

Understanding the genetic complexity of puberty timing across the allele frequency spectrum

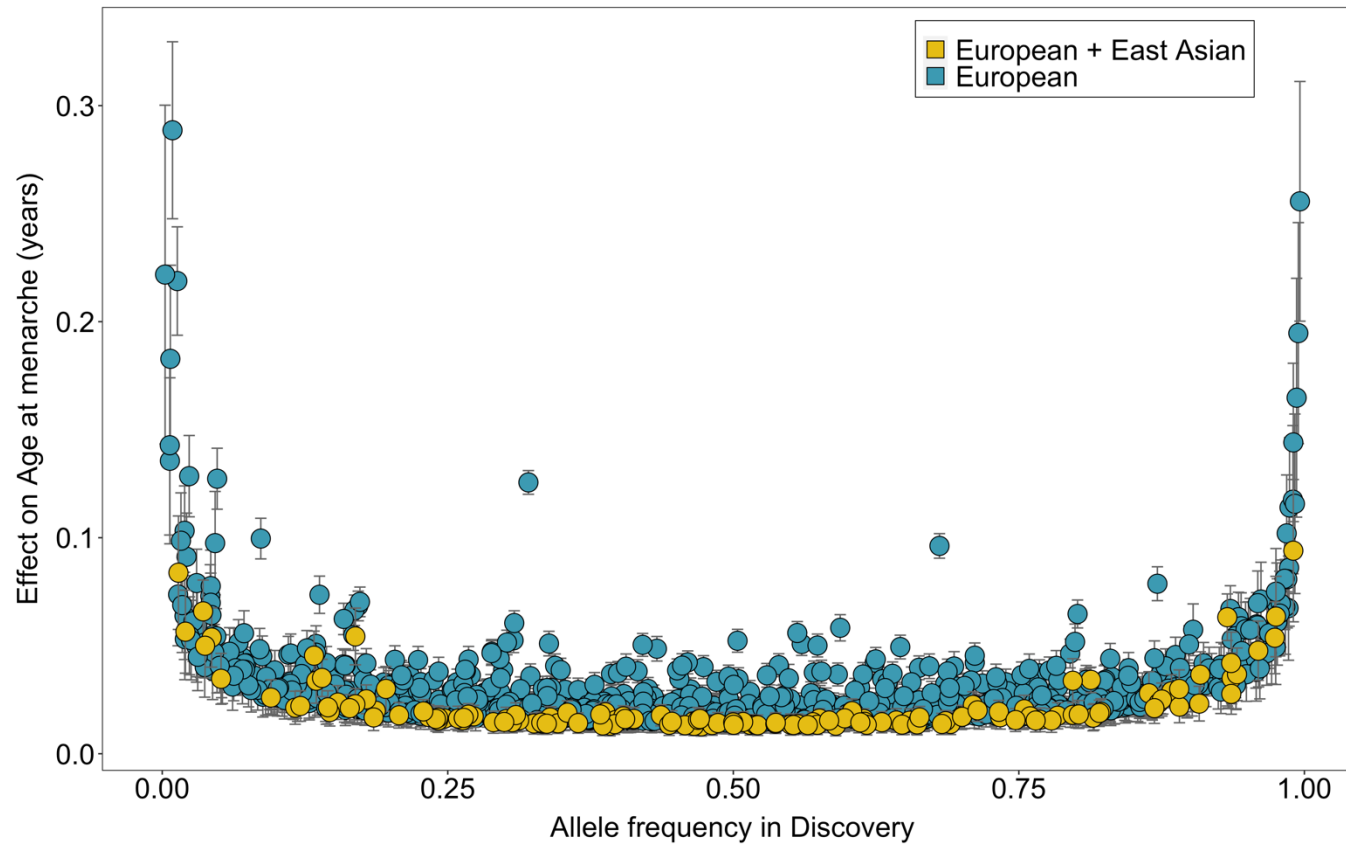
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Supplementary information

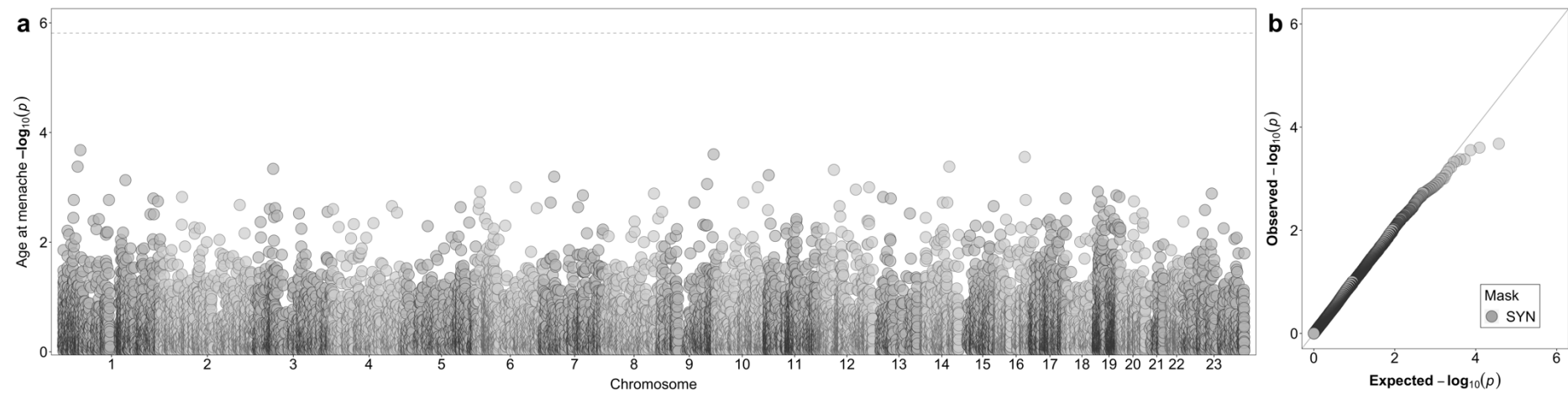
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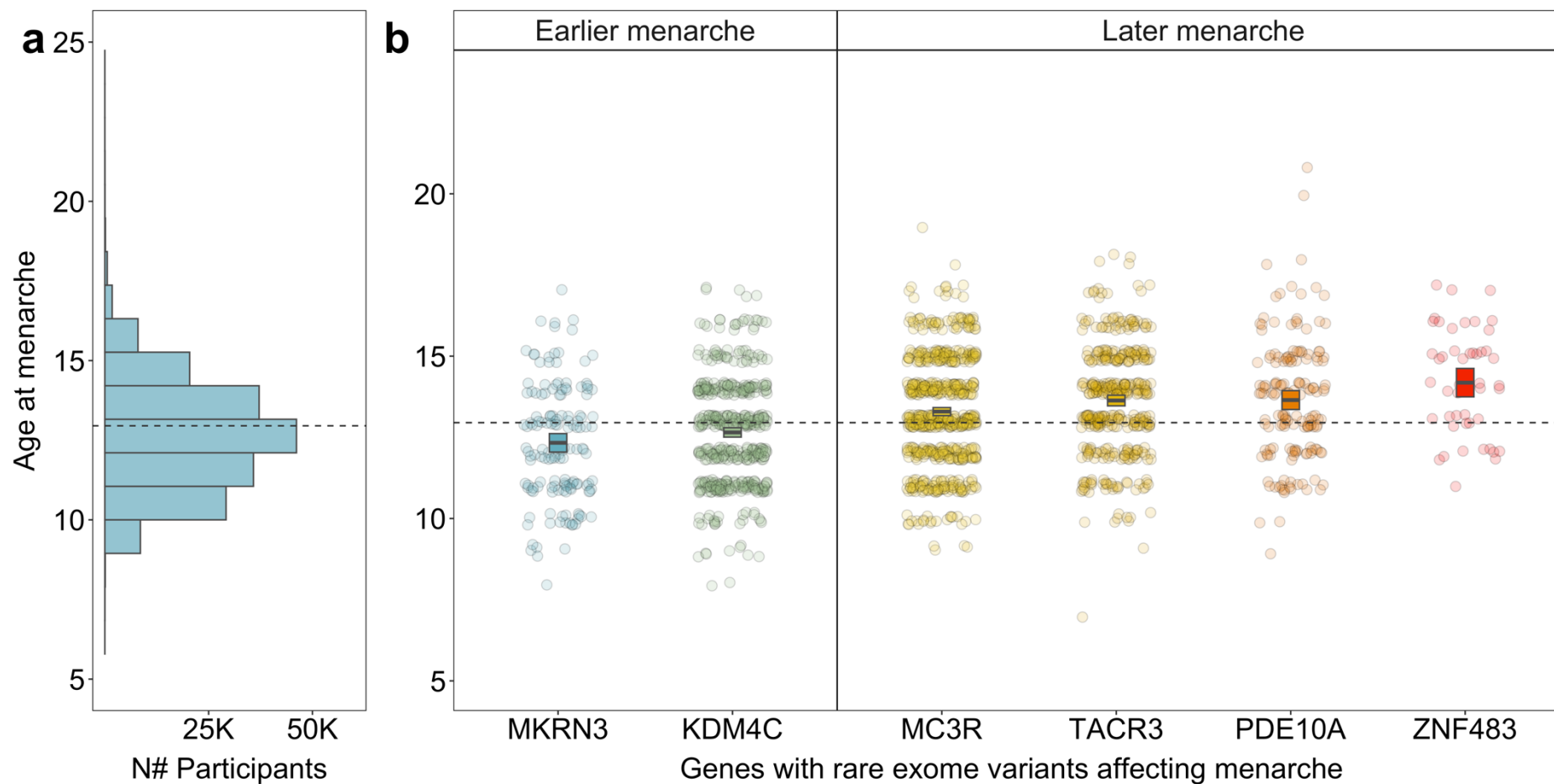
Supplementary Figures



