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, 7 ' F D V H F R Q W U R O U D W L R S H U 4x10^{-7} % L R E D Q N F R U R U H F W H G L 126,253 pairwise tests). As noted, there was >70% pow HW U W R G H W H F W L Q W H U D F W 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 F D V H F R Q W U R O U D W L R S H U 8 .= %10^{-10} L R E D Q N Z H W K % R O D H G U adjustment for 503 genome-wide analyses). As noted, for genome set variants with MAF •10%, there was >75% power to detect interaction with a T2D-joint set variant of MAF=5%.