Supplementary Information

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

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SUPPLEMENTARY NOTE 1 Additional acknowledgements

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The Swedish Twins Registry Study (SWEDISHTWINS, REPLICATION_STR)

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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)

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The Whitehall Study

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Human islets gene expression

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The ASAP study

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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
$P_{\text{heterogeneity}}$ adjusted for multiple testing ($P_{\text{heterogeneity}} < 0.05/36$ or $P_{\text{heterogeneity}} < 0.05/19$) 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 $P < 5 \times 10^{-8}$ 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.