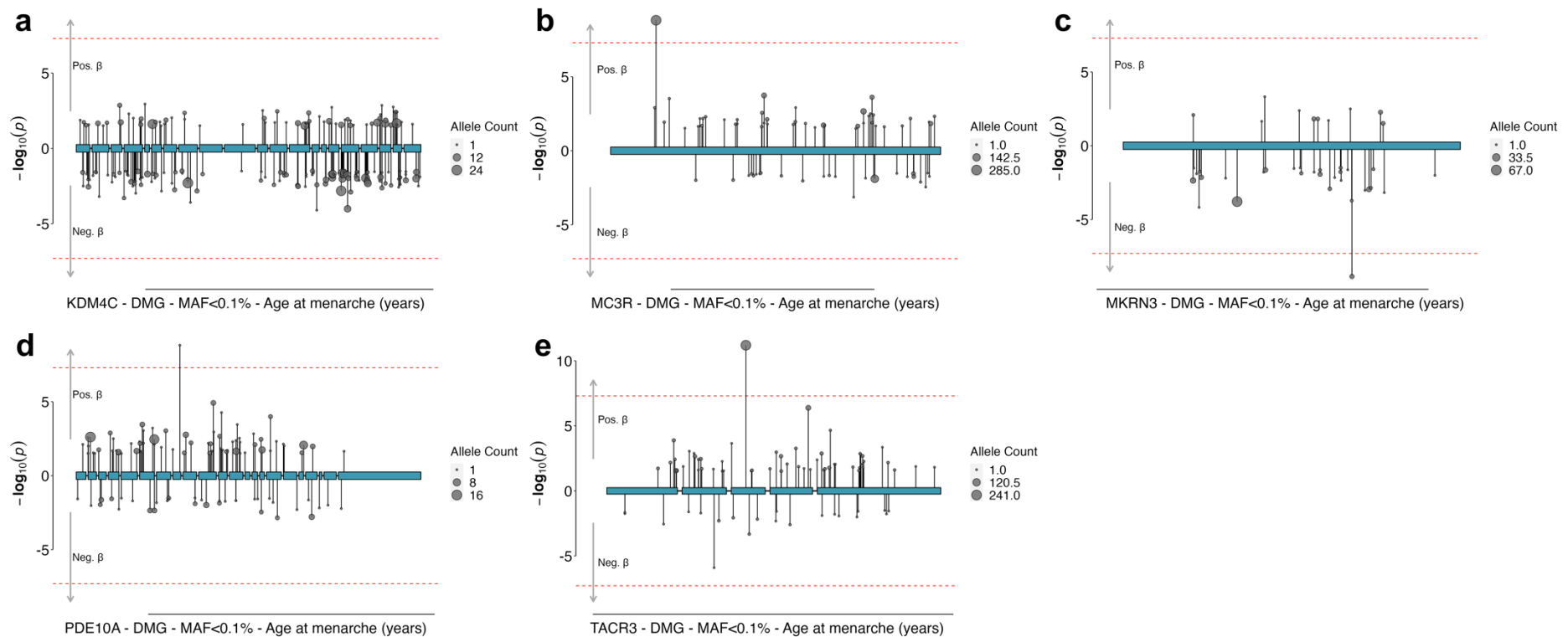
Supplementary Figure 1 | Distribution of effect sizes across 1080 independent signals with age at menarche (AAM). For each signal the effect size estimate and 95% confidence intervals are shown from the corresponding Discovery analysis, i.e. from the European-only or the ancestry combined meta-analysis, as indicated by point colours. Estimates are aligned towards the menarche-increasing alleles. Extended data are shown in Supplementary Table 2.



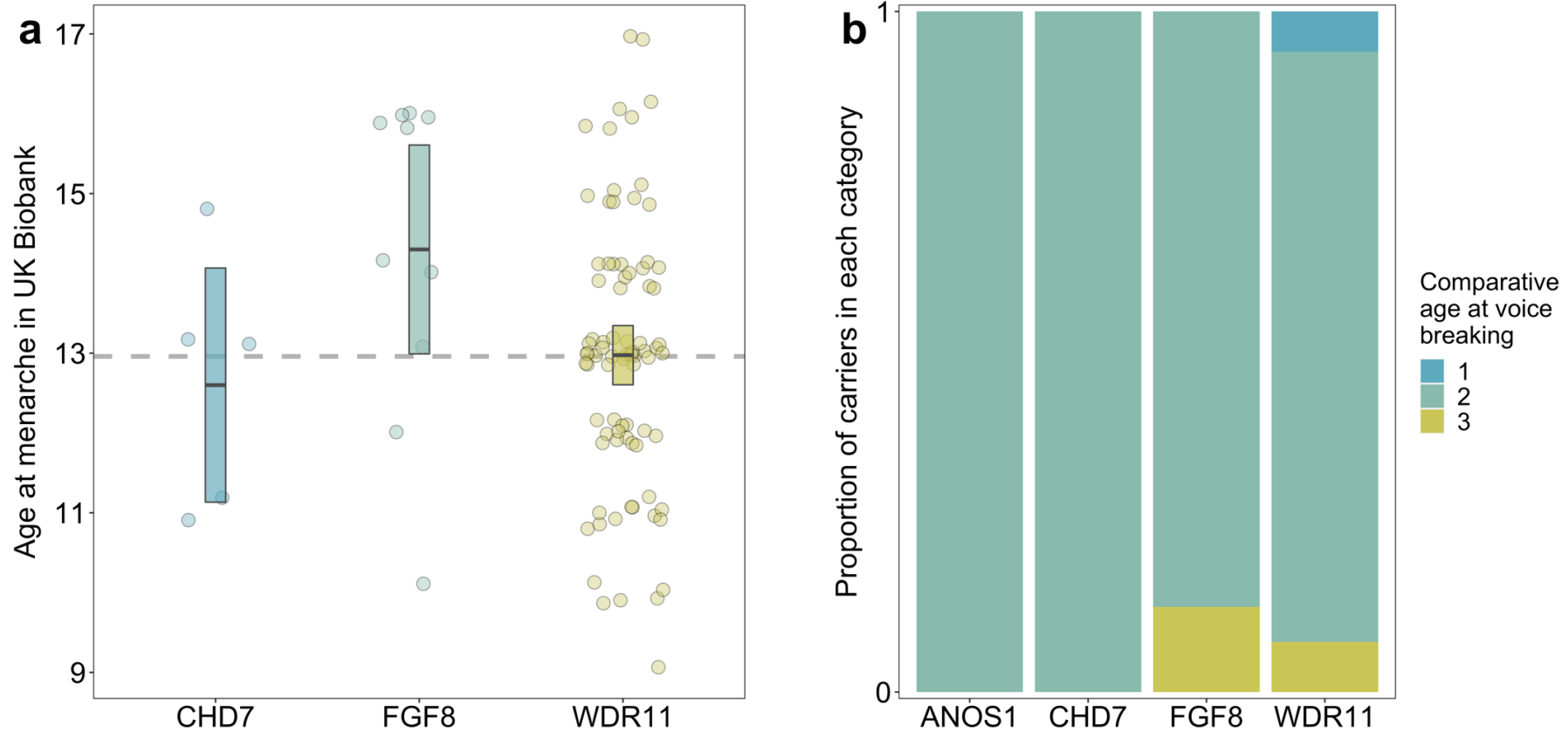
Supplementary Figure 2 | Synonymous variant associations with AAM. (a) Manhattan plot showing the gene burden associations from BOLT-LMM with age at menarche for the synonymous variant mask, as a negative control analysis. The horizontal line indicates the exome-wide significance threshold ($P < 1.54 \times 10^{-6}$). (b) Quantile-quantile (QQ) plot of the gene burden associations from BOLT-LMM for the synonymous variant mask.



