**Supplemental Digital Content 1**

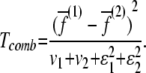
Review of the methods employed for analysis and statistical calculations of the pooled data. 1-12

Stage 1 - QC filtering of the frequency data in the pooled samples

Single nucleotide polymorphisms (SNPs) from each pool were prioritized for individual genotyping based on several different criteria outlined below. For all methods we excluded rare SNPs (true allele frequencies less than 5% in either the Caucasian population or predicted in the control pool sample) and the 5% of SNPs showing the highest variability as indicated by the size of the standard deviation among measures from the replicate assays. In addition, we excluded all markers used for the estimation of copy number variations in the genome. These filtering methods resulted in reduction of the SNPs available for statistical analysis from 620,901 (initial number of interrogated SNPs for each sample) to 447,283 SNPs.

Stage 2 - Ranking by test statistics

The test statistic was based on p-values estimated using the following test (Tcomb) which combines experimental and sampling errors:



This statistic combines:

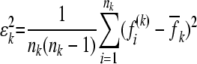
1. chi-square statistic T1for testing differences between two proportions (allele frequencies) in cases and controls accounting for the sampling variance:

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| --- | --- |
| A description... |  |

where is the mean of the allele frequencies over *nk* pool replicates, A description...is the binomial sampling variance and *Nk* is number of controls and cases respectively (*k* = 1,2).

b) *Z-*statistics for testing the difference in mean allele frequencies between cases and controls:

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| A description... |  |

Where is the square of the standard error due to experimental error. The use of this statistic (which follows an approximate normal distribution with one degree of freedom under the null hypothesis of equal allele frequencies for cases and controls) takes into account the two single available sources of error: sampling error and experimental error.

Whereas stage 2 analyzed markers independently, a multimarker approach may provide for smoothing of measurement noise and identify loci with lower odds ratio by leveraging linkage disequilibrium between adjacent SNPs. A sliding-window approach of mean test statistic values (as delineated in stage 2) was implemented for four different window sizes (5, 10, 20 and 30 consecutive SNPs) across all windows throughout the genome. The results of sliding-window analysis were compared with the results of the single SNP analysis of markers from stage 2. The sliding-window analysis also served as both a validation of the highest ranking SNPs selected from stage 2 (i.e. high ranking SNPs from stage 2 should be reflected in the high rank of different sized windows around its locus), as well as a tool for selecting additional SNPs with relative lower ranking in relation to the selected arbitrary threshold value of statistical significance (10-7 < p < 10-6).

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