CORIELL
PERSONALIZED MEDICINE
COLLABORATIVE

Multi-Variant Risk Reporting in the Coriell Personalized Medicine Collaborative (CPMC®) Research Study

APPENDIX: Aneurysm

Single Nucleotide Polymorphism (SNP) Identification

To be considered for use in multigenic risk reporting for aneurysm we required each SNP to: 1) show statistically significant association with aneurysm after correction for multiple testing and be replicated in at least one independent population sample (Yasuno et al., 2010; Yasuno et al., 2011), 2) be unlinked with all other SNPs in the final model ($R^2 < 0.2$), 3) be captured in the current version of the Affymetrix 6.0 Genotyping Array, 4) pass Coriell's internal SNP genotyping quality controls, and 5) be approved by the ICOB.

SNPs associated with aneurysm were initially identified in the NIH GWAS catalog (www.genome.gov/gwastudies). References from this catalog were then used in parallel with PubMed searches to explore the extent of the literature support for association. In this case, variants were evaluated in multiple population samples with consistent results. We therefore find no reason not to report RR values from the same model to all CPMC participants.

Model

The CPMC model of aneurysm relative risk (RR), calculated via REGENT, includes four ICOB-approved, CLIA-validated SNPs captured by the current Affy 6.0 Genotyping Platform: rs6841581, rs9298506, rs9315204, and rs12413409 (also see Table 1 for input parameters). We used a prevalence of 0.028. Odds ratios from the listed citations were converted to relative risk (RR) values as described in the white paper. For variants with minor allele frequencies > 0.50, we inverted RR values as described in the white paper.

SNP	MAF	Ncase	Ncontrol	RR_het	RR_hom	Citation
rs6841581	0.19	2780	12515	0.81	0.68	Yasuno_2011
rs9298506	0.21	5891	14181	0.79	0.65	Yasuno_2010
rs9315204	0.25	5891	14181	1.19	1.38	Yasuno_2010
rs12413409	0.11	5891	14181	0.78	0.64	Yasuno_2010

Evaluation

Figure 1 displays excellent consistency of categorical boundaries determined by REGENT.model across 100 simulations. Figure 2 displays excellent consistency of the proportion of individuals assigned to a given category by REGENT.model.

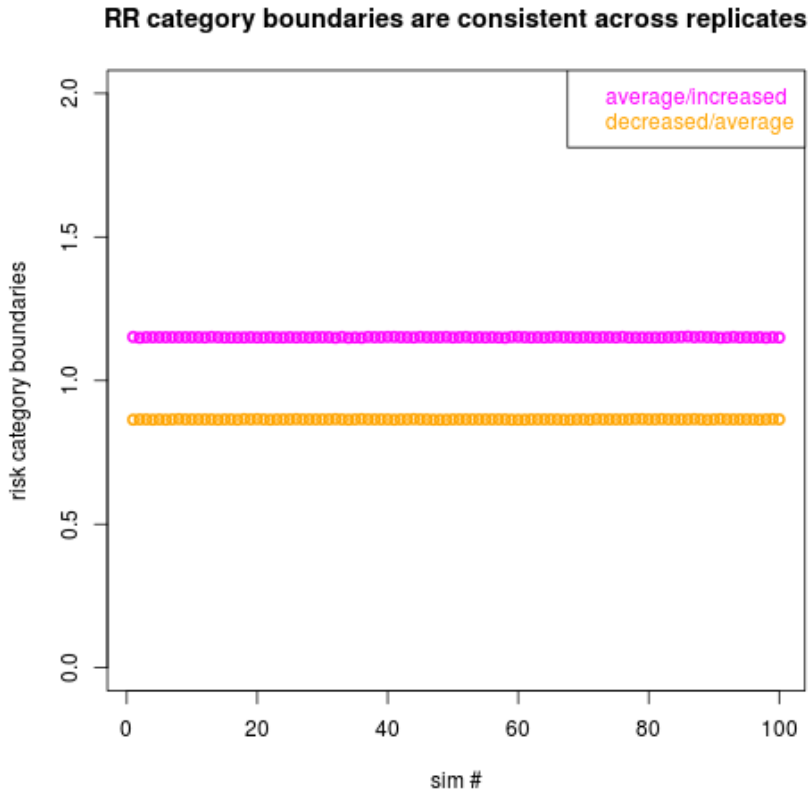

Figure 1.

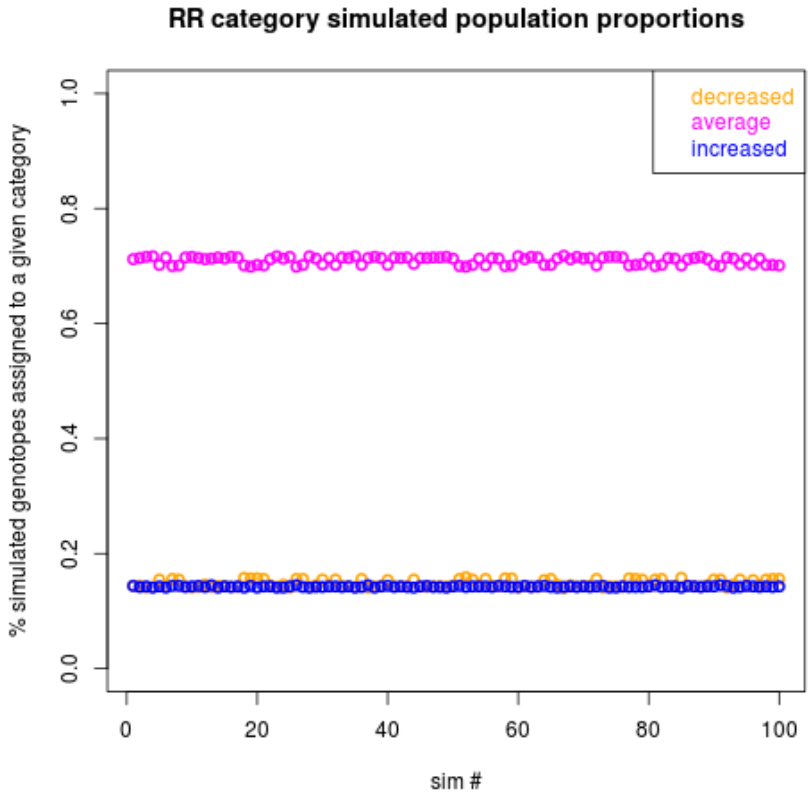

Figure 2.

References

Yasuno, et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nat Genet.* 2010 May;42(5):420-5.

Yasuno, et al. Common variant near the endothelin receptor type A (ENDRA) gene is associated with intracranial aneurysm. *PNAS.* 2011 Dec;108(49):19707-12.