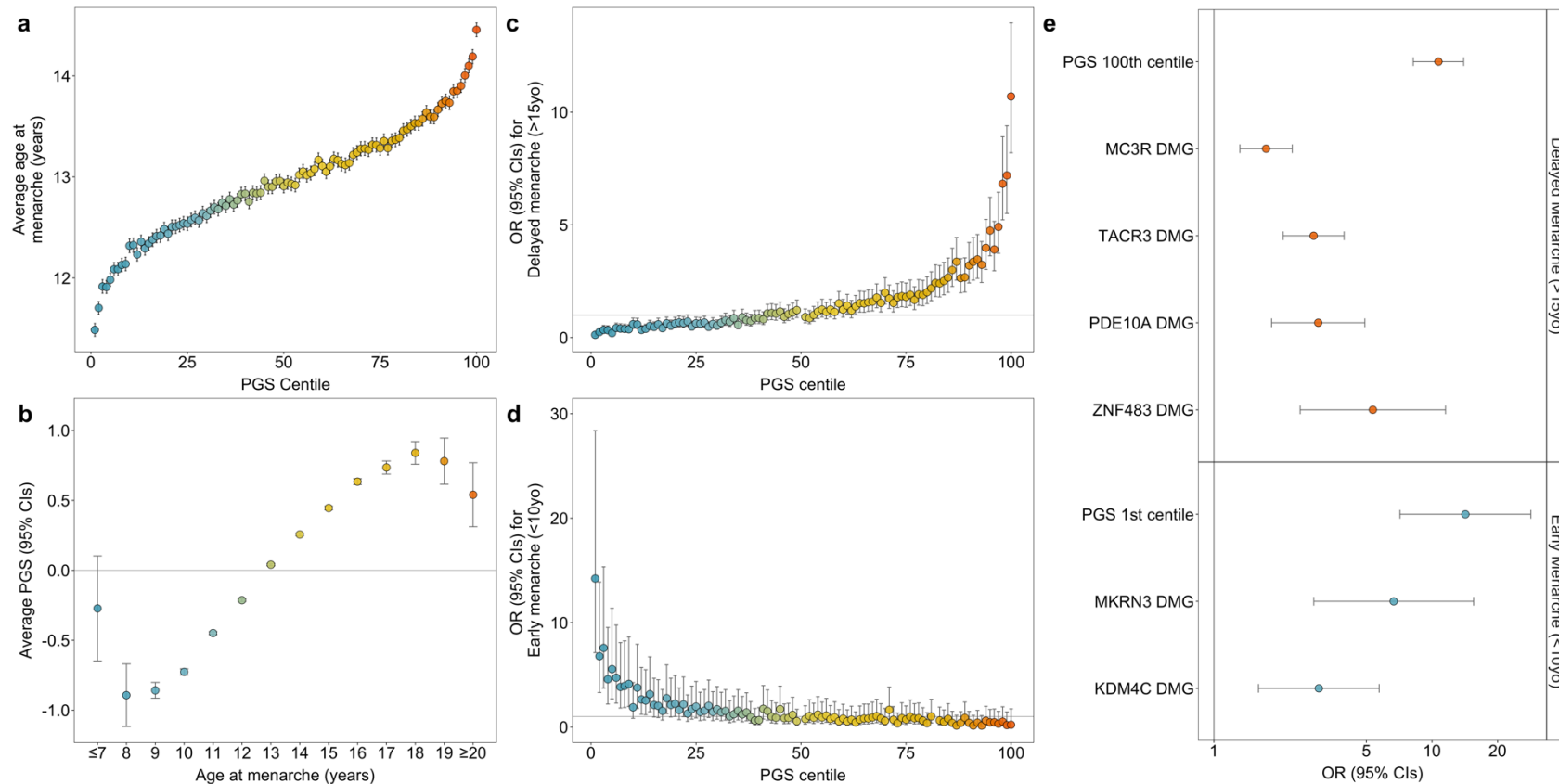
Supplementary Figure 3 | Distribution of age at menarche (AAM) in UK Biobank. Reported AAM in: (a) All white European unrelated female participants (N=187,941) (b) Carriers of qualifying rare variants in the associated genes. The horizontal dotted line indicates the mean AAM among non-carriers (N=185,929). Mean and 95% confidence intervals (CIs) for each carrier group are indicated by horizontal bars and boxes.



