

Supplemental Figure Legends

Supplemental Figure 1: Schematic of the gene-gene interaction analyses performed in this study

The figure demonstrates the two approaches that were used for the interaction analyses in this study – single variant- and polygenic score-based. The single variant analyses were based on the variants in the *T2D-joint set* (comprising of the *T2D-risk set* and the *T2D-variance set*); the polygenic score-based analyses were implemented using one overall polygenic score and six partitioned polygenic scores (pPS) that were constructed based on variants in the *T2D-risk set*.

Supplemental Figure 2: Power estimates for the pairwise gene-gene interaction analysis for variants in the *T2D-joint set*

The blue curve shows the power estimate for the pairwise interaction analysis for the *T2D-joint set* variants (MAF=5%) as a function of the interaction effect. The power calculation was based on the following parameters: (i) main effect OR on T2D=1.1; (ii) sample size=376,375, with a T2D case:control ratio (per UK Biobank) of 0.044; (iii) $\alpha=4 \times 10^{-7}$ ($\alpha=0.05$, corrected for 126,253 pairwise tests). As noted, there was >70% power to detect interactions of $OR \geq 1.5$ between two *T2D-joint set* variants of MAF=5%.

A similar power estimate curve for two *T2D-joint set* variants of MAF=50% has also been shown (black dotted curve).

Supplemental Figure 3: Power estimates for the gene-gene interaction between variants from the *T2D-joint set* and the *genome set*

The curve shows the power estimate for the interaction analysis between variants from the *T2D-joint set* (MAF=5%) and the *genome set*, as a function of the MAF of the *genome set* variant. The power calculation was based on the following parameters: (i) main effect OR on T2D for *T2D-joint set* variant=1.1; (ii) main effect OR on T2D for *genome set* variant=1.0; (iii) interaction effect OR between the variants=1.5; (iv) sample size=375,736, with a T2D case:control ratio (per UK Biobank) of 0.044; and (v) $\alpha=10^{-10}$ ($\alpha=0.05$, with Bonferroni adjustment for 503 genome-wide analyses). As noted, for *genome set* variants with $MAF \geq 10\%$, there was >75% power to detect an interaction with a *T2D-joint set* variant of MAF=5%.

Supplemental Figure 4: Quantile-quantile plots for the gene-gene interaction analysis using a polygenic score-based approach

A polygenic score (PS)-based approach was used to perform a gene-gene interaction analysis with genome-wide variants. The quantile-quantile plots demonstrate the results of the genome-wide interaction analysis for the following seven PS for T2D: overall PS, pPS_{adiposity}, pPS_{IS1}, pPS_{IS2}, pPS_{IA}, pPS_{dyslipidemia} and pPS_{mix}.

(pPS = partitioned polygenic scores; IS = insulin secretion; IA = insulin action)

Supplemental Figure 5: Manhattan plots demonstrating the results for the gene-gene interaction analysis using a polygenic score-based approach

A polygenic score (PS)-based approach was used to perform a gene-gene interaction analysis with genome-wide variants. The Manhattan plots demonstrate the results of the genome-wide interaction analysis for the following seven PS for T2D: overall PS, pPS_{adiposity}, pPS_{IS1}, pPS_{IS2}, pPS_{IA}, pPS_{dyslipidemia} and pPS_{mix}.

The red horizontal line in each plot demarcates the Bonferroni-corrected significance threshold ($p=7 \times 10^{-9}$, accounting for seven GWAS).

(pPS = partitioned polygenic scores; IS = insulin secretion; IA = insulin action)