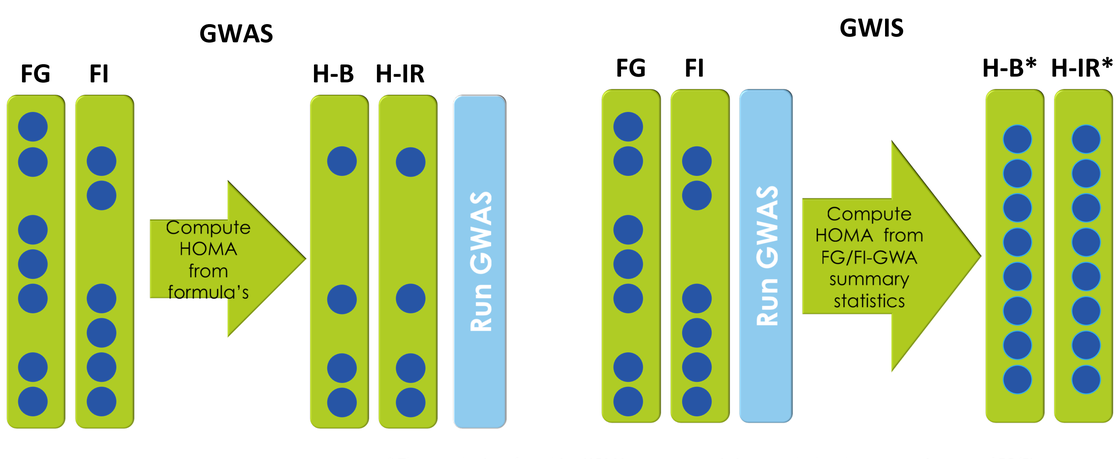
Genome-Wide Inferred Statistics for β-cell function and Insulin Resistance

Dorret I. Boomsma[1,2], Iryna O. Fedko[1], Michel G. Nivard[1], Jouke-Jan Hottenga[1,2], XC-Pleiotropy group, MAGIC Investigators, Reedik Mägi[3], Inga Prokopenko[4]

[1]Department of Biological Psychology, Vrije Universiteit Amsterdam, The Netherlands (di.boomsma@vu.nl) [2]EMGO+ institute for Health and Care Research, VUMC, Amsterdam, The Netherlands [3]Estonian Genome Center, University of Tartu, Tartu, 51010, Estonia [4]Department of Genomics of Common Disease, School of Public Health, Imperial College London, London W12 0NN, UK

Homeostatic Model Assessment of β-cell function (HOMA-B) and Insulin Resistance (HOMA-IR) are calculated from Fasting Glucose (FG) and Fasting Insulin (FI) values. They are commonly used glycaemic indices that provide mechanistic insight in to the etiology of T2D. HOMA-B reflects β-cell function in terms of insulin secretion, and HOMA-IR is an estimate of insulin sensitivity. The estimation of HOMA-B/-IR requires FI and FG have been assessed in the same individual. Cohorts for which FG or FI has not been measured cannot contribute to a GWAS of HOMA . As a consequence published HOMA-B/-IR GWAS meta-analyses featured a smaller sample size compared to GWAS of FG/FI. The recently developed Genome Wide Inferred Statistics (GWIS) approach (Nieuwboer et al. 2016) approximates SNP effects on HOMA-B or HOMA-IR based on known SNP effects on FG and FI and some minimal contextual information about the relation between FI and FG, and sample overlap (see Methods and Figure 1). Here, we infer analytically the GWAS summary statistics for HOMA-B/-IR based on FG/FI recent GWAS meta-analysis results from the MAGIC (Lagou 2016, in preparation) using GWIS.

Figure 1. Schematic comparing GWIS and GWAS for HOMA.



* The sample size of resulting HOMA summary statistics are calculated as geometric mean of FG/FI

METHODS

- **Phenotype:** HOMA-B/-IR were calculated from the FG/FI measures using formulas: HOMA-B=(20×FI)/(FG–3.5); HOMA-IR=(FG×FI)/22.5, where FG is measured in mmol/l and FI is in mU/l units
- **FG/FI summary statistics:** We obtained the summary statistics from the latest GWAS meta-analysis of FG/FI, performed by the Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC) in up to 88,320/64,090 individuals respectively
- **HOMA summary statistics:** We inferred HOMA summary statistics using formulas and information about mean of FG/FI respectively. Additionally, we corrected for sample overlap between two GWASs and excluded SNPs with small sample size (N < 35,000) to avoid spurious results.