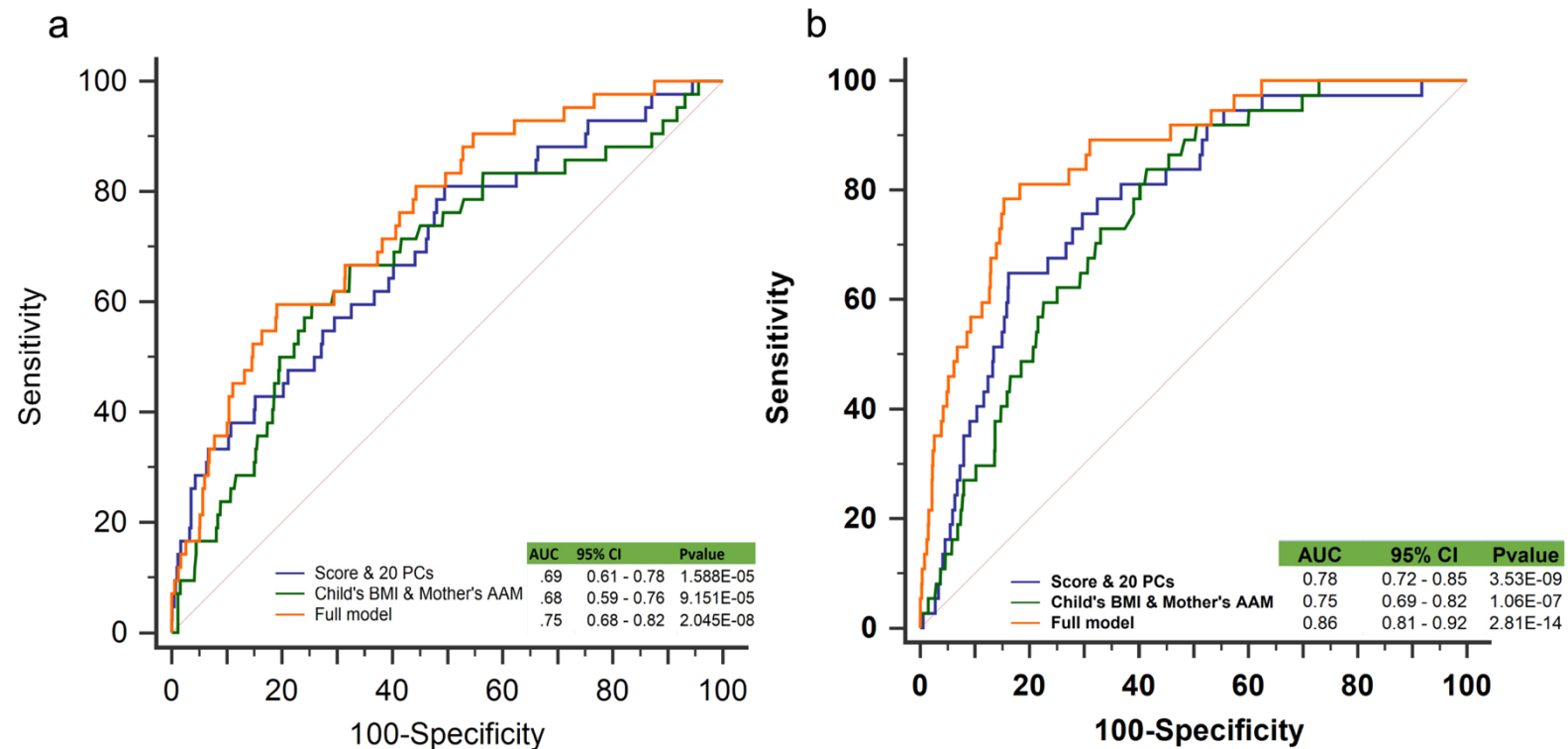
Supplementary Figure 4 | Variant-level associations with AAM in identified genes in UK Biobank. Rare exome variant associations from BOLT-LMM with AAM for variants in *KDM4C* (a), *MC3R* (b), *MKRN3* (c), *PDE10A* (d) and *TACR3* (e). The equivalent plot for *ZNF483* can be found in Fig. 3. Variant collapsing masks included variants with a minor allele frequency (MAF) < 0.1% and annotated as either high-confidence protein truncating variants (HC_PTV) or HC_PTV plus missense variants with a high CADD score (≥ 25 , denoted DMG). Each variant association is represented by a circle and vertical line: the line length indicates the P-value ($-\log_{10}(p)$), in the direction of its effect on AAM in carriers of the rare allele, and the circle size indicates the number of carriers of each variant (i.e. allele count). Exons are indicated by the blue boxes.



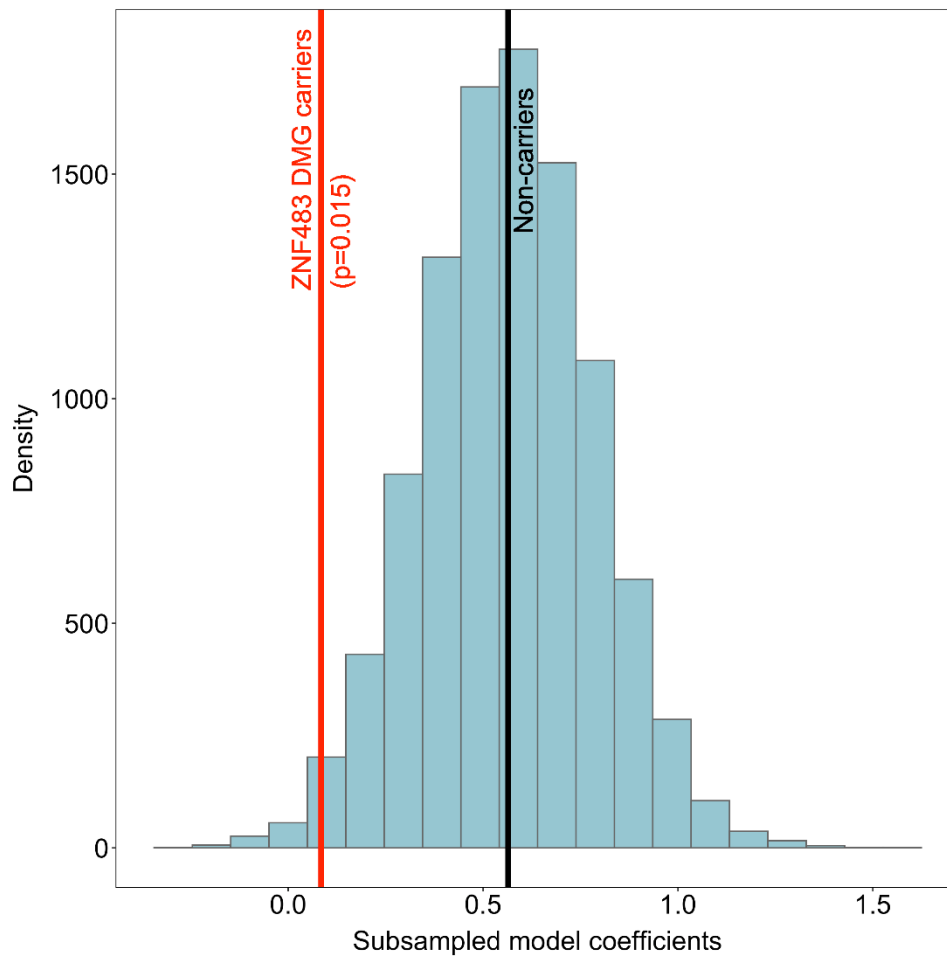
Supplementary Figure 5 | Puberty onset in carriers of IHH panel genes in UK Biobank. (a) Distribution of age at menarche (AAM) in UK Biobank white European unrelated female participants carrying qualifying rare variants in IHH panel genes. The horizontal dotted line indicates mean AAM among non-carriers (N=185,929). Mean and 95% confidence intervals (CIs) for each carrier group are indicated by horizontal bars and boxes. (b) Comparative age at voice breaking in men carrying qualifying rare variants in IHH panel genes. 1 indicates self-reported “younger than average age” at voice breaking, 2 “average age” and 3 “later than average age”.



