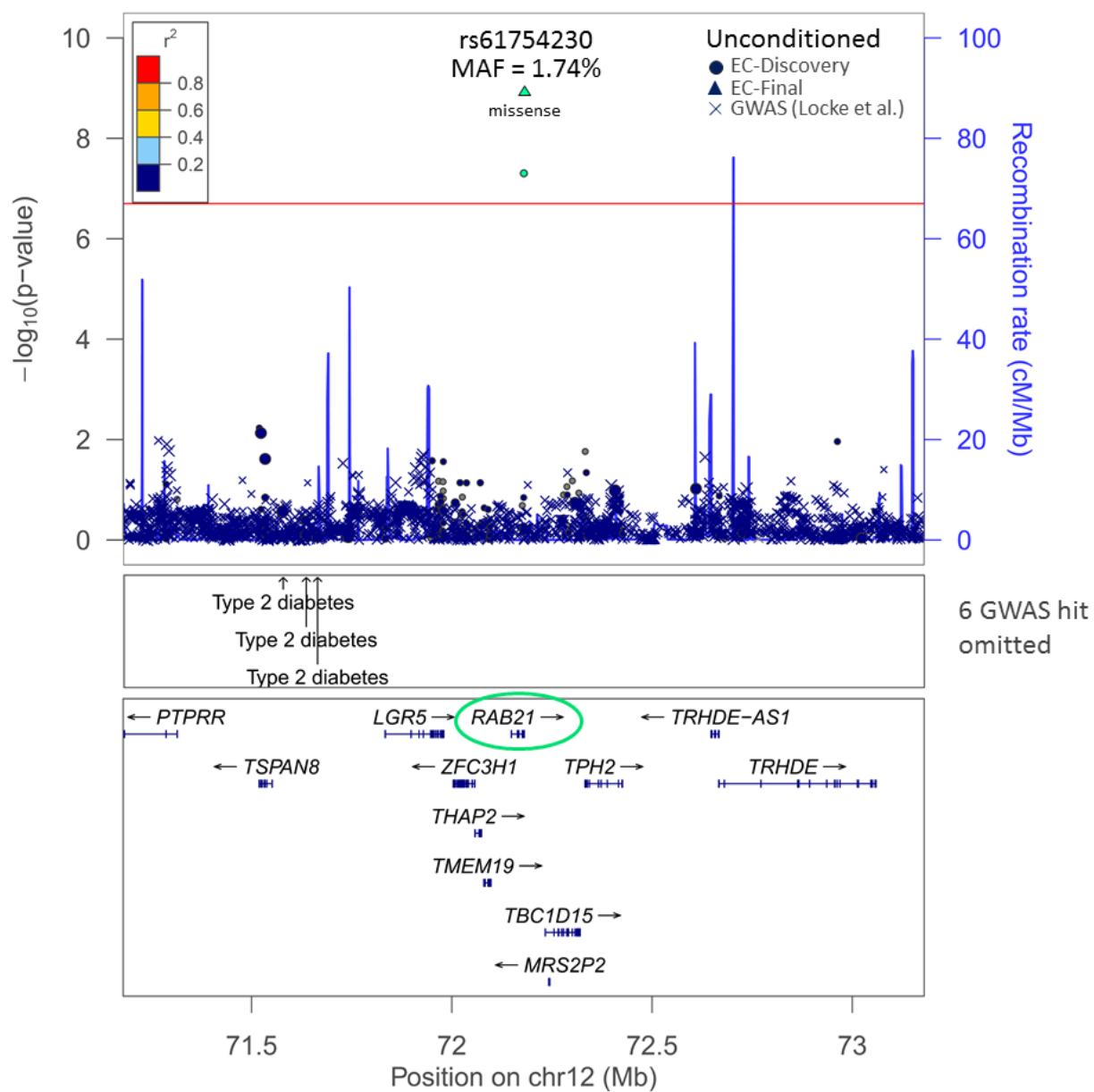
ZBTB7B - All-ancestries sex-combined additive



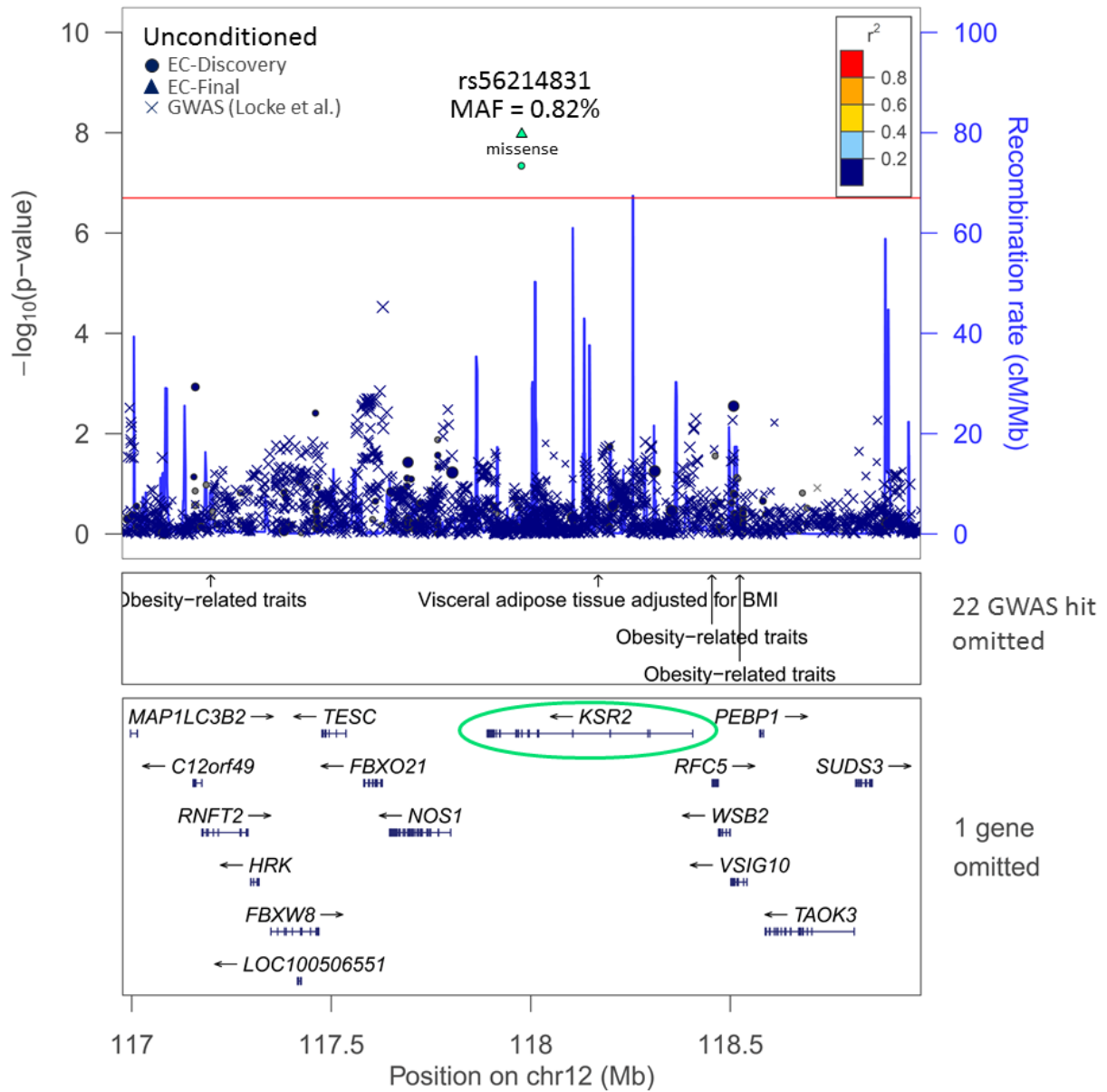
RAPGEF3 - All-ancestries sex-combined additive



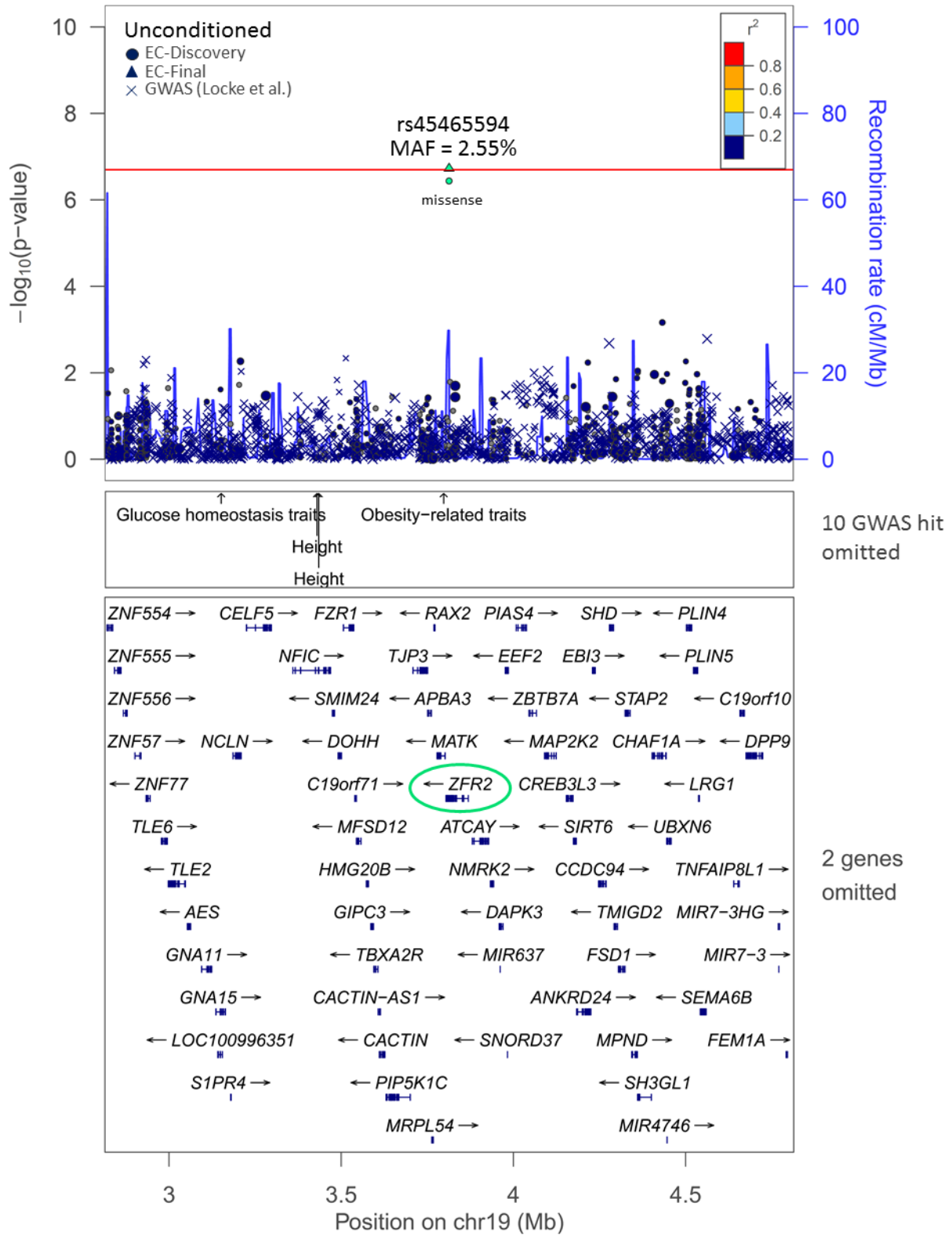
RAB21 - All-ancestries sex-combined additive



