

# Rare Variant Association Methods and their Performance with Population Structure

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# Figures

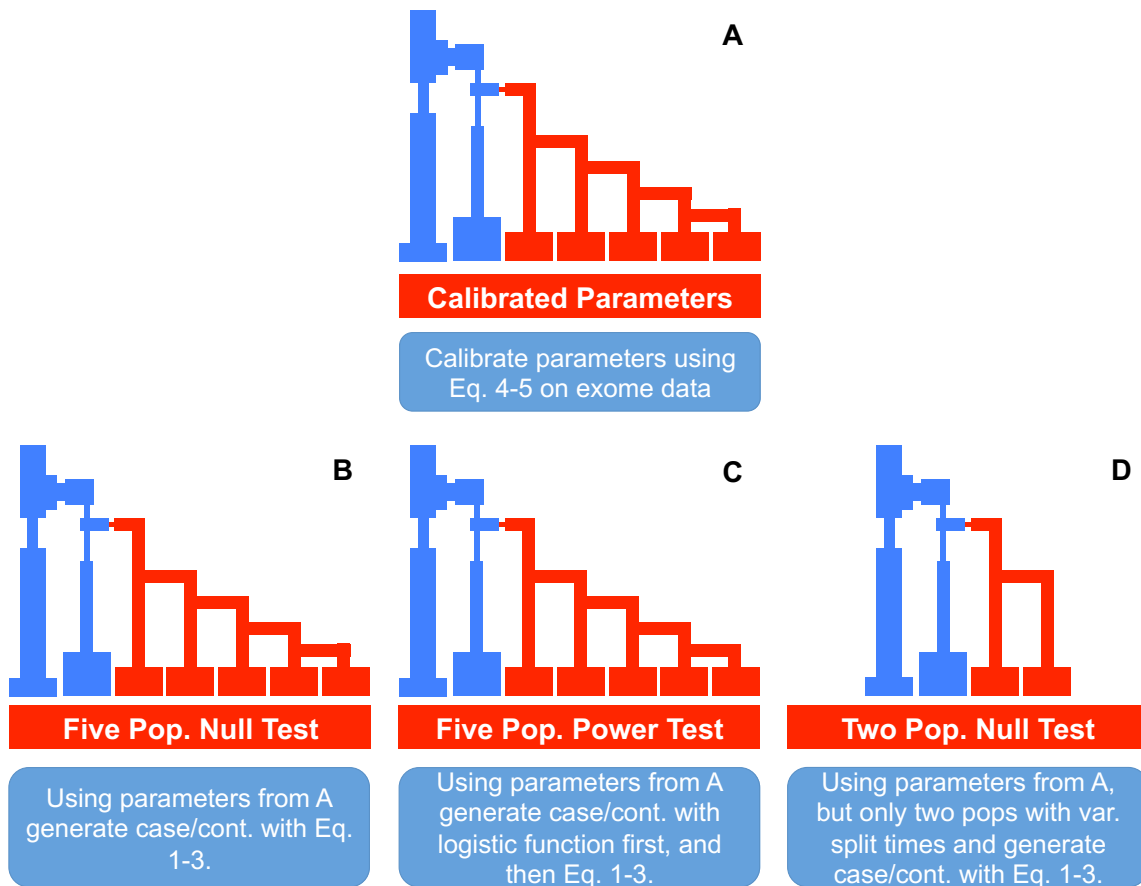


Figure S1: Simulation scenarios for the various analyzes. A) This is a reproduction of Figure 1 from the main text. B) Data produced by this scenario were used to test spurious association rates with five populations. C) Similar to B, data was combined with a logistic regression to generate ‘causative’ variants in order to test for power. D) is a slimmed down version of B where the parameter of split time was varied to test questions of divergence vs spurious association rates.