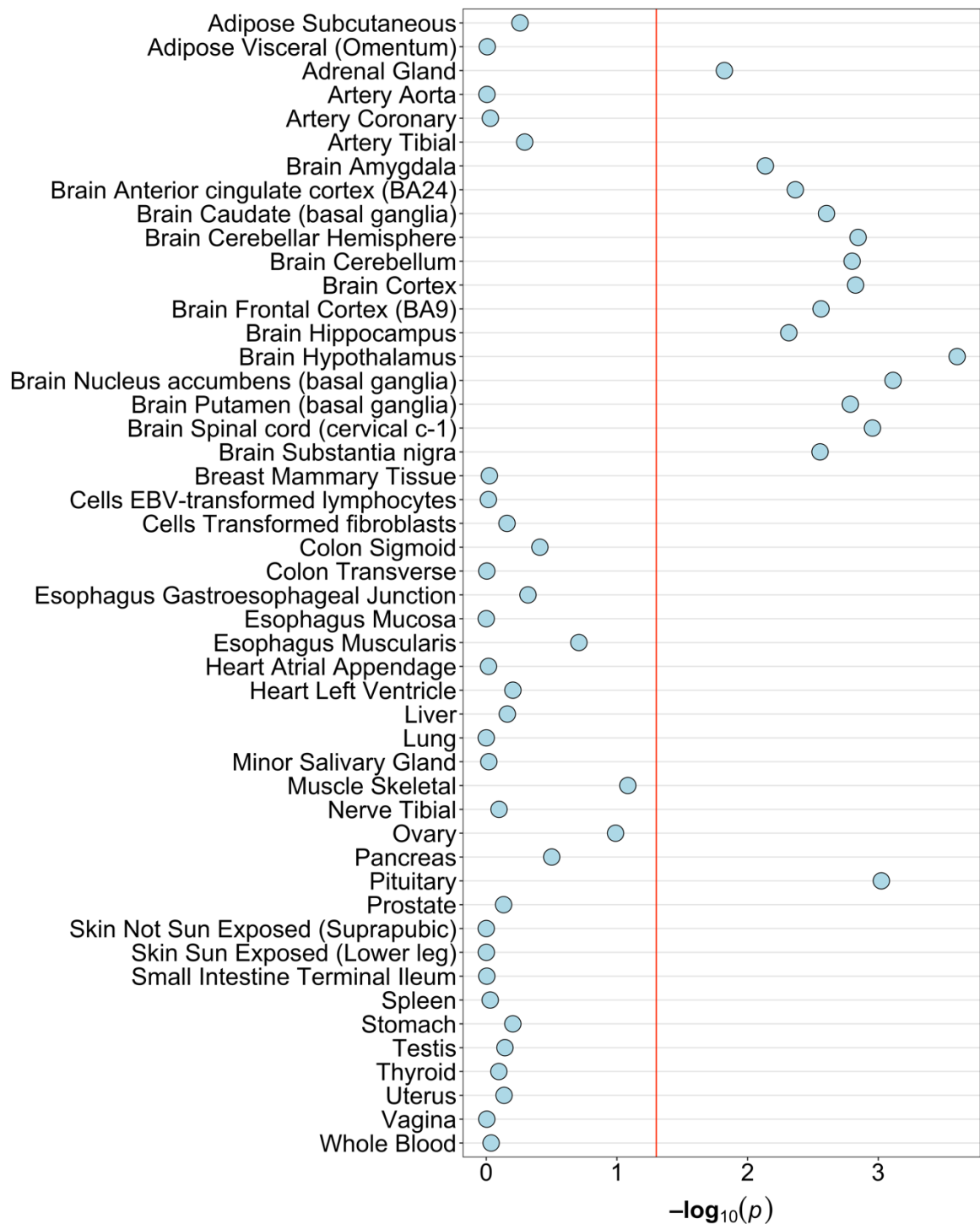
Supplementary Figure 6 | Polygenic score (PGS) associations with age at menarche (AAM). The PGS for AAM was derived using summary statistics from the European-only MA and excluding UK Biobank, and then applied to white European, unrelated female participants in UK Biobank (N=187,941). (a) Means with 95% confidence intervals (CIs) of AAM by PGS centile (N=1,880 per centile). (b) Means with 95% CIs of standardised PGS by AAM. (c-d) Associations of each PGS centile compared to the 50th PGS centile (OR with 95% CIs) with (c) delayed menarche (menarche after 15 years) and (d) early menarche (menarche before 10 years). Controls were women who reported menarche at 12 or 13 years. PGS centiles with fewer than 2 participants were omitted. (e) Gene burden associations between qualifying variants in the exome-identified genes compared to extreme PGS centiles, with delayed or early menarche defined as above, presented as ORs with 95% CIs. Extended data are shown in Supplementary Tables 8-10.



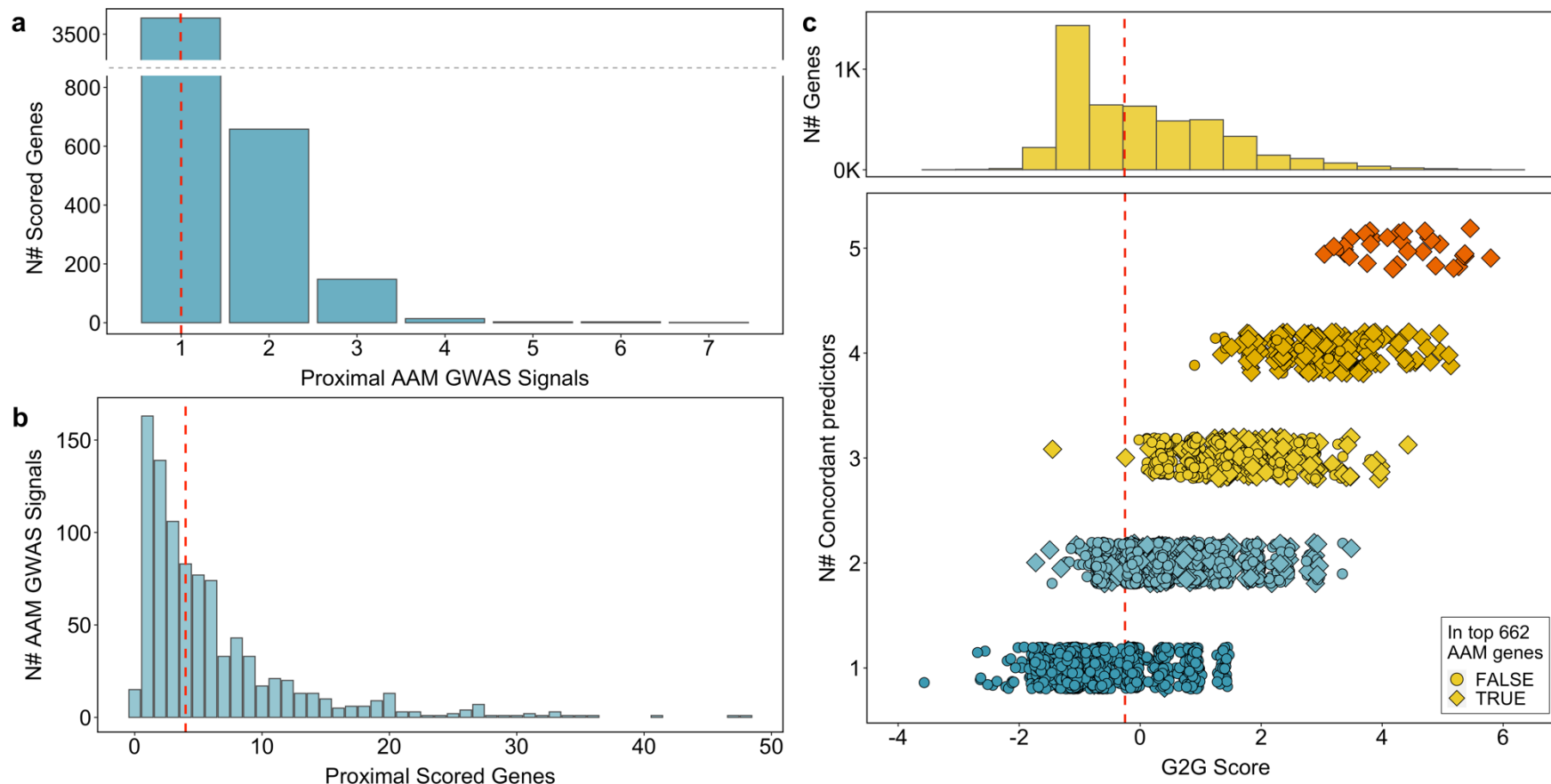
Supplementary Figure 7 | Receiver operating characteristic (ROC) curve for predicting extremes of age at menarche (AAM) in the ALSPAC study. Predictive performance of linear regressions adjusting for the genetic, clinical, and combined predictor and presented as ROC graphs against (a) early AAM and (b) delayed AAM in the ALSPAC study (N= 3,140). Extended data are shown in Supplementary Table 11.