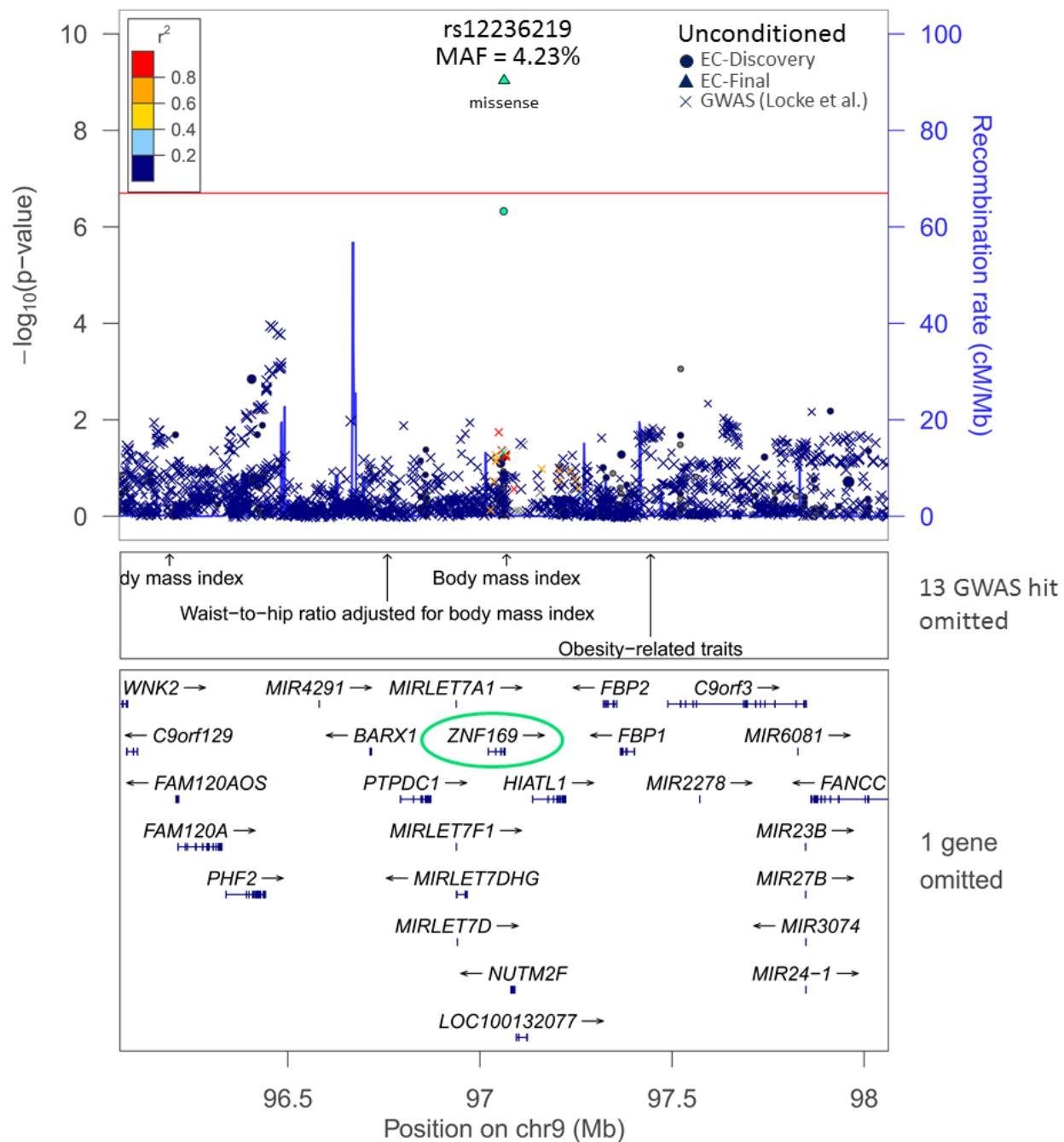
KSR2 - All-ancestries sex-combined additive