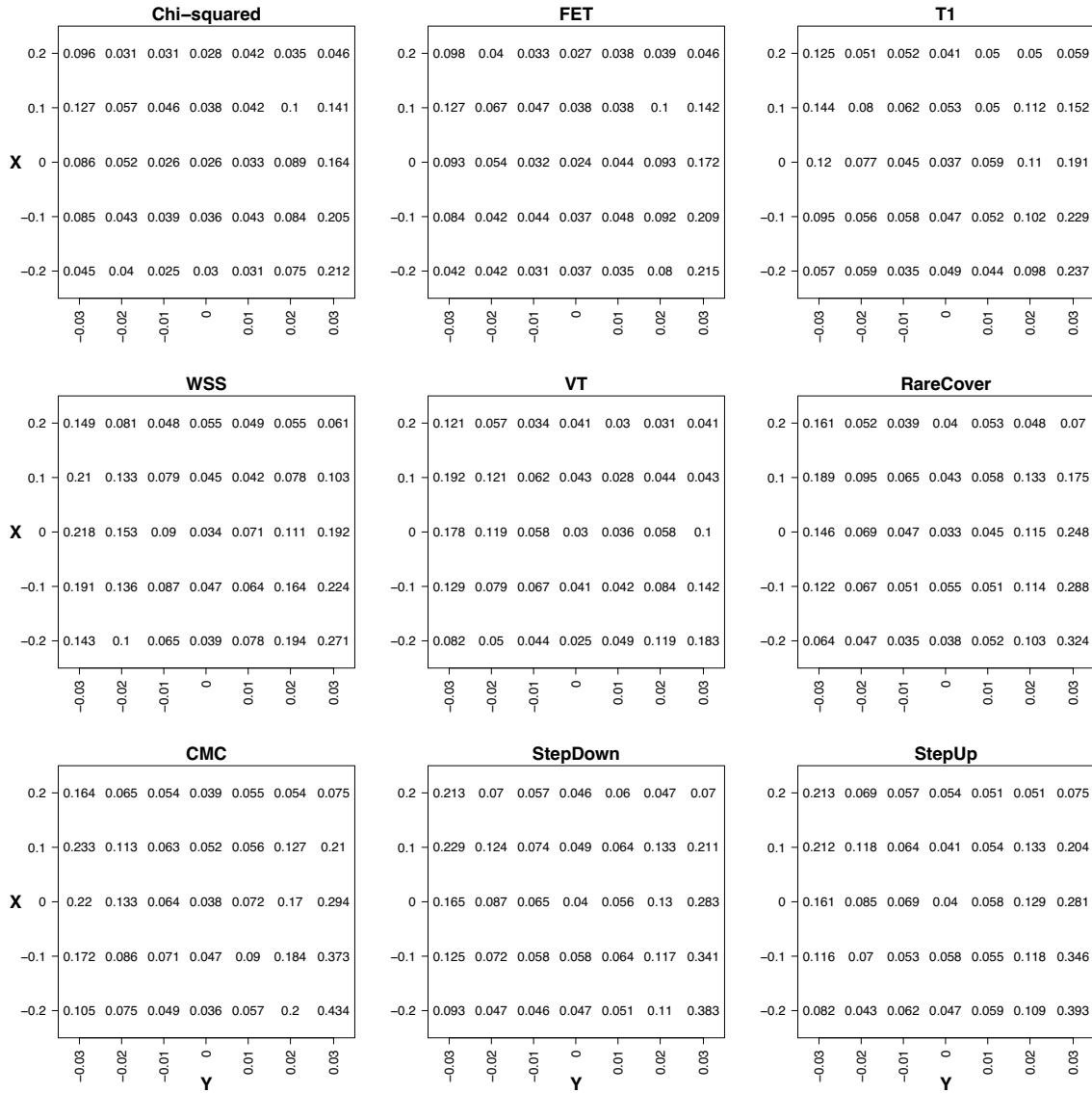


Figure S2: Same as Figure 2 of the main text, only with the values of the spurious association rate instead of a color spectrum.

