Supplementary Information

Sex-dimorphic genetic effects and novel loci for fasting glucose and insulin variability.

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SUPPLEMENTARY NOTE 1 Additional acknowledgements

Age, Gene Environment Susceptibility Reykjavik Study (AGES)

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The SCARFSHEEP study

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The Swedish Twins Registry Study (SWEDISHTWINS, REPLICATION_STR)

This work was supported by grants from the US National Institutes of Health (AG028555, AG08724, AG04563, AG10175, AG08861), the Swedish Research Council, the Swedish Heart-Lung Foundation, the Swedish Foundation for Strategic Research, the Royal Swedish Academy of Science, and ENGAGE (within the European Union Seventh Framework Programme, HEALTH-F4-2007-201413). Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University, Uppsala University Hospital and the Swedish Research Council for Infrastructures.

The THISEAS Study (THISEAScases, THISEAScontrols)

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The TWINGENE Study

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The TwinsUK Study

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The Microisolates in South Tyrol Study (MICROS)

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The Uppsala Longitudinal Study of Adult Men (ULSAM, REPLICATION_ULSAM)

Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University, Uppsala University Hospital and the Swedish Research Council for Infrastructures. This project was supported by grants from the Swedish Research Council, the Swedish Heart-Lung Foundation, the Swedish Foundation for Strategic Research, the Royal Swedish Academy of Sciences, Swedish Diabetes Foundation, Swedish Society of Medicine, and Novo Nordisk Fonden.

The Whitehall Study

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The MolOBB study

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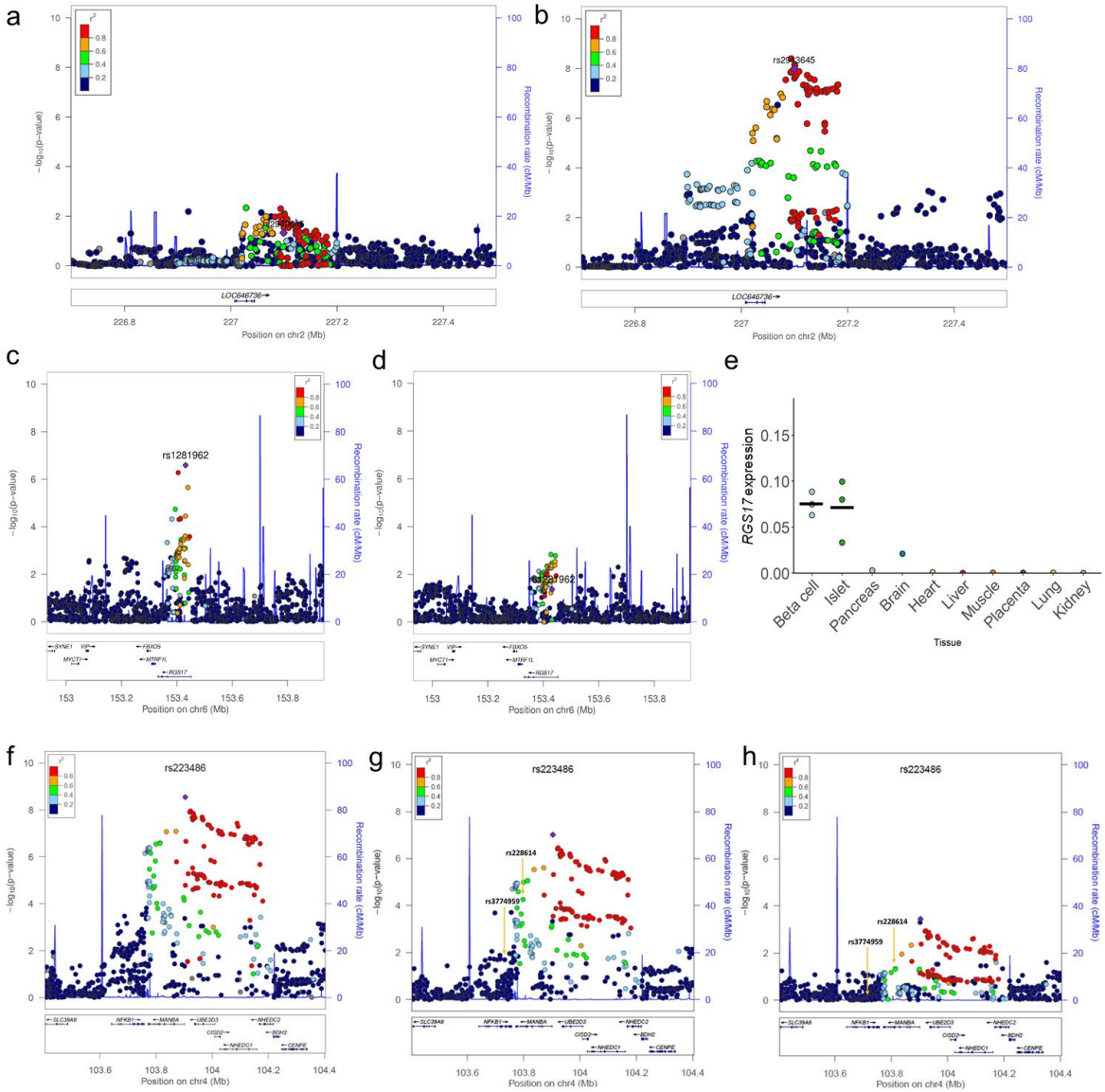
Human islets gene expression