ZFR2 - All-ancestries women additive

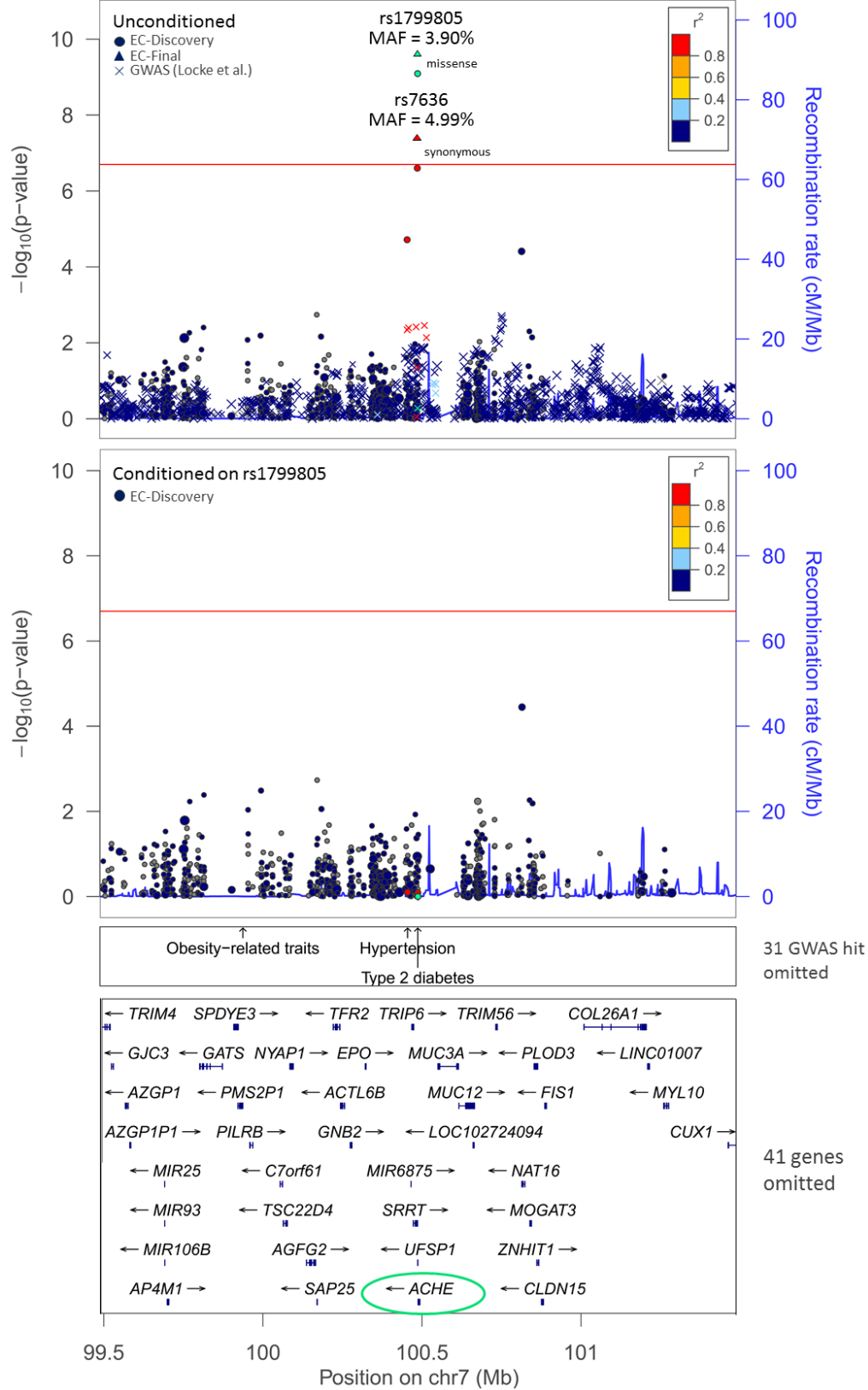


ZNF169 - Europeans sex-combined additive

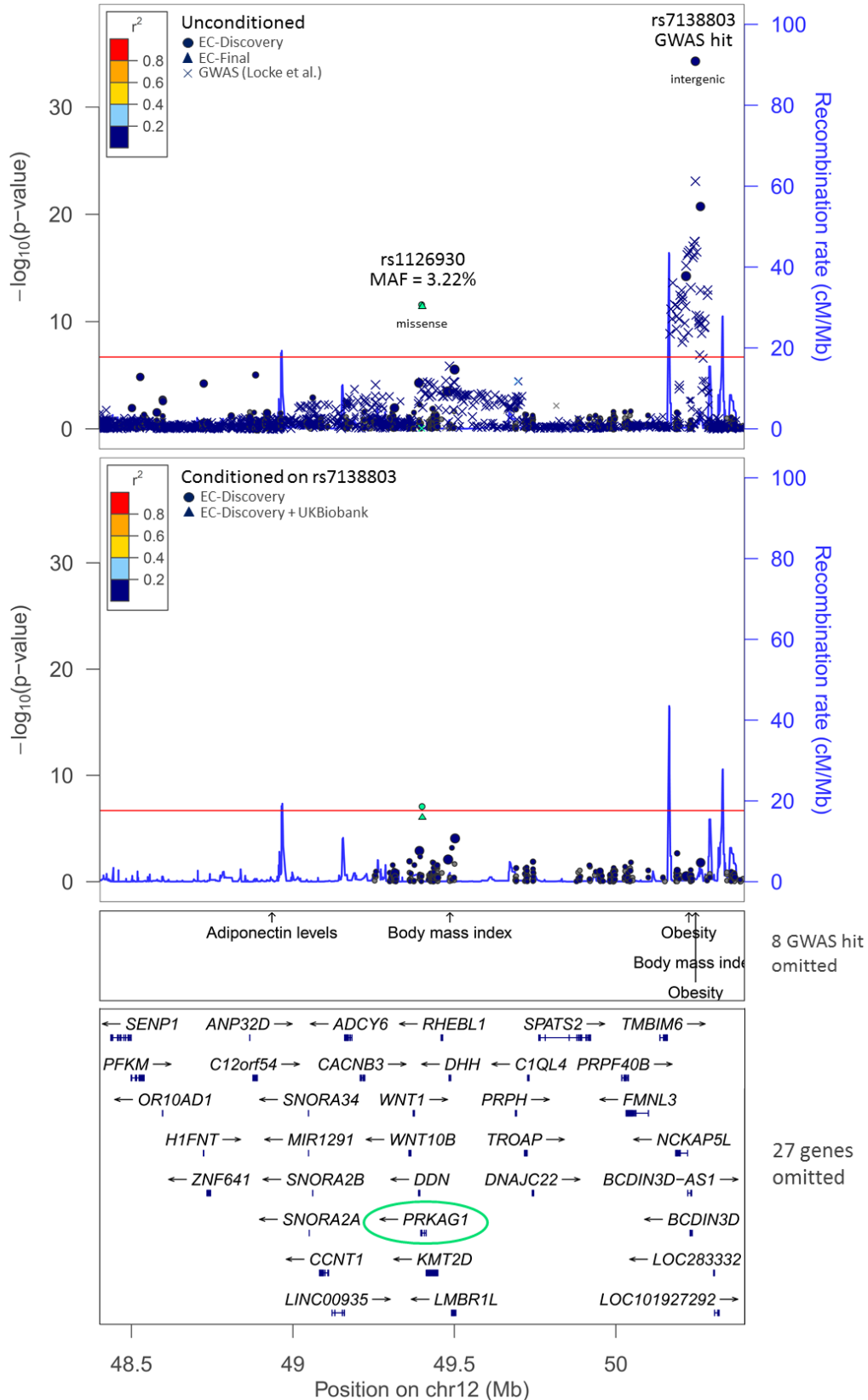


B

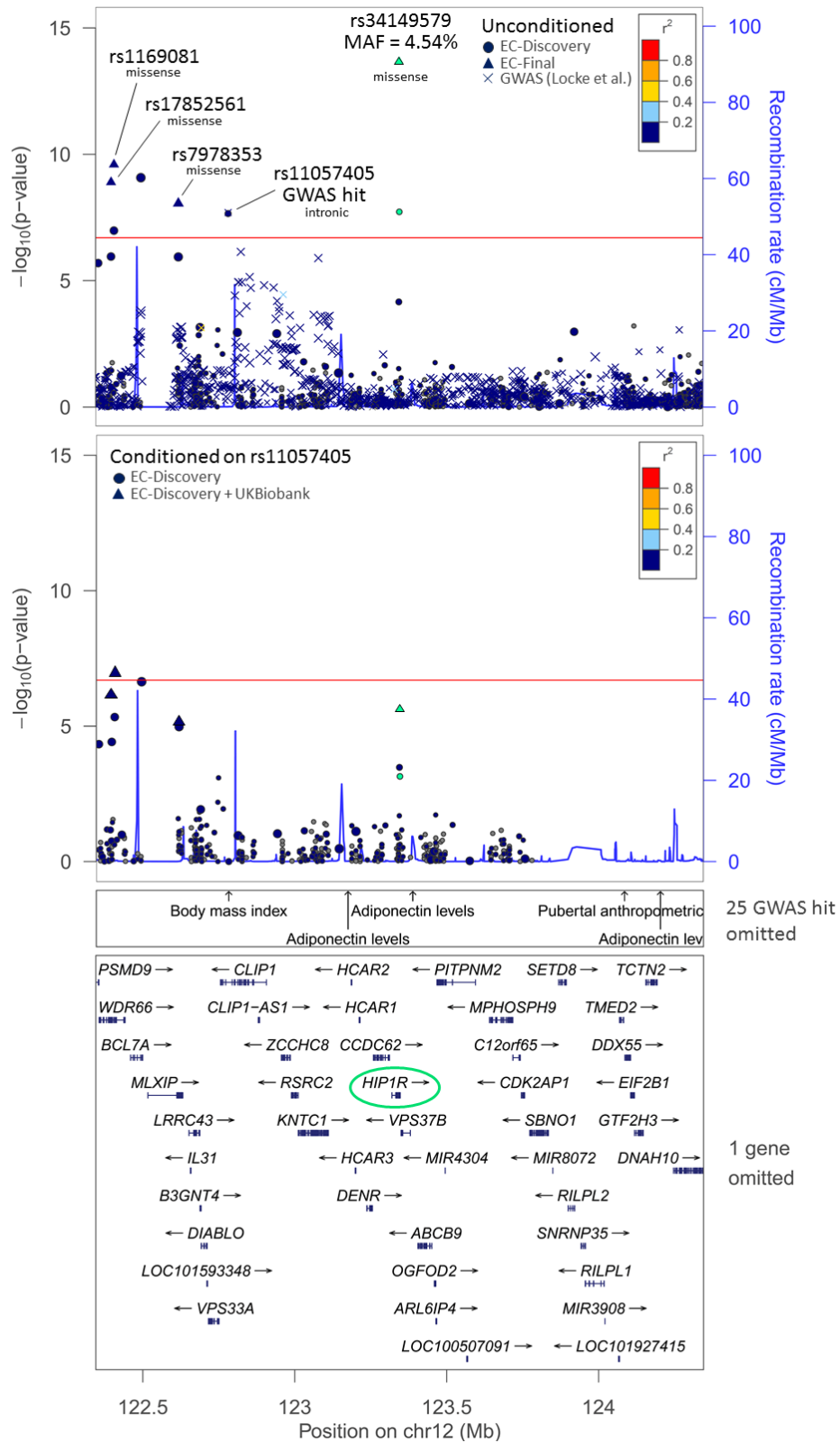
ACHE - All-ancestries sex-combined additive



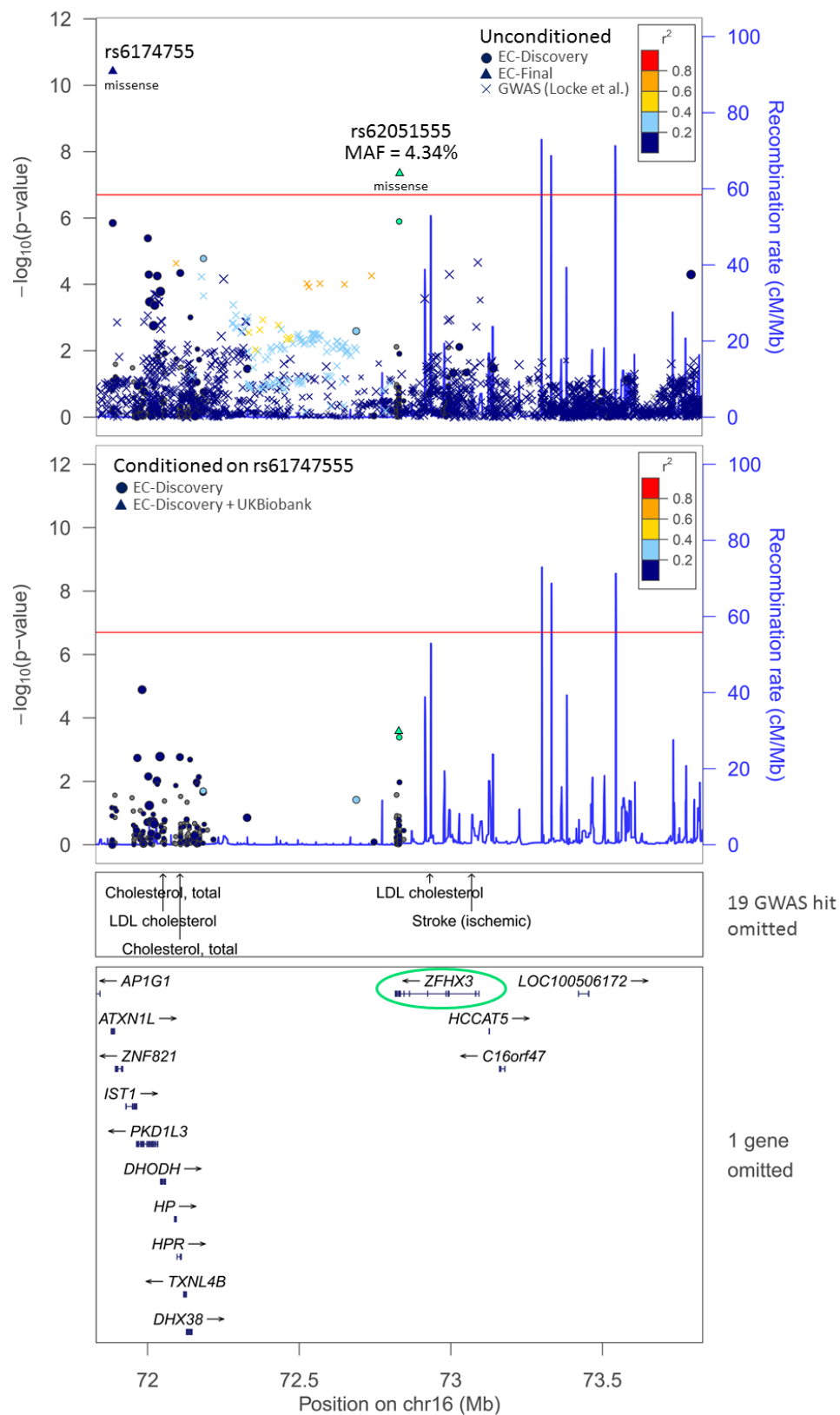
PRKAG1 - All-ancestries sex-combined additive