DISCUSSION

- The sample size of inferred HOMA-B/-IR analyses is up to 75,240 non-diabetic individuals of European descent.
- The gain in power obtained from doubled sample size of HOMA GWIS compared to the previously published GWAS meta-analysis (Dupuis et al. 2010) allowed to detect one novel HOMA-B (*FOXA2*) and three novel HOMA-IR loci (*LYPLAL1, PER4, PPP1R3B*).
- Results of our analysis demonstrated that with increased power to discover association, the HOMA-IR analysis begins to reveal significant loci. A previous lack of overlap between T2D and insulin resistance points to a lack of power to discover insulin resistance loci.
- Ability to compute the summary statistics in partially overlapping samples demonstrated advantage of GWIS inference-based method over direct analytical GWAS for composite phenotypes.

RESULTS

Figure 2. Manhattan plot of HOMA-B

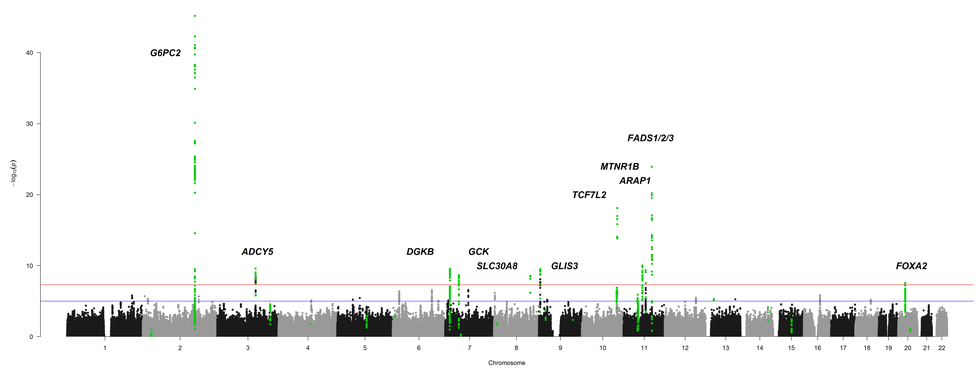
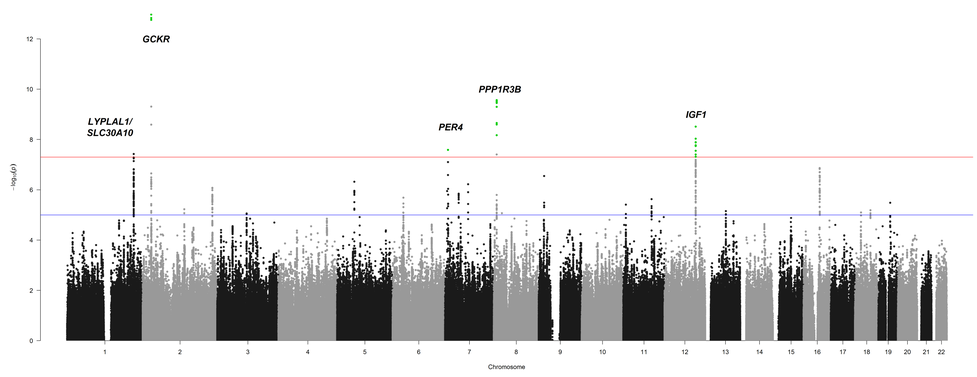


Figure 3. Manhattan plot of HOMA-IR



CONCLUSION

- We implemented a novel GWIS method and gained power compared to previously published HOMA GWAS. We reported one novel HOMA-B and three novel HOMA-IR related loci.

Nieuwboer et al (2016). GWIS: Genome-wide inferred statistics for functions of multiple phenotypes. The American Journal of Human Genetics, 99(4), 917-927.
Dupuis et al. (2010). New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nature genetics, 42(2), 105-116.