This work was supported by grants from the Swedish Research Council (including project grants Dnr. 521-2010-2633 to Va.Ly. and 521-2010-3490, strategic research area grant EXODIAB Dnr. 2009-1039, and Linnaeus grant Dnr. 349-2006-237), as well as equipment grants from Wallenberg (KAW 2009-0243) and Lundberg Foundation (grant number 359). L.G. is supported from an Advanced Research Grant from the European Research Council (GENETARGET-T2D, GA 269045) and grants from Pfizer and Va.Ly. from the Novo Nordisk Foundation. Human pancreatic islets were provided by the Nordic Network for Clinical Islet Transplantation by the courtesy of O. Korsgren, Uppsala, Sweden with financial support from EXODIAB and JDRF. Furthermore, this research was supported by Fondazione CARIPARO ("RNA sequencing for quantitative transcriptomics" PhD Program), PRAT 2010 CPDA101217 ("Models of RNA sequencing data variability for quantitative transcriptomics"). We thank Britt-Marie Nilsson and Anna-Maria Veijanovska-Ramsay at Lund University for their technical assistance.

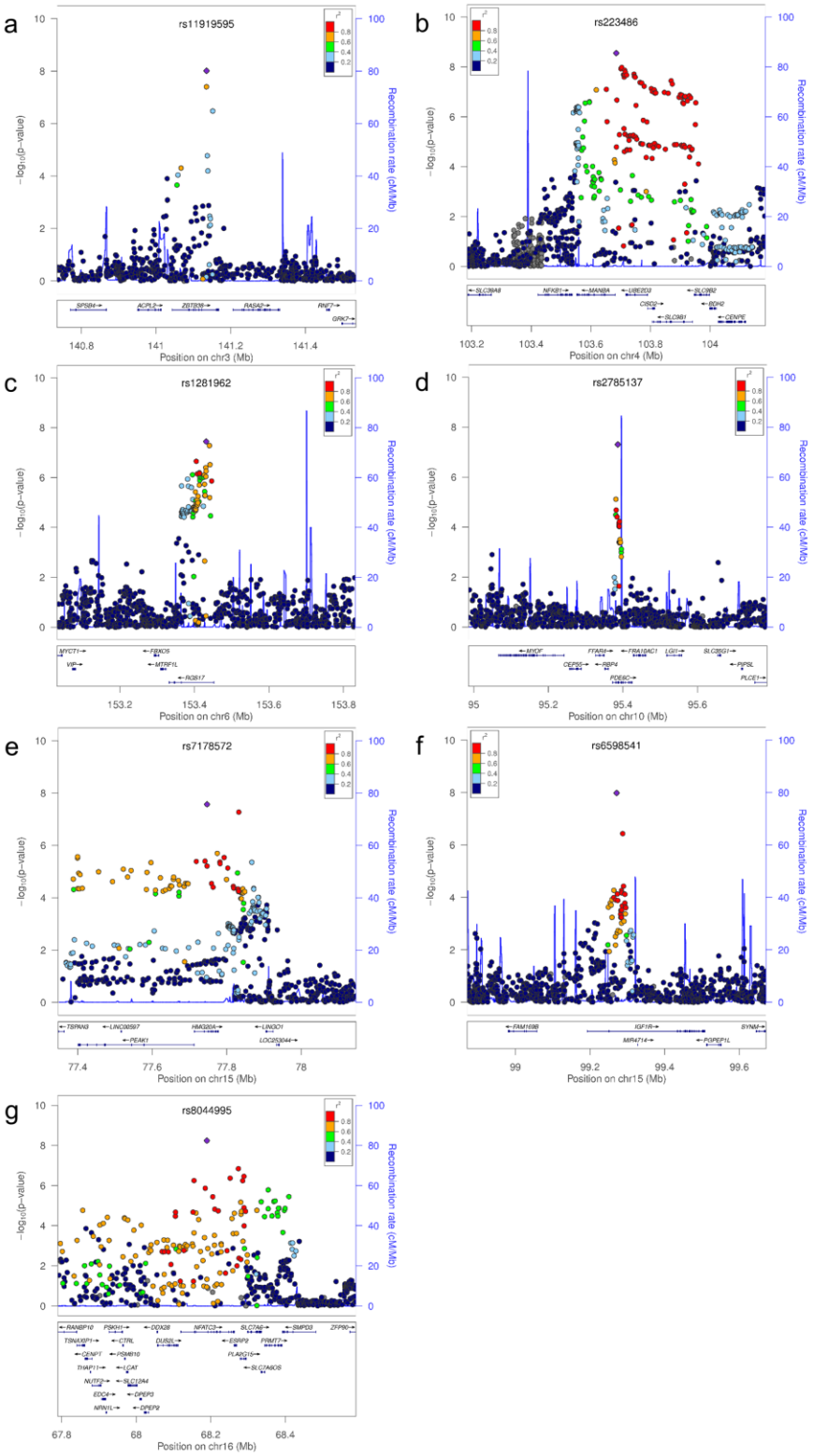
The ASAP study

Swedish Research Council [12660], The Swedish Heart-Lung Foundation [201202729].