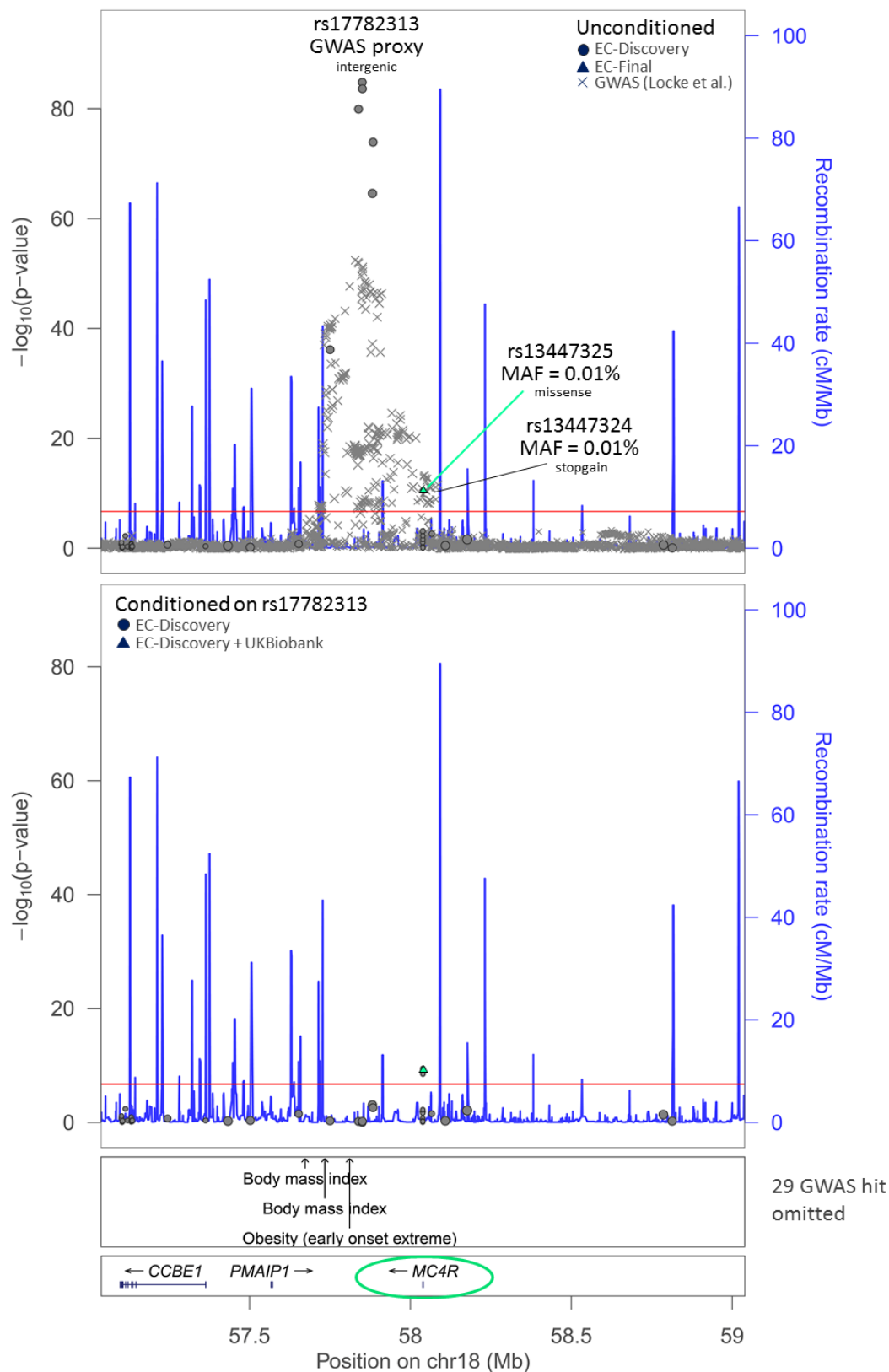
HIP1R - All-ancestries sex-combined additive



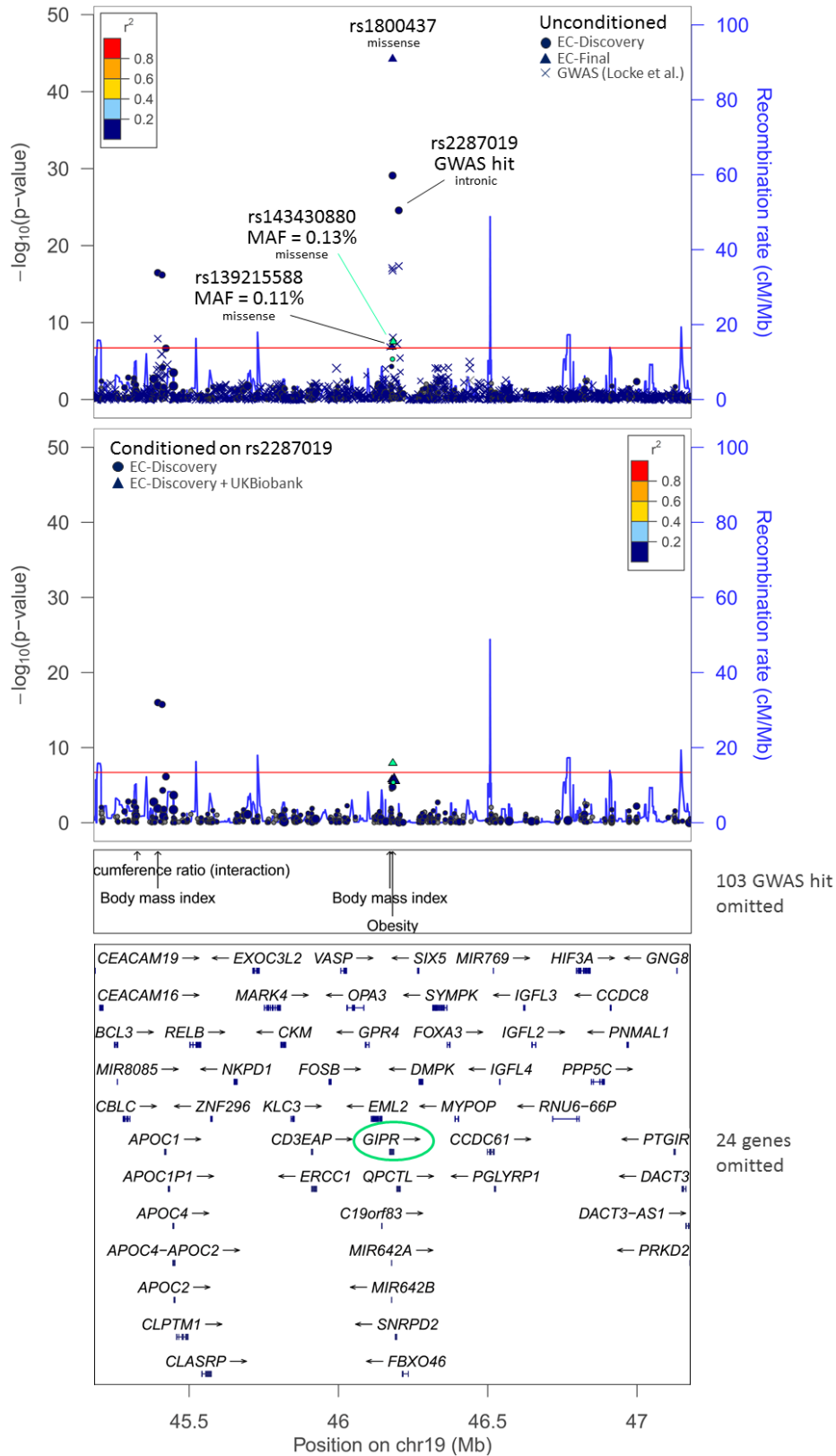
ZFH3 - All-ancestries sex-combined additive