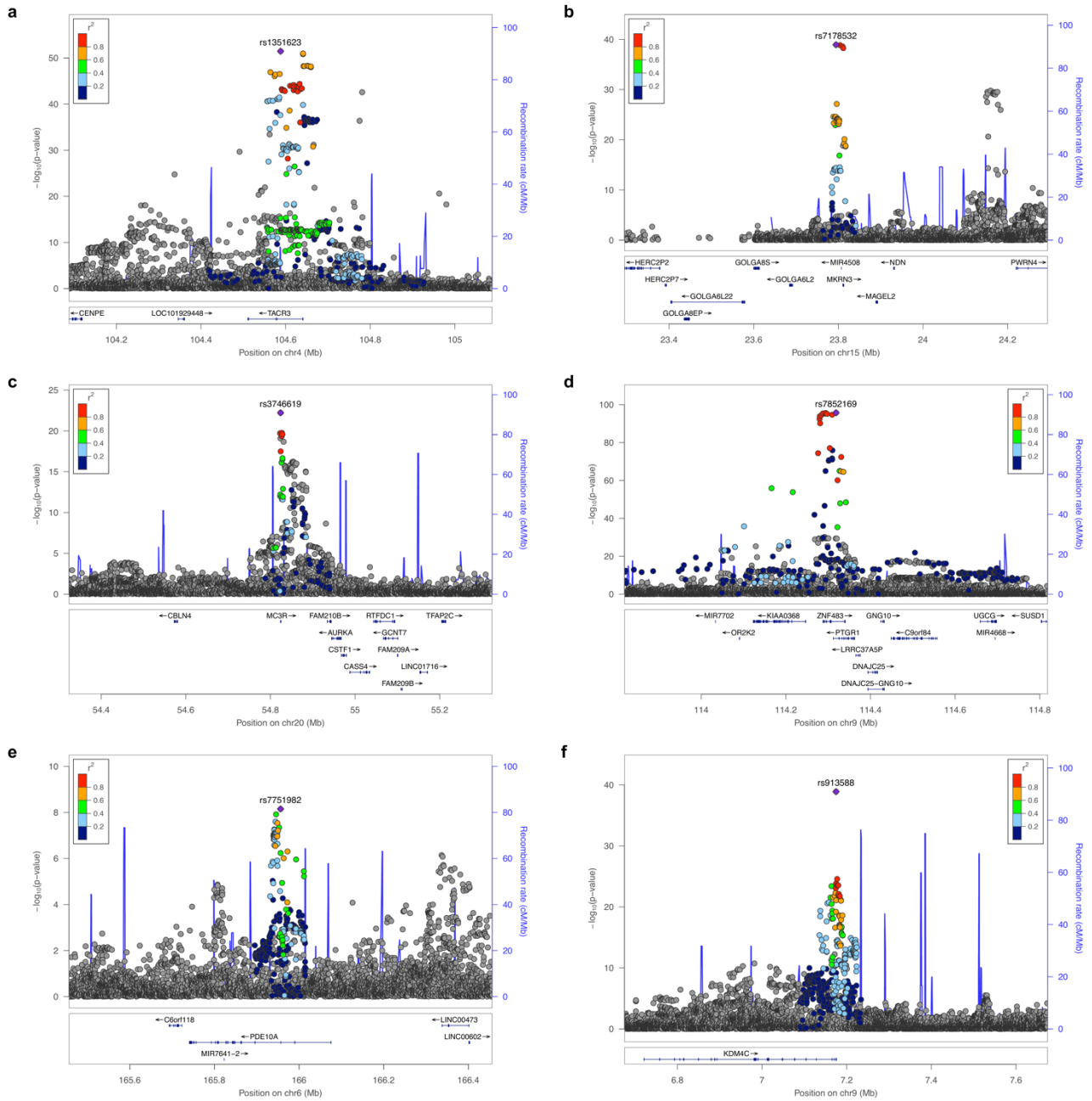
Supplementary Figure 8 | Epistatic interaction between the polygenic score (PGS) and carriage of rare damaging variants in *ZNF483* on age at menarche (AAM). Blue columns indicate the beta coefficients for the PGS-AAM association among 10,000 random subsamples of 49 white European unrelated female non-carriers in UK Biobank, tested in a linear model. The beta coefficient from the full sample of non-carriers is indicated by the black vertical line (0.564 years per SD, SE 0.003, $P < 2 \times 10^{-16}$) and the beta coefficient seen in *ZNF483* variant carriers is indicated by the red vertical line (difference in coefficients: -0.480, SE 0.214, $P = 0.025$). The probability of observing a beta coefficient smaller than that in *ZNF483* variant carriers was estimated as the proportion of subsampled coefficients that were smaller than 0.084 (i.e., 0.564-0.480).



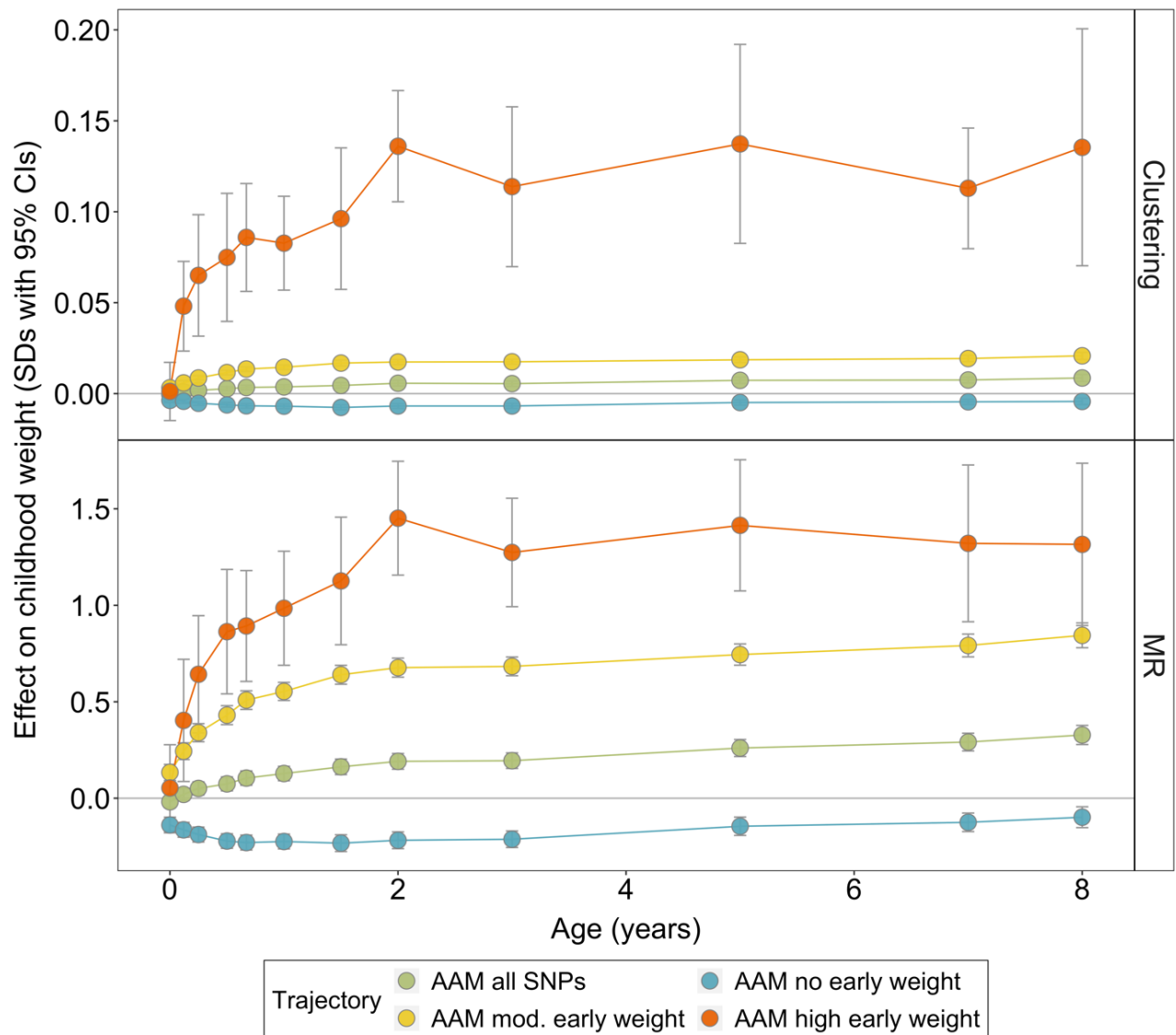
Supplementary Figure 9 | Tissue enrichment for age at menarche (AAM) GWAS associations. Linkage-disequilibrium score regression to specifically expressed genes (LDSC-SEG) was used to test for enrichment for AAM GWAS associations among European-only samples among genes specifically expressed across the different GTEx tissues. LDSC-SEG unadjusted P-values represent a one-sided test that the coefficient is greater than zero. Extended data are shown in Supplementary Table 17.