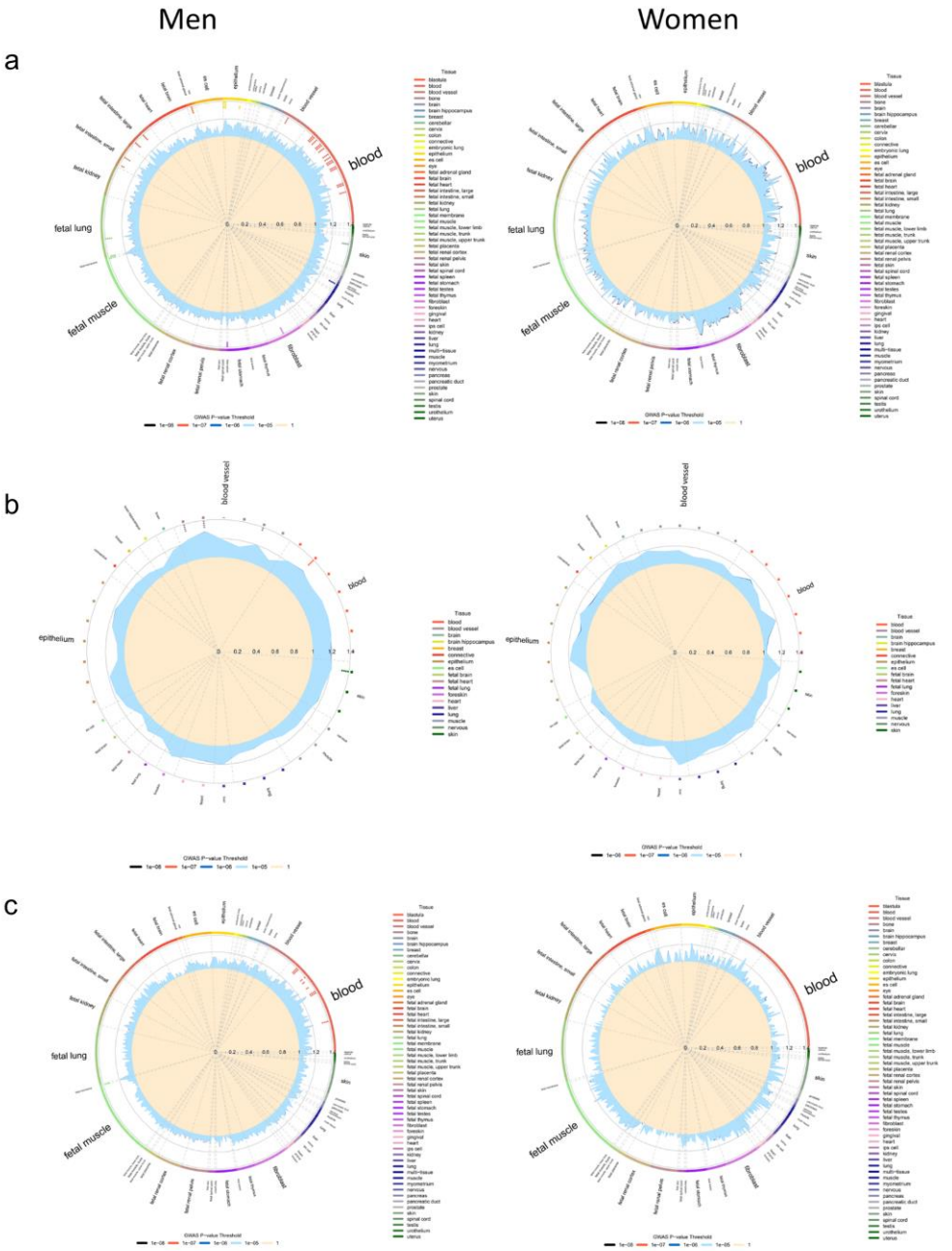
SUPPLEMENTARY FIGURES



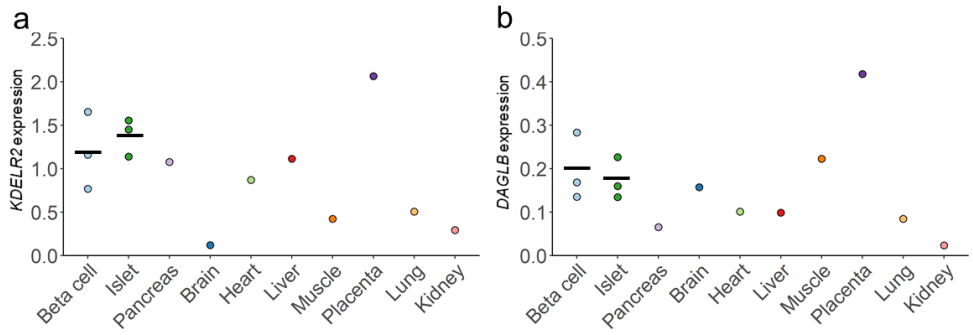
Supplementary Figure 1. Regional and tissue expression plots.
(a) female-specific and **(b)** male-specific for established *IRS1* locus with sex-dimorphic effects on FI, **(c)** female-specific and **(d)** male-specific on FG for novel *RGS17* locus; e) *RGS17* tissue expression relative to three housekeeping genes (PPIA, B2M and HPRT). For beta cell (n=3) and islets (n=3) data, lines are means. Quantitative RT-PCR was carried out using cDNAs from three human donors (beta-cells and islets). The other tissues were commercial cDNAs (one point observation); Regional plots for **(f)** novel *MANBA/UBE2D3* locus with homogeneous effects between men and women (no conditioning), **(g)** association analysis of *MANBA/UBE2D3* signal conditioned on ulcerative colitis (rs3774959) established variant and **(h)** association analysis of *MANBA/UBE2D3* signal conditioned on multiple sclerosis (rs228614) established variant.