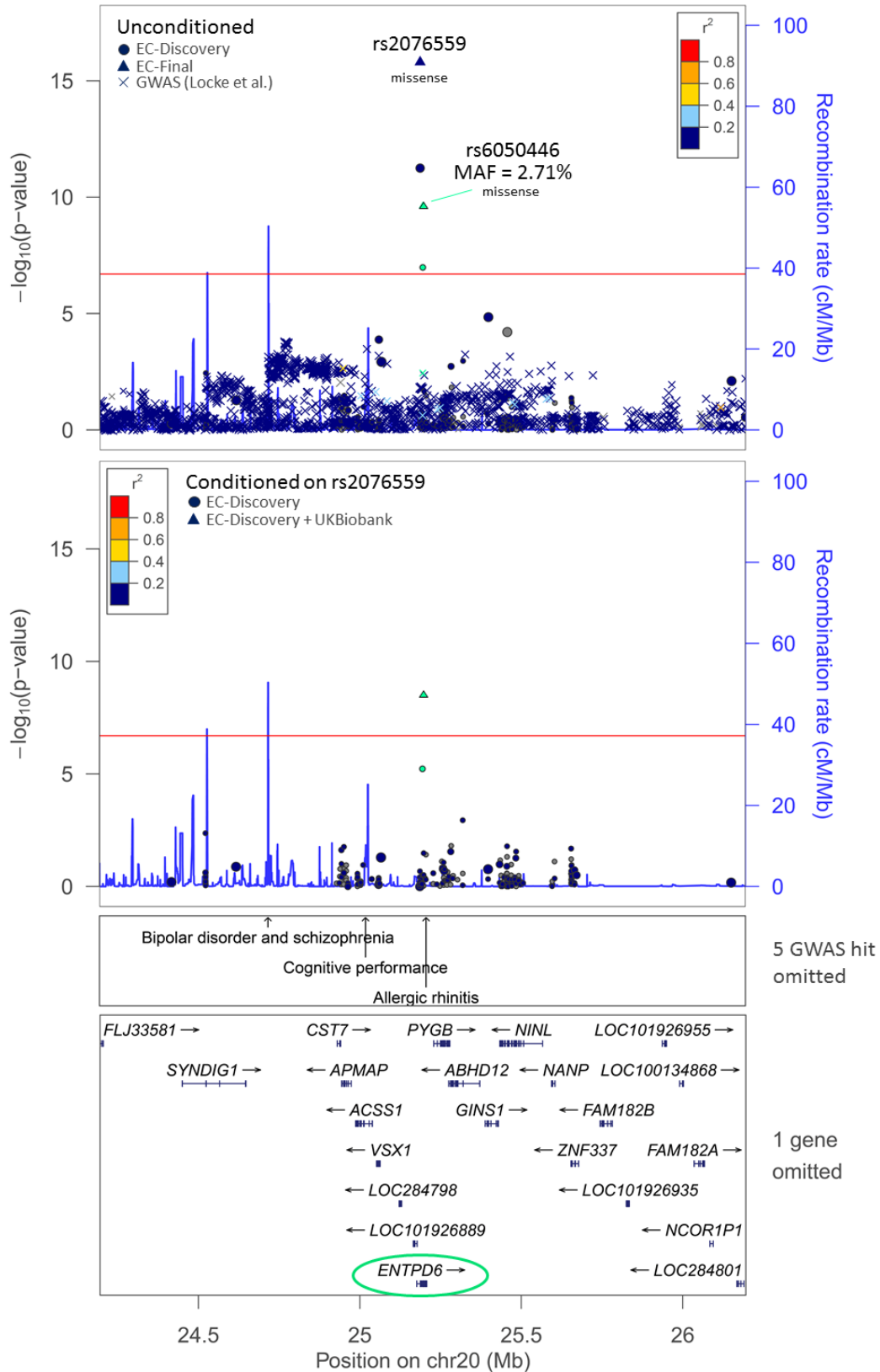
MC4R - All-ancestries sex-combined additive



GIPR - All-ancestries sex-combined additive



ENTPD6 - All-ancestries sex-combined additive



Supplementary Figure 6 | Relationship of allele frequencies and effect sizes of novel SNVs between European-ancestry and other ancestry populations (see also Supplementary Table 7). Panel A shows the data for the minor alleles of 14 low-frequency and rare SNVs. Panel B shows the data for the BMI-increasing allele of the 41 common SNVs.