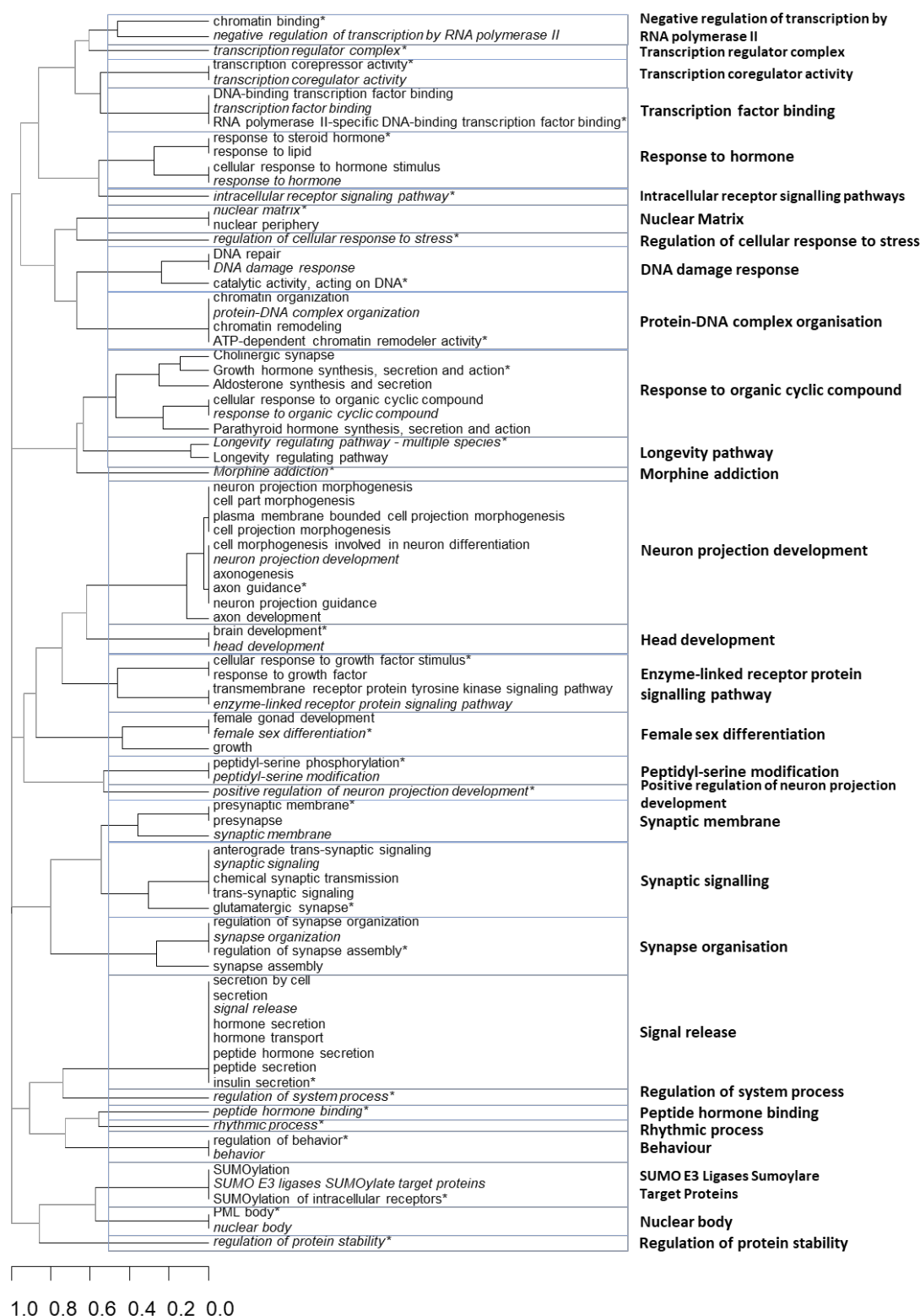
Supplementary Figure 10 | Distribution of age at menarche (AAM) GWAS signals and genes, as identified by GWAS to Genes (G2G). (a) Based on the European-only GWAS meta-analysis, 4,668 genes were implicated by G2G as potential regulators of AAM. Most were proximal to (within 500kb) only 1 GWAS signal (median signals per gene: 1; range: 1 to 7). (b) Conversely, each GWAS signal was annotated to be proximal (within 500kb) to (median) 4 genes (range: 0 to 48). (c) The 4,657 genes had a median G2G score -0.25 (range -3.57 to 5.88) derived from a maximum of 6 predictors (up to 5 observed). The 665 high confidence AAM genes were defined as the top-scoring gene at each independent AAM signal with at least 2 concordant predictors. Extended data are shown in Supplementary Table 13.



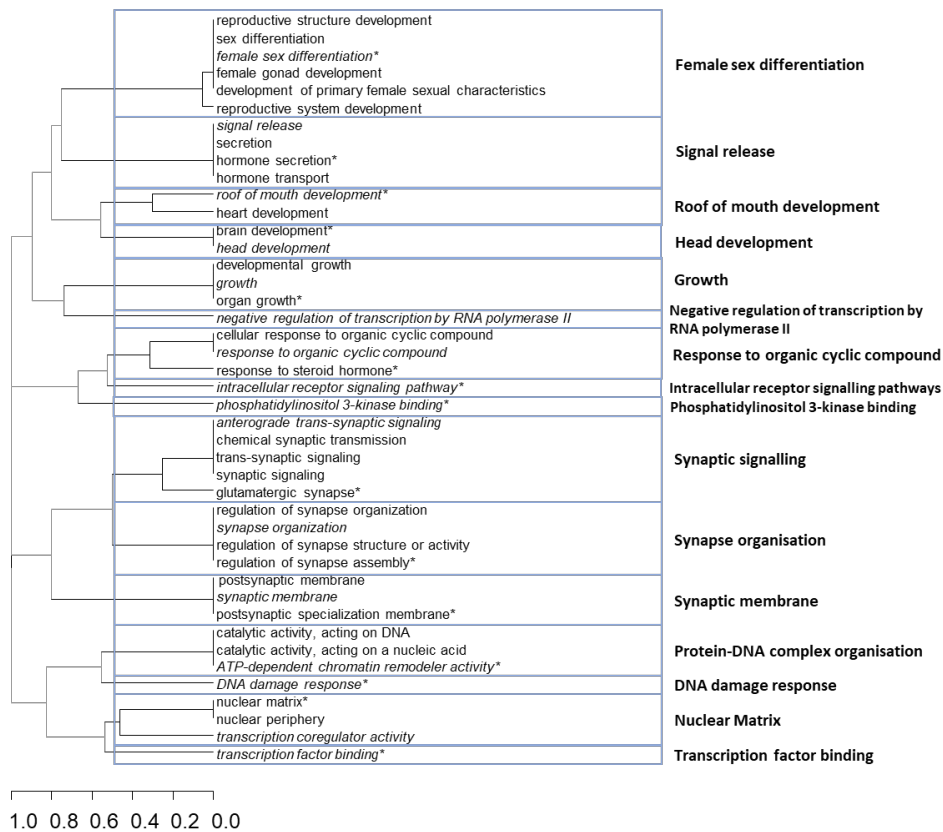
Supplementary Figure 11 | GWAS loci proximal to the six exome-wide significantly associated genes. Associations among European-only samples in regions surrounding the 6 genes ($\pm 500\text{kb}$) identified via exome-wide rare variant associations with AAM; (a) *TACR3*, (b) *MKRN3*, (c) *MC3R*, (d) *ZNF483*, (e) *PDE10A*, and (f) *KDM4C*.