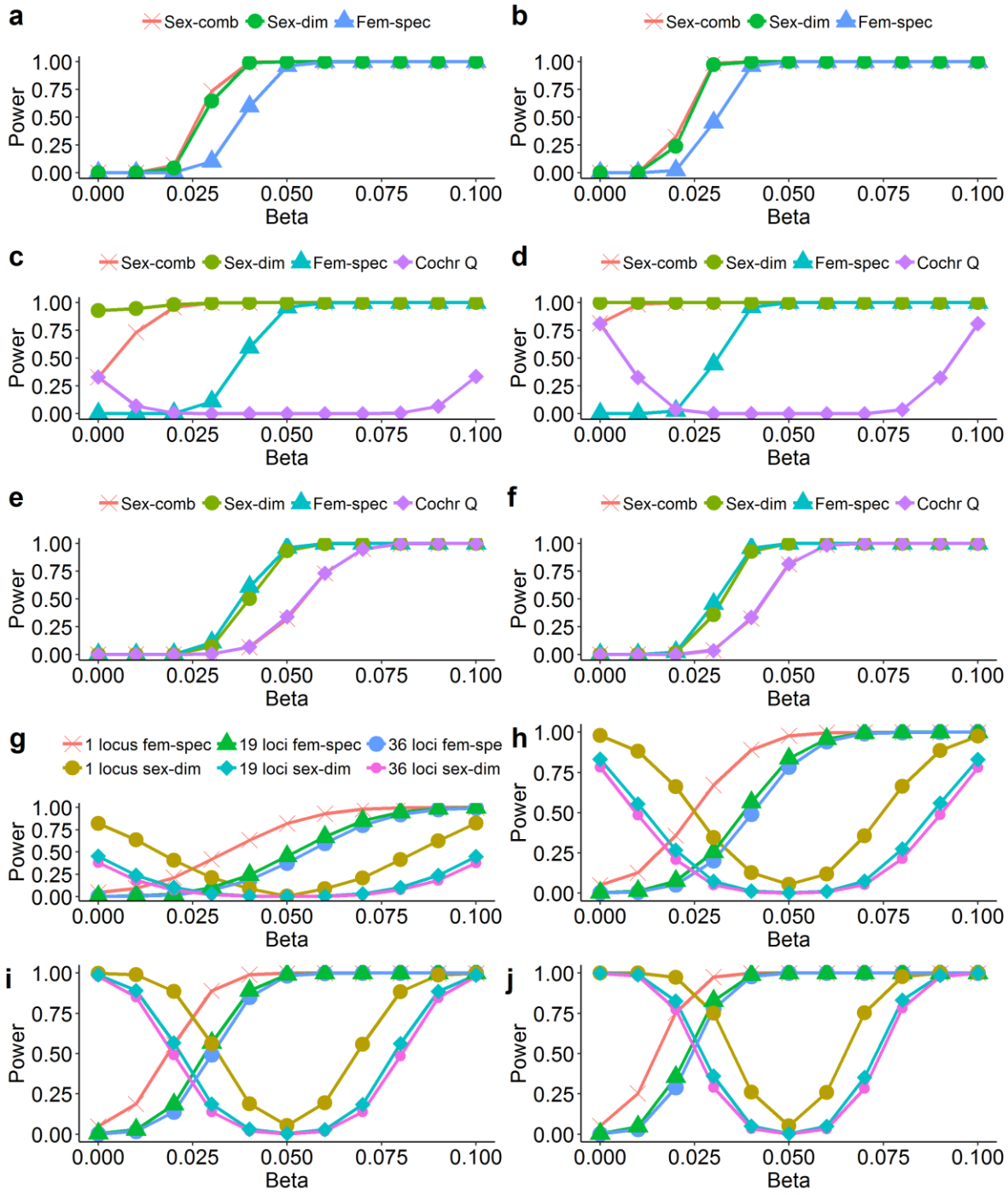
Supplementary Figure 2. Regional plots for novel loci with sex-combined effects on FG. **(a)** *ZBTB38*, **(b)** *MANBA/UBE2D3*, **(c)** *RGS17*, **(d)** *PDE6C*, **(e)** *HMG20A*, **(f)** *IGF1R* and (g) *NFATC3*.