A

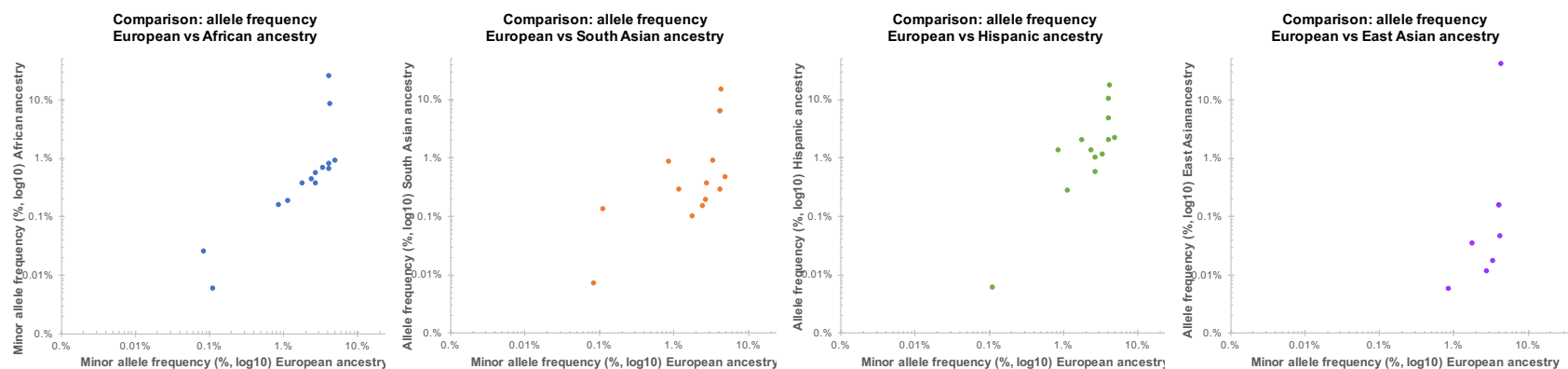
European vs African

European vs South Asian

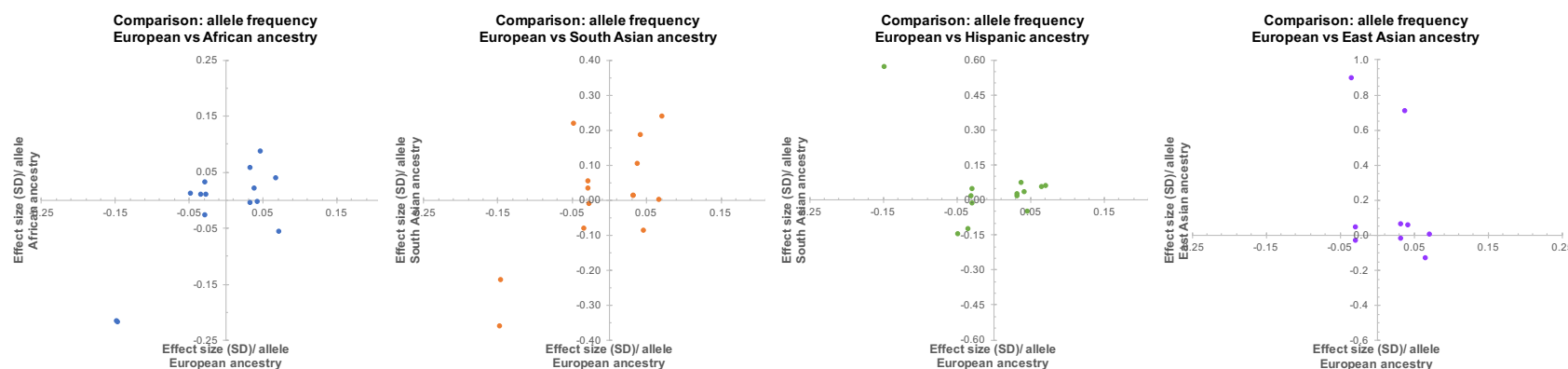
European vs Hispanic

European vs East Asian

Allele frequencies



Effect sizes



B

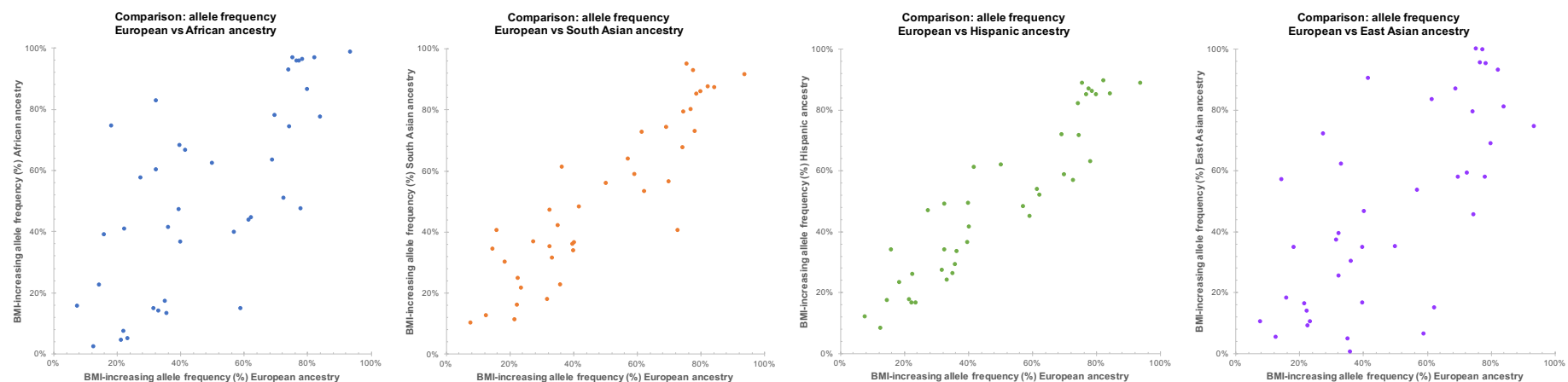
European vs African

European vs South Asian

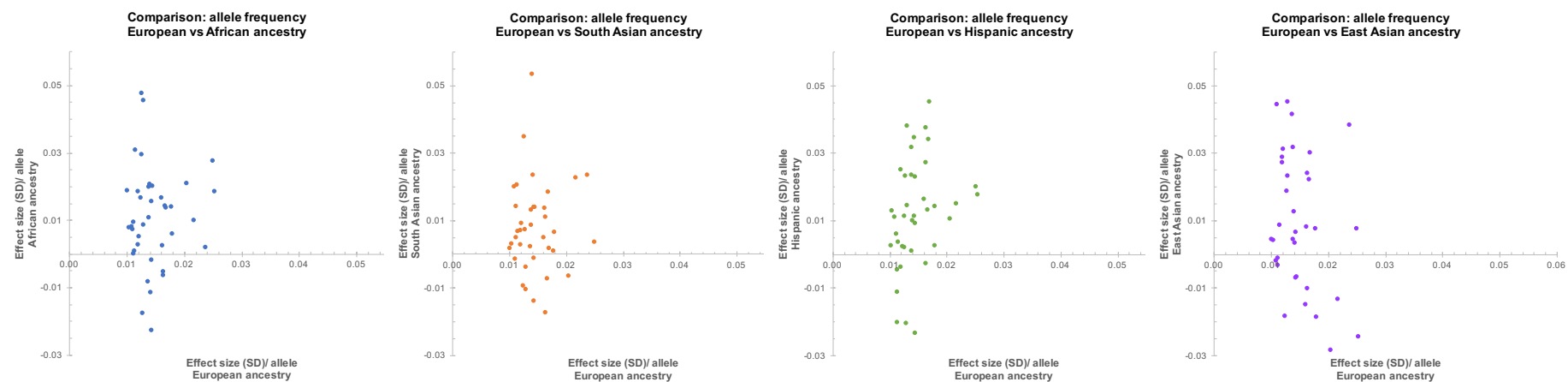
European vs Hispanic

European vs East Asian

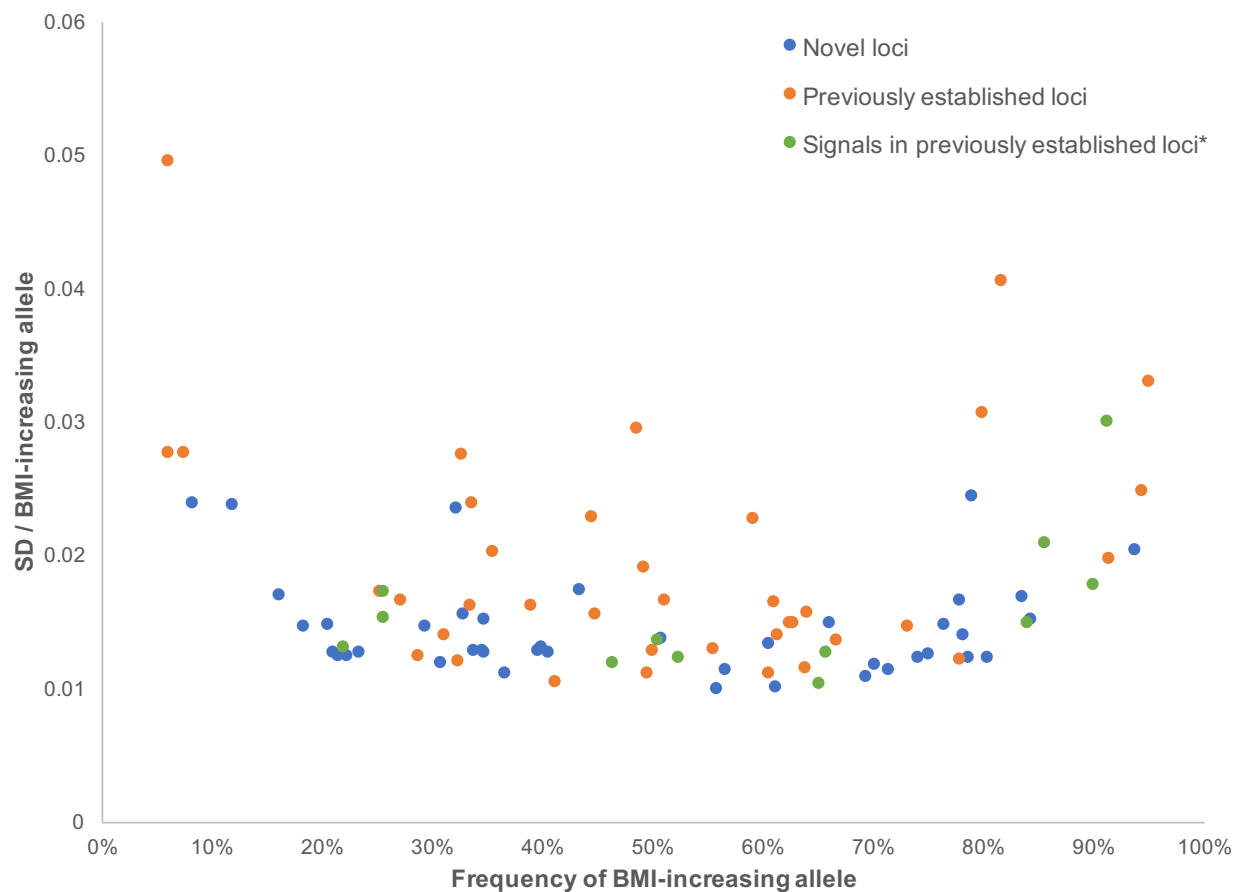
Allele frequencies



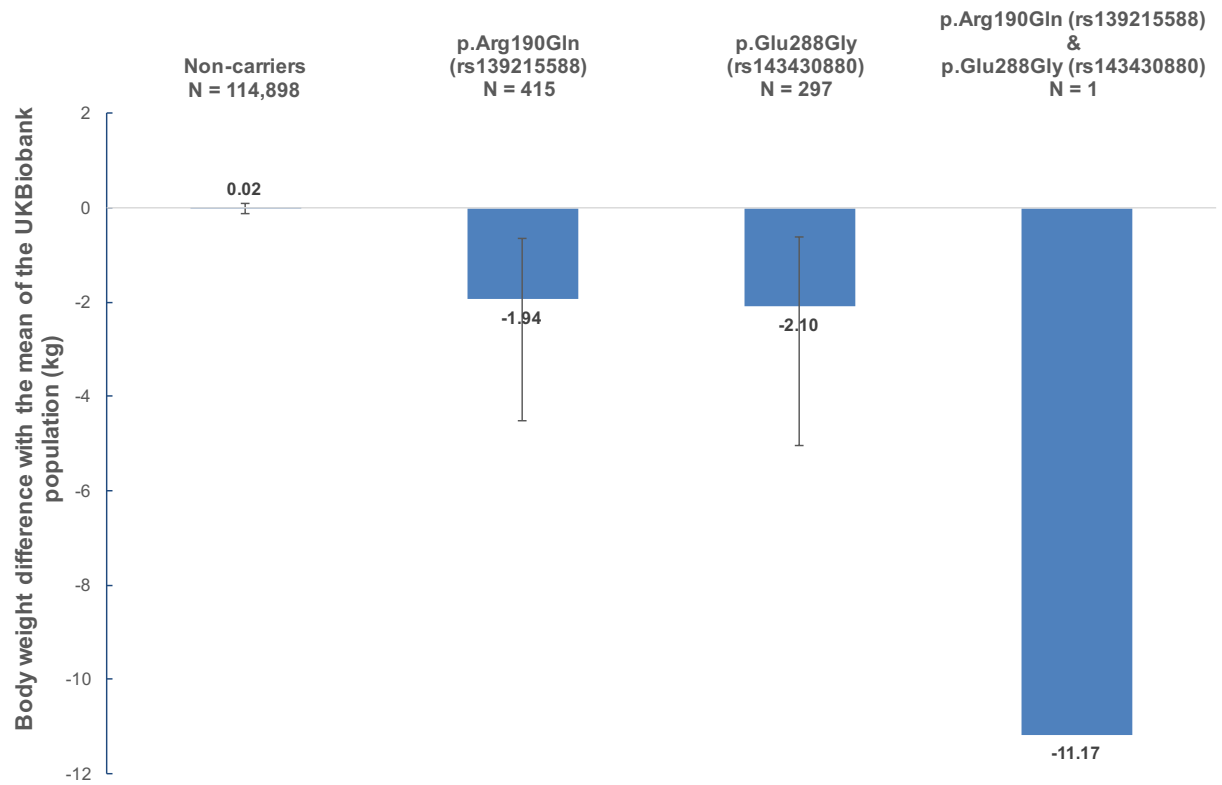
Effect sizes



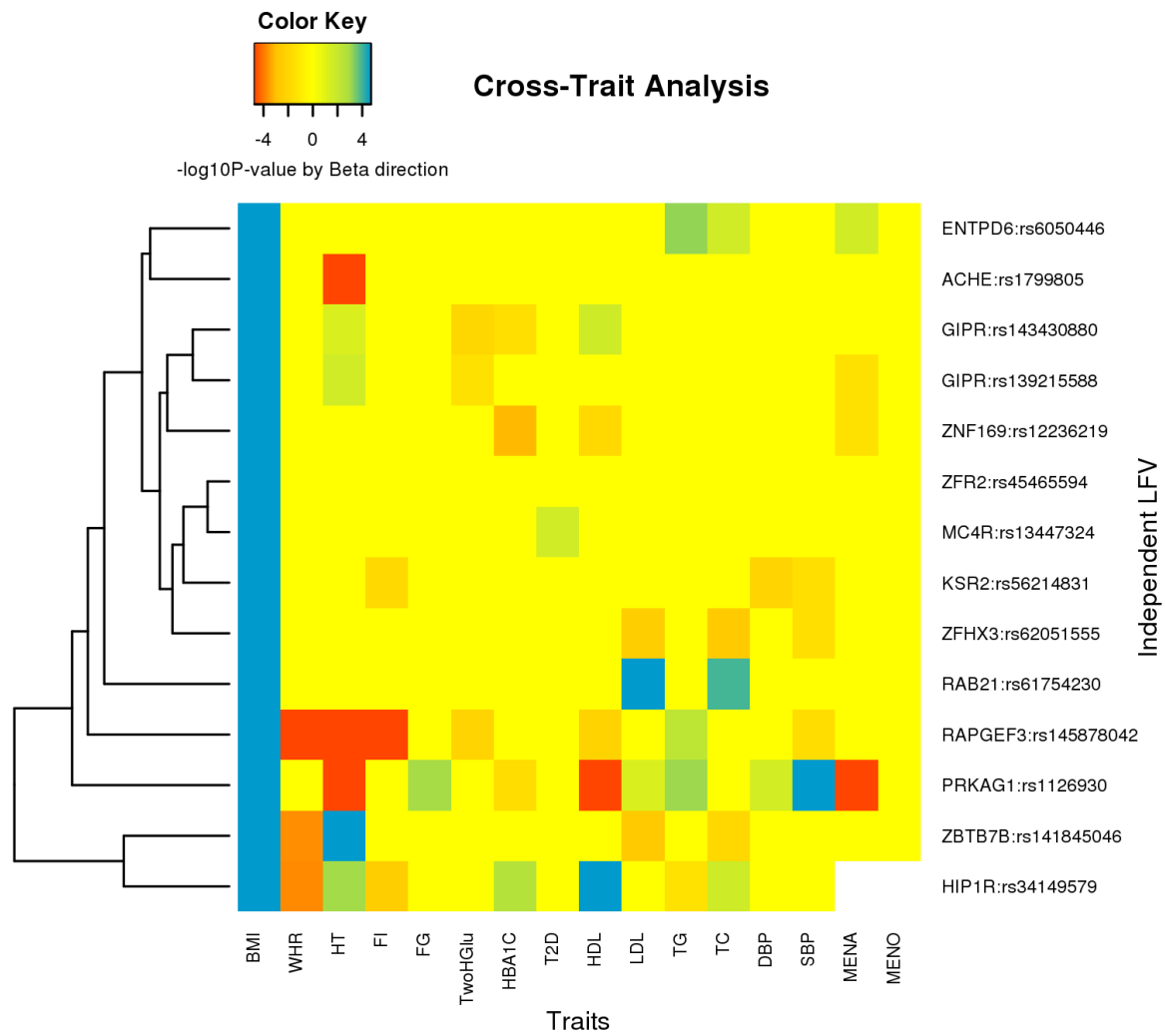
Supplementary Figure 7 | Effect sizes (y-axis) of the 92 common coding variants by their BMI-increasing allele frequency. Effect sizes are expressed in SD per allele (**Supplementary Table 4**). Blue dots represent the 42 novel loci, orange dots represent loci that have been identified before in GWAS for obesity traits, and green dots represent association signals in previously established loci, but for which conditional analyses was not able to convincingly determine the signal as secondary or not (i.e. the previously established lead SNP was not available on the chip).