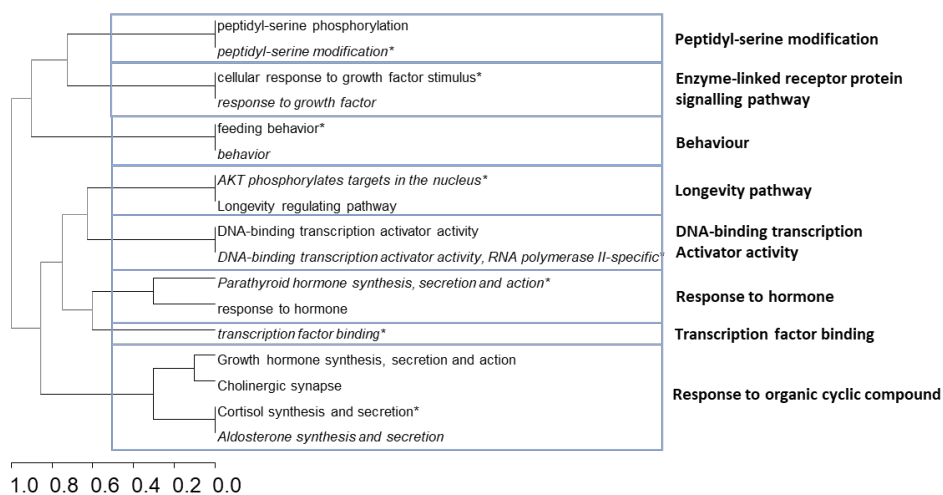
Supplementary Figure 12 | Mean childhood body weight trajectory for each of the three age at menarche (AAM) GWAS SNP clusters (aligned to AAM-decreasing alleles). Mendelian randomisation (MR) estimates with 95% confidence intervals (CIs) for all 1080 AAM signals, and the three AAM SNP clusters as separate exposures, on childhood body weight at 12 time-points (n=26,681 children). Extended data are shown in Supplementary Tables 21 and 22.



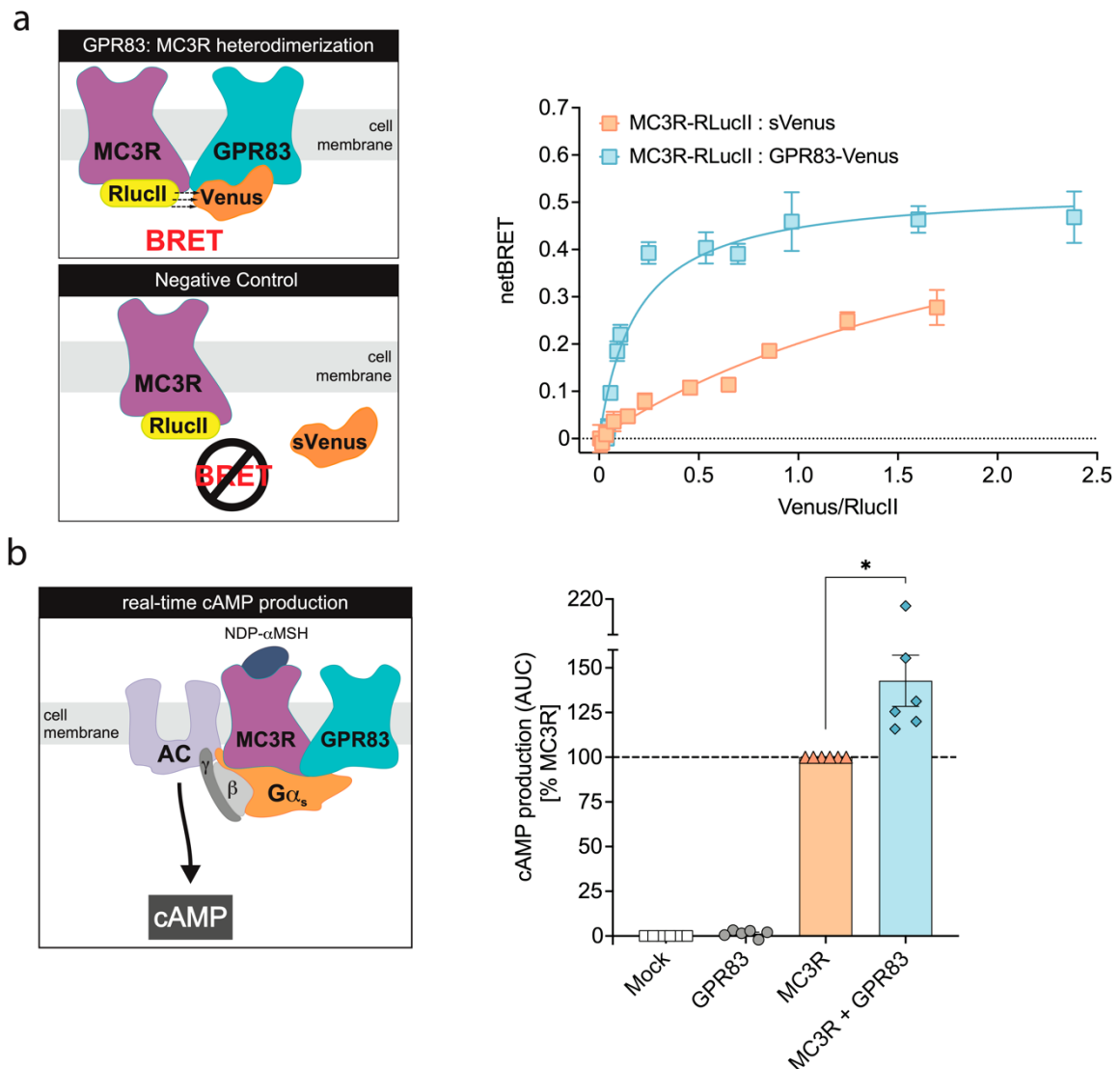
Supplementary Figure 13 | Dendrogram showing clustering of biological pathways enriched for the 665 high confidence AAM genes. In each cluster, the most significantly associated pathway is highlighted in italics and the most highly enriched pathway is marked by an asterisk. Extended data are shown in Supplementary Tables 23-24.



Supplementary Figure 14 | Clustering of biological pathways enriched for AAM genes in the “early weight gain” trajectory. In each cluster the most significant pathway is highlighted in italics and the most highly enriched pathway is marked with an asterisk. Extended data are shown in Supplementary Tables 25-26.



Supplementary Figure 15 | Clustering of biological pathways enriched for AAM genes in the “no early weight gain” trajectory. In each cluster the most significant pathway is highlighted in italics and the most highly enriched pathway is marked with an asterisk. Extended data are shown in Supplementary Tables 25-26.



Supplementary Figure 16 | GPR83-MC3R heterodimerization modulates canonical MC3R-cAMP signalling pathway. (a) BRET saturation curve from HEK293 cells co-transfected with a constant amount of MC3R-RlucII donor construct and increasing amounts of the GPR83-Venus acceptor construct, indicating a specific and saturable GPR83-MC3R interaction. The selectivity of the observed signal was further supported by the observation that co-expression of MC3R-RlucII with a soluble acceptor (sVenus) led to lower BRET signals that progressed linearly over the same range of acceptor/donor ratios. (b) NDP- α MSH-stimulated cAMP production area under the curve calculation from HEK293 cells transfected with *MC3R* or co-transfected with both *MC3R* and *GPR83*. The time-resolved data are shown in Figure 6. Data are expressed as a percentage of maximal control response [% MC3R] and plotted as mean \pm standard error from 6 independent experiments. Statistical significance was determined by unpaired t-test with Welch's correction; * $P < 0.05$. Extended data are shown in Supplementary Tables 29-31.

Consortia membership

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Haikou: Hainan Provincial CDC – Jinyan Chen, Ximin Hu, Xiaohuan Wang. Meilan CDC – Zhendong Guo, Huimei Li, Yilei Li, Min Weng, Shukuan Wu.

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OCAC

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23andMe

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The Biobank Japan

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China Kadoorie Biobank

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MoBa

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 41% of the pregnancies. The cohort includes approximately 114.500 children, 95.200 mothers and 75.200 fathers. The current study is based on version 10 of the quality-assured data files released for research in Novel Tools for Early Childhood Predisposition to Obesity. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (no. 2012/67). The Medical Birth Registry (MBRN) is a national health registry containing information about all births in Norway.

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Data from the Norwegian Mother, Father and Child Cohort Study and the Medical Birth Registry of Norway used in this study are managed by the national health register holders in Norway (Norwegian Institute of public health) and can be made available to researchers, provided approval from the Regional Committees for Medical and Health Research Ethics (REC), compliance with the EU General Data Protection Regulation (GDPR) and approval from the data owners. The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply through helsedata.no. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

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