Supplementary Figure 3. **GARFIELD enrichment analysis.** Enrichment results for the sex-specific FG meta-analysis summary statistics: **(a)** peaks, **(b)** histone modifications and **(c)** chromatin states.



Supplementary Figure 4. Tissue expression of genes within the novel *ZNF12* locus.
(a) *KDELR2* and **(b)** *DAGLB*. Expression is relative to three housekeeping genes (*PPIA*, *B2M* and *HPRT*). For beta cell (*n*=3) and islets (*n*=3) data, lines are means. Quantitative RT-PCR was carried out using cDNAs from three human donors (beta-cells and islets). The other tissues were commercial cDNAs (one point observation).



Supplementary Figure 5. Power of tests for detecting sex heterogeneity through simulations.

Power of sex-combined, sex-dimorphic and female-specific analyses, as well as Cochran's Q-test to detect associations for evidence of sex heterogeneity under three scenarios of sex-effects: no sex heterogeneity at **(a)** CAF=0.2, and **(b)** CAF=0.5, effects on both sexes with the presence of heterogeneity between them at **(c)** CAF=0.2 and **(d)** CAF=0.5, an effect specific to one sex only, e.g. women at **(e)** CAF=0.2 and **(f)** CAF=0.5. Power of the current sample size to detect sex heterogeneity at established FG (n=36) and FI (n=19) loci using the approach that ignores $P_{\text{sex-dimorphic}}$ and considers only $P_{\text{heterogeneity}}$<0.05 or

$P_{heterogeneity}$ adjusted for multiple testing ($P_{heterogeneity}$<0.05/36 or $P_{heterogeneity}$<0.05/19) under two scenarios of sex-effects: an effect specific to one sex only, e.g. women and effects on both sexes with the presence of heterogeneity between them considering four CAFs: **(g)** CAF=0.05, **(h)** CAF=0.1, **(i)** CAF=0.2, (j) CAF=0.5. The power at $P<5x10^{-8}$ is given for all three tests: sex-combined, sex-dimorphic and female-specific. Colour coding for panels (g-j) is given on panel (g). The power for the heterogeneity test implemented in GWAMA (Cochran's Q-test) is also given. Simulations were based on 70,000 men and 70,000 women. For each parameter setting, 10,000 replicates of data were generated. CAF is the causal variant allele frequency and beta is the effect size in SD units in women. Within each scenario, we considered two CAFs (0.2 and 0.5) and a range of betas (from 0 to 0.1) representing the effect size in SD units in women. For the no sex-heterogeneity setting, the beta in men is the same as in women; for the sex-dimorphic setting, the beta in men is fixed at 0.05 SD units; for the female-specific setting, the beta in men is fixed at zero.