Supplementary Figure 8 | Effects of the two rare SNVs (p.Arg190Gln, p.Glu288Gly) in *GIPR* on BMI in the UK Biobank (N = 115,611, Interim release). Y-axis shows the difference from mean BMI in the UKBiobank, after adjusting for age and sex.

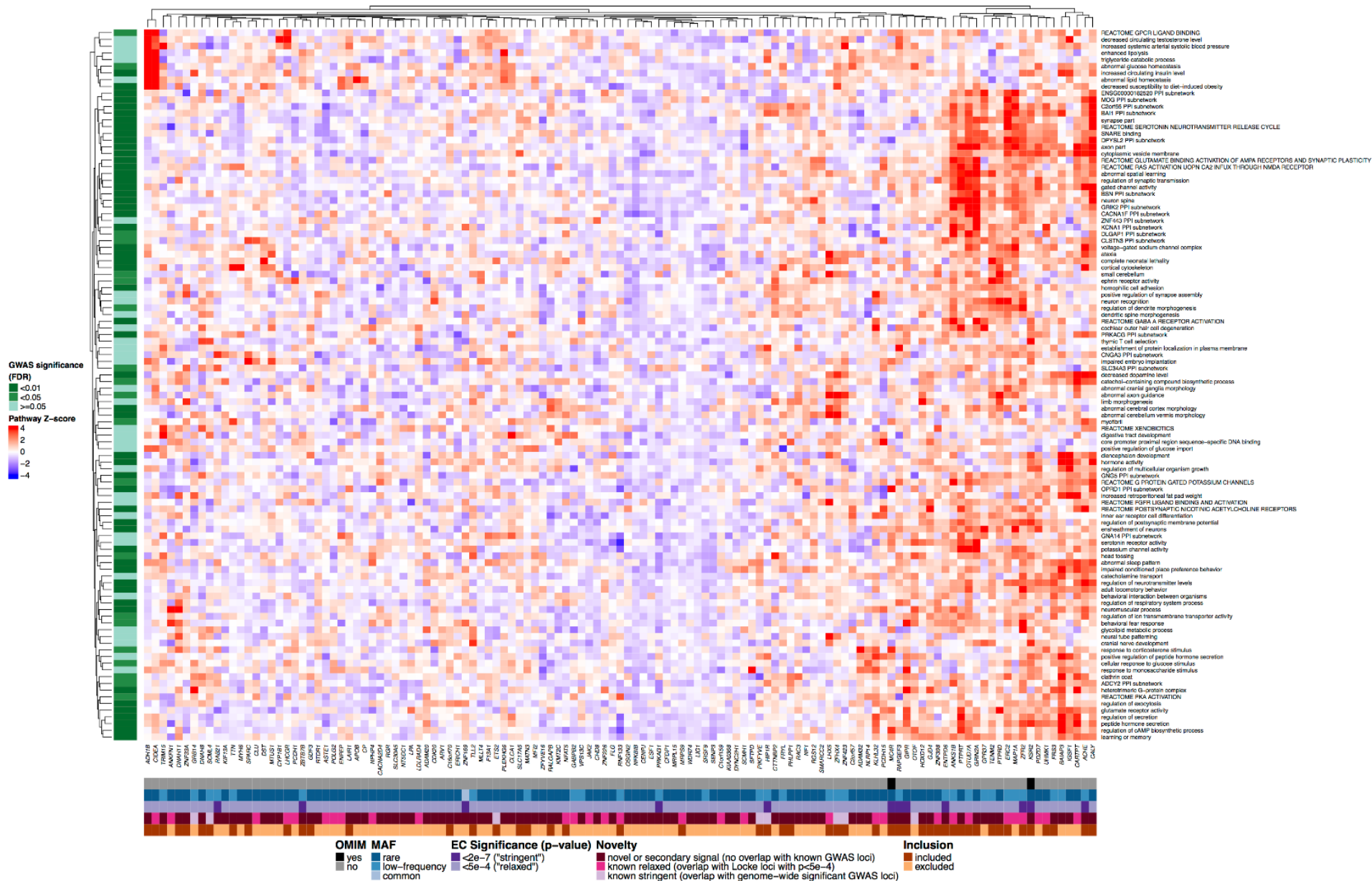


Supplementary Figure 9 | Heatmaps of cross-trait associations for the novel R/LF independent loci identified in the final combined meta-analysis. Heatmap squares are $-\log_{10}(P\text{-values})$ with red-to-blue shading based on beta effect direction for the BMI-increasing allele in the final combined meta-analysis (blue). Green-to-blue shading hits correspond to positive beta effects with P -values between 0.05 and $<2E-5$, orange-to-red shading hits correspond to negative beta effects with P -values between 0.05 to $<2E-5$, yellow squares are not significant ($P>0.05$), and white squares are missing values. Clustering was done using the complete linkage method with Euclidean distance measure for the loci. SNVs clustering together are more significantly associated with the same set of traits.

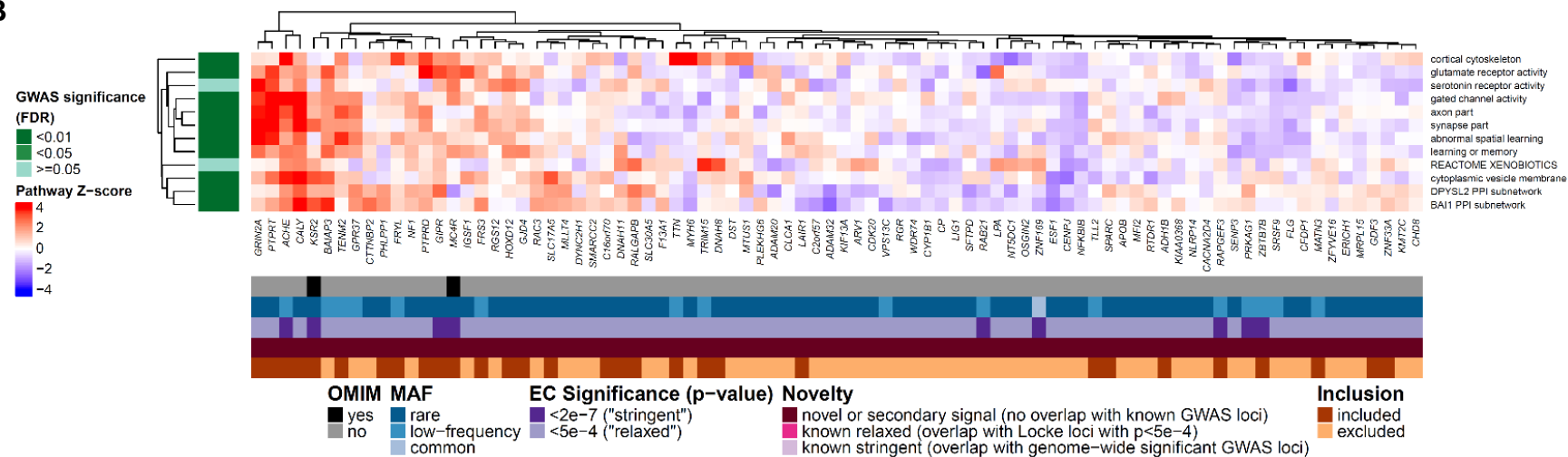


Supplementary Figure 10 | Heatmaps showing full DEPICT gene set enrichment results A) of rare and low frequency nonsynonymous SNVs (from main text figure 2), B) of novel rare and low frequency nonsynonymous SNVs, and C) nonsynonymous SNVs of all allele frequencies. For any given square, the color indicates how strongly the corresponding gene (shown on the x-axis) is predicted to belong to the reconstituted gene set (y-axis). This value is based on the gene's z-score for gene set inclusion in DEPICT's reconstituted gene sets, where red indicates a higher and blue a lower z-score. To visually reduce redundancy and increase clarity, we chose one representative "meta-gene set" for each group of highly correlated gene sets based on affinity propagation clustering (**Online Methods, Supplementary Information**). Heatmap intensity and DEPICT *P*-values (see *P*-values in **Supplementary Tables 17-19**) correspond to the most significantly enriched gene set within the meta-gene set. Annotations for the genes indicate (1) whether the gene has an OMIM annotation as underlying a monogenic obesity disorder (black and grey), (2) the minor allele frequency of the significant ExomeChip (EC) variant (shades of blue; if multiple variants, the lowest-frequency variant was kept), (3) whether the variant's *P*-value reached array-wide significance ($<2 \times 10^{-7}$) or suggestive significance ($<5 \times 10^{-4}$) (shades of purple), (4) whether the variant was novel, overlapping "relaxed" GWAS signals from Locke et al.³ (GWAS $P < 5 \times 10^{-4}$), or overlapping "stringent" GWAS signals (GWAS $P < 5 \times 10^{-8}$) (shades of pink), and (5) whether the gene was included in the gene set enrichment analysis or excluded by filters (shades of brown/orange) (**Online Methods and Supplementary Information**). Annotations for the gene sets indicate if the meta-gene set was found significant (shades of green; FDR < 0.01 , < 0.05 , or not significant) in the DEPICT analysis of GWAS results from Locke et al.³

