Development and Evaluation of a Genomic Risk Score for Obesity

Daniel Belsky[1,2]
Avshalom Caspi[2,3]
Karen Sugden[2,3]
Benjamin Williams[2,3]
Terrie Moffitt[2,3]

1. Gillings School of Public Health, University of North Carolina at Chapel Hill
2. Duke University Institute for Genome Science and Policy
3. Institute of Psychiatry, Kings College London

Objective. To develop and evaluate a method to derive a genomic risk score from published GWAS data.

Background. The rapidly declining costs of genotyping and the increasing availability of genetically informed datasets offer investigators in the social sciences an opportunity to integrate genetic information into their research. However, for phenotypes influenced by large numbers of genomic loci each with small effect size, identifying a promising set of variants to examine can be a challenge. The rapid pace of gene discovery research, in particular the proliferation of genome-wide association studies, creates large quantities of data that are challenging to synthesize. Methods are needed that enable research teams to take a snapshot of what is known about the genetics of a phenotype at a point in time and distill from this snapshot a set of markers that can be genotyped in their own samples or followed up in genetically informed datasets that contain rich phenotypic and environmental data.

Design. The study was conducted in two parts. In Part 1, a genomic risk score (GRS) for obesity was developed using published GWAS data and web-based tools for whole genome analysis. In Part 2, the GRS was evaluated using data from the Atherosclerosis Risk in the Community (ARIC) study obtained from dbGaP.

Methods.

Part 1) Genomic risk score development using web-based tools for whole-genome analysis of reference-genome datasets: The NHGRI GWAS Catalog was searched to identify all GWAS of obesity-related phenotypes in European-descent samples. All SNPs meeting a significance criterion of $p<10^{-5}$ in these GWAS (hereafter "risk SNPs") were analyzed using data from the International HapMap Consortium and the web-based genome-analysis toolkit at SeattleSNPs to identify replicated or genome-wide significant loci to include in a genomic risk score (GRS). Briefly, patterns of linkage disequilibrium

(LD) were examined among GWAS-identified risk SNPs to construct "LD Blocks" of risk SNPs and evaluate block-wide statistical significance and cross-GWAS replication. LD blocks were retained for inclusion in the GRS if they were replicated in ≥2 GWAS or if they contained a SNP achieving genome-wide significance ($p<10^{-8}$) in at least 1 GWAS. The default LD threshold to define blocks was set at $R^2 \geq 0.95$ and then systematically relaxed to evaluate the sensitivity of the derived GRS to the LD threshold.

Part 2) GRS evaluation using empirical genotype and phenotype data from the ARIC cohort: Tag SNPs for each replicated/genome-wide significant LD block were selected from among the SNPs in the ARIC genotype dataset that met quality control criteria. Genotypes for tag SNPs were extracted for all ARIC participants with valid genotype data and obesity-associated alleles were summed across SNPs to compute participants' GRSs under 3 weighting schemes: un-weighted (the sum of BMI-increasing alleles); replication weighted (BMI-increasing alleles were first multiplied by the ratio of GWAS replications for the LD block(s) they tagged to the average replication rate across all SNPs in the GRS); and empirically weighted (SNPs were weighted by their bivariate association with BMI in the ARIC sample). Empirical weights were calculated separately for black and white ARIC participants. GRSs were then evaluated using 3 performance metrics: The proportion of variance in BMI explained by the GRS (R^2); The area under the receiver operating characteristic curve for obesity (AUC); and the integrated discrimination index for obesity (IDI). All analyses were conducted separately for black and white ARIC participants and were adjusted for a quadratic specification of age, gender, and the ARIC study center at which data were collected. Analyses evaluating the GRS included both European-descent (white, n=8,286) and African-descent (black, n=2,442) samples.

Results.

Part 1: A search of the NHGRI GWAS Catalog identified 16 GWAS meeting inclusion criteria. Analysis of published data yielded a set of 519 obesity-risk SNPs clustered in 159 LD blocks of which 69 replicated across GWAS or were genome-wide significant ($p<10^{-8}$). These 69 LD blocks were carried forward into Part 2. Sensitivity analyses revealed that relaxing the LD threshold used to define blocks did not substantively change the risk loci identified, but more generous LD thresholds yielded fewer LD blocks each comprising more risk SNPs. The full set of 69 LD blocks was carried forward into Part 2.

Part 2: A set of 54 tag SNPs were selected to capture variation across the 69 LD blocks identified in Part 1. This set included multiple SNPs in the genes TMEM18, BDNF, FTO, and MC4R. BMI prediction

analyses comparing the set of SNPs around each gene to a randomly selected SNP from the set supported the inclusion of all SNPs for all 4 genes. GRSs were computed for ARIC participants by summing BMI-increasing alleles across the 54 tag SNPs. Among whites, the GRS was normally distributed (M=49, SD=10) and each additional risk allele was associated with a 0.05 point increase in BMI (95% CI 0.04-0.06) and a 0.4% point increase in the probability of being obese (95% CI 0.03-0.05). The obesity GRS explained approximately 1% of the variance in BMI (95% CI 0.72%-%1.63), discriminated obese participants slightly better than chance (AUC = 0.55, 95% CI 0.53-0.56) and, when added to a baseline model including age, age^2, gender, and dummy variables coding the location where the ARIC visit was conducted, modestly improved the sensitivity of model to predict obesity net of any decrement in model specificity (IDI=0.01, $p<10^{-14}$). When combined with the baseline model, the GRS also improved the proportion of variance explained in BMI from 3% to just over 4% (95% CI 0.71%-1.57% for the change, $p<1x10^{-6}$) and increased the AUC from 0.56 to 0.59 (95% CI 0.02-0.04 for change, $p<1x10^{-8}$). Among blacks, the GRS explained less variance in BMI (R^2=0.0017) and afforded about 1/4 the net improvement in sensitivity of obesity prediction, but performed comparably with respect to discrimination of obese participants.

Conclusions. It is feasible to construct an a priori measure of genomic risk using published data and web-based genome-analysis tools. The a priori genomic risk score for obesity developed in Par 1 of this study performed comparably to the set of variants identified in a recent GWAS of BMI that included nearly a quarter million subjects and better than sets of variants identified in any previous GWAS. Therefore, this method is promising as a means to derive genome-wide measures of risk for phenotypes showing evidence of influence by large numbers of genomic loci with small effect size and for which multiple GWAS have been conducted.

It is important to note the obesity GRS was derived from GWAS of European-descent samples and performed poorly among African-descent participants in the ARIC study. The genome-wide approach to risk measurement illustrated in this study requires that the sample in which the GRS is to be used share ethnic heritage with the samples in the association studies from which the GRS is derived. In addition, the relatively greater genome-wide LD for European- as compared to African-descent populations raises some concern as to how well this method will generalize beyond European-descent samples. As more GWAS of non-European-descent samples become available, it will become feasible to evaluate the generalization of this method.