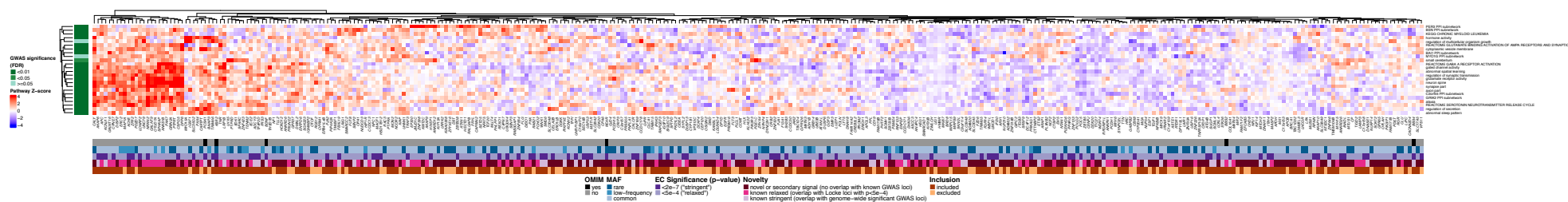
A



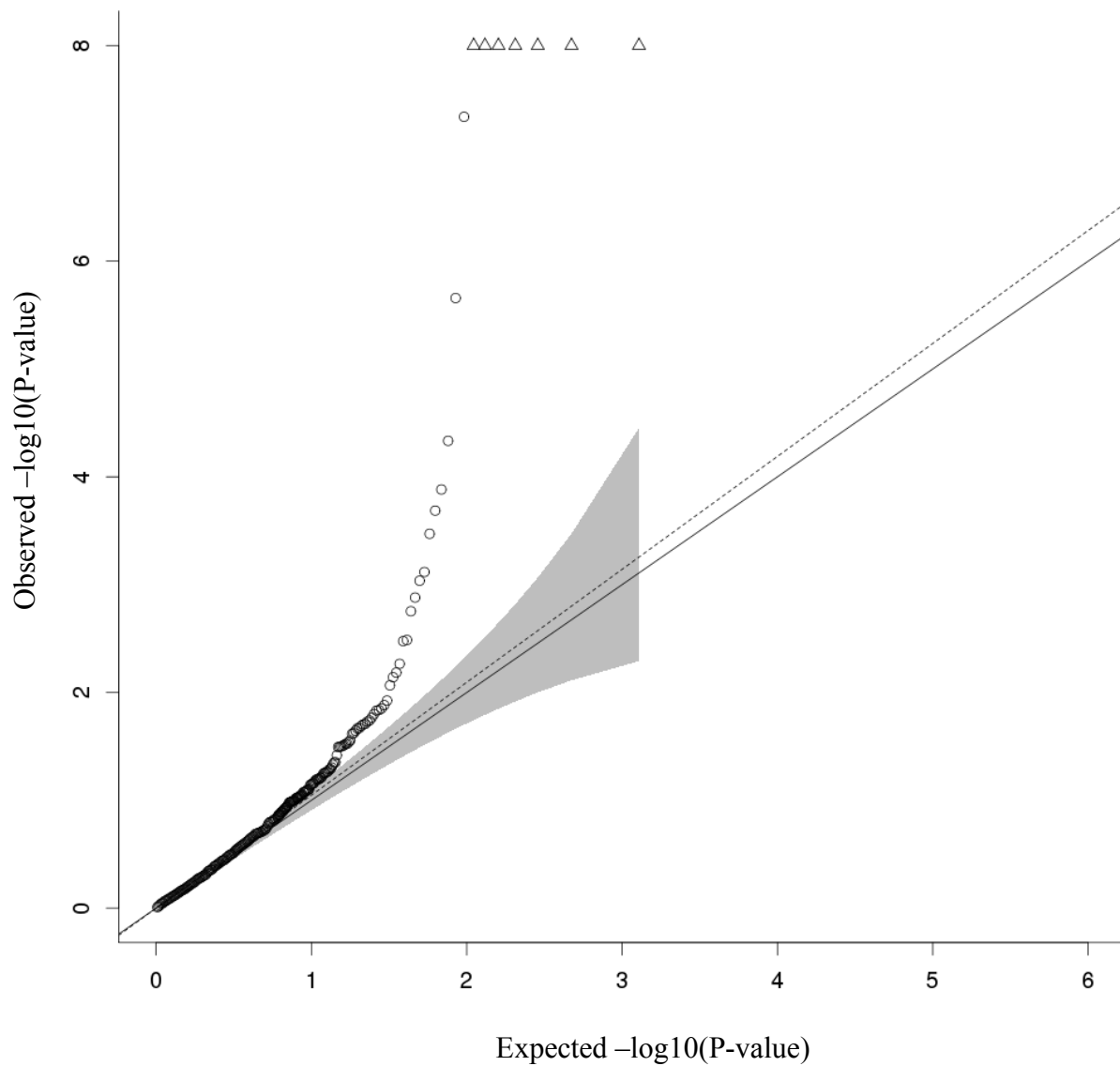
B



C

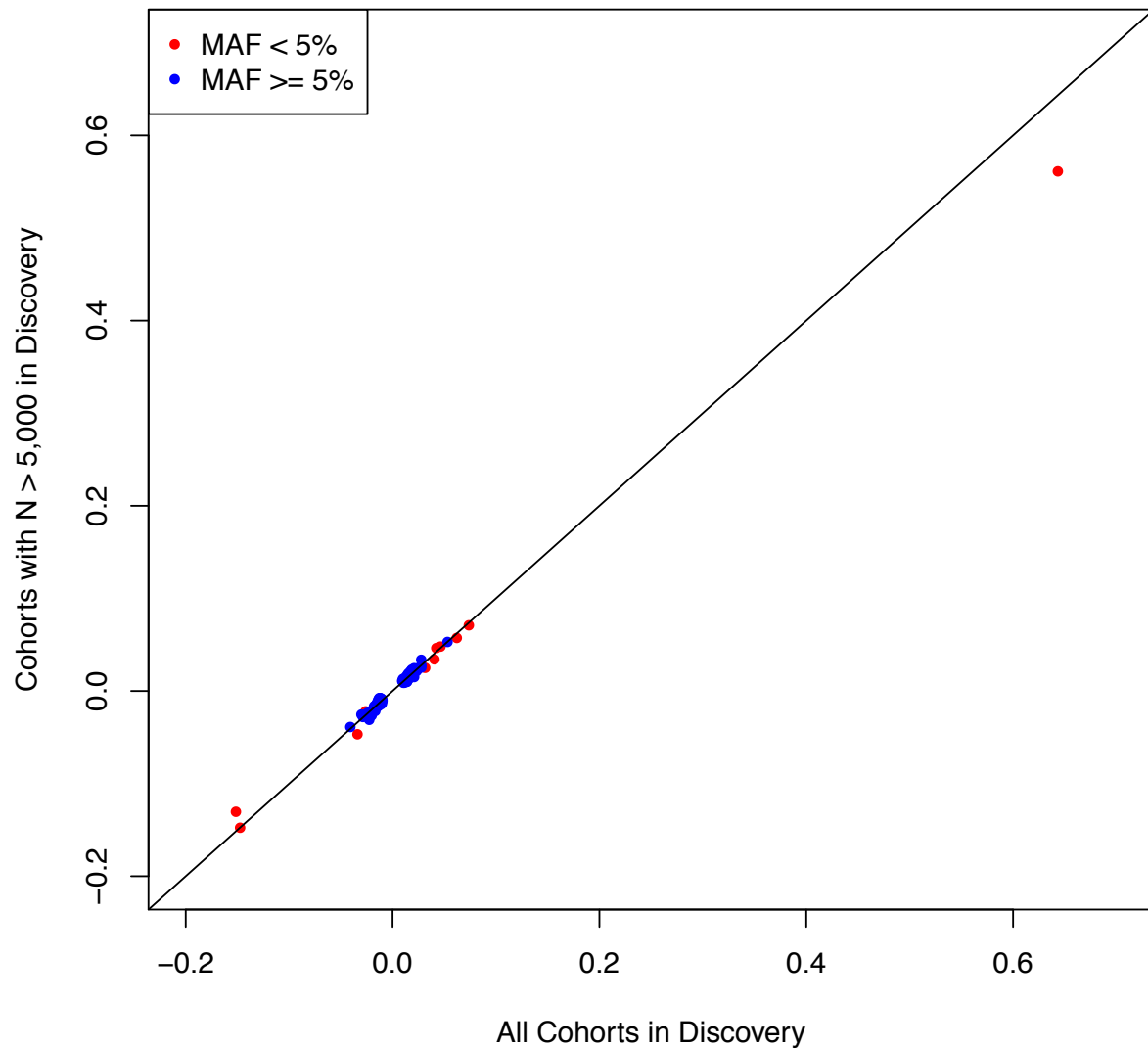


Supplementary Figure 11 | Quantile-quantile plot for BMI associations for rare and low-frequency coding SNVs located in monogenic and syndromic genes of obesity. Single variant association results obtained in the final combined meta-analysis are enriched for coding SNVs located in monogenic and syndromic genes of obesity (see gene list and results in **Supplementary Table 21**).



Supplementary Figure 12 | Scatter plot comparison of the effect sizes for all variants that reached significance in the European-ancestry-discovery results ($n = 526,508$) and results including only studies with sample sizes of more than 5,000 individuals ($n = 317,511$).

5.



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