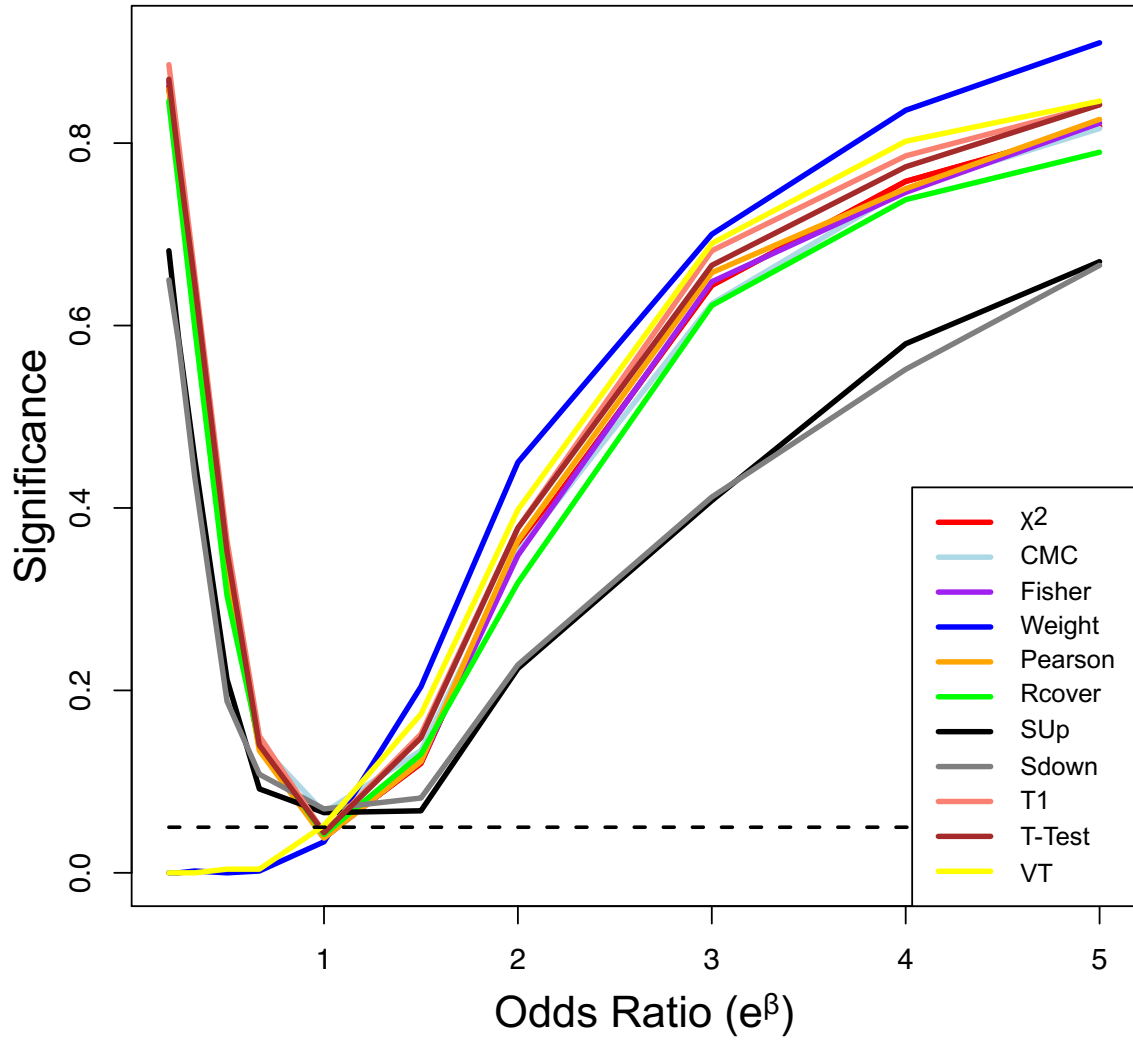


Figure S3: A simple single population power analysis of the 11 methods implemented in CCRARE. 9 of these are included in the main analysis. Case/control status were simulated under a T1 logistic regression model for 1000 cases and controls. The dotted line indicates an  $\alpha$  equal to 0.05.

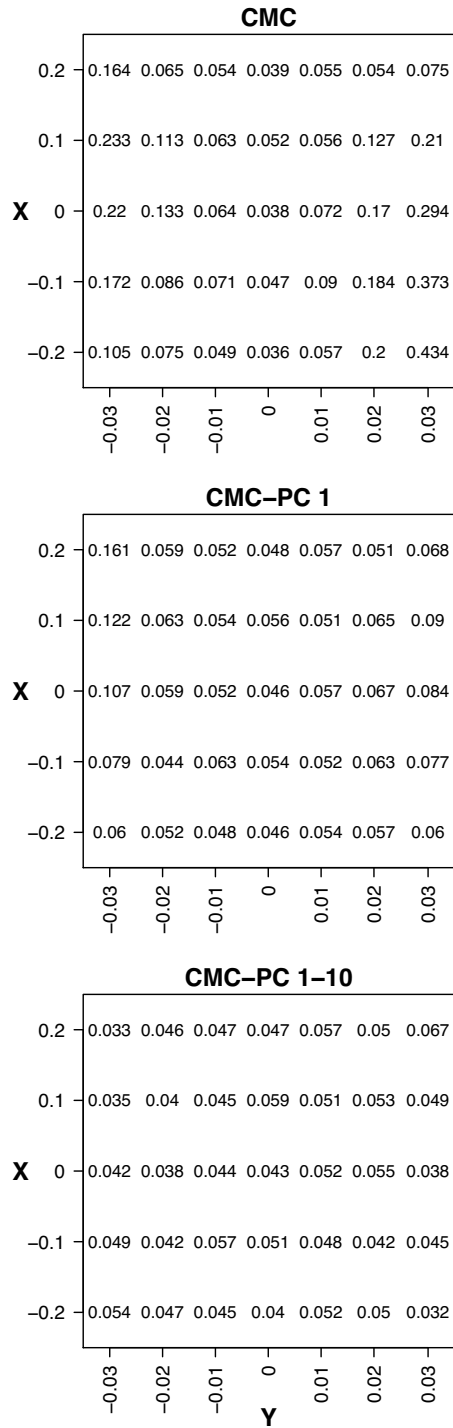


Figure S4: Same as Figure 3 of the main text, only with the values of the spurious association rate instead of a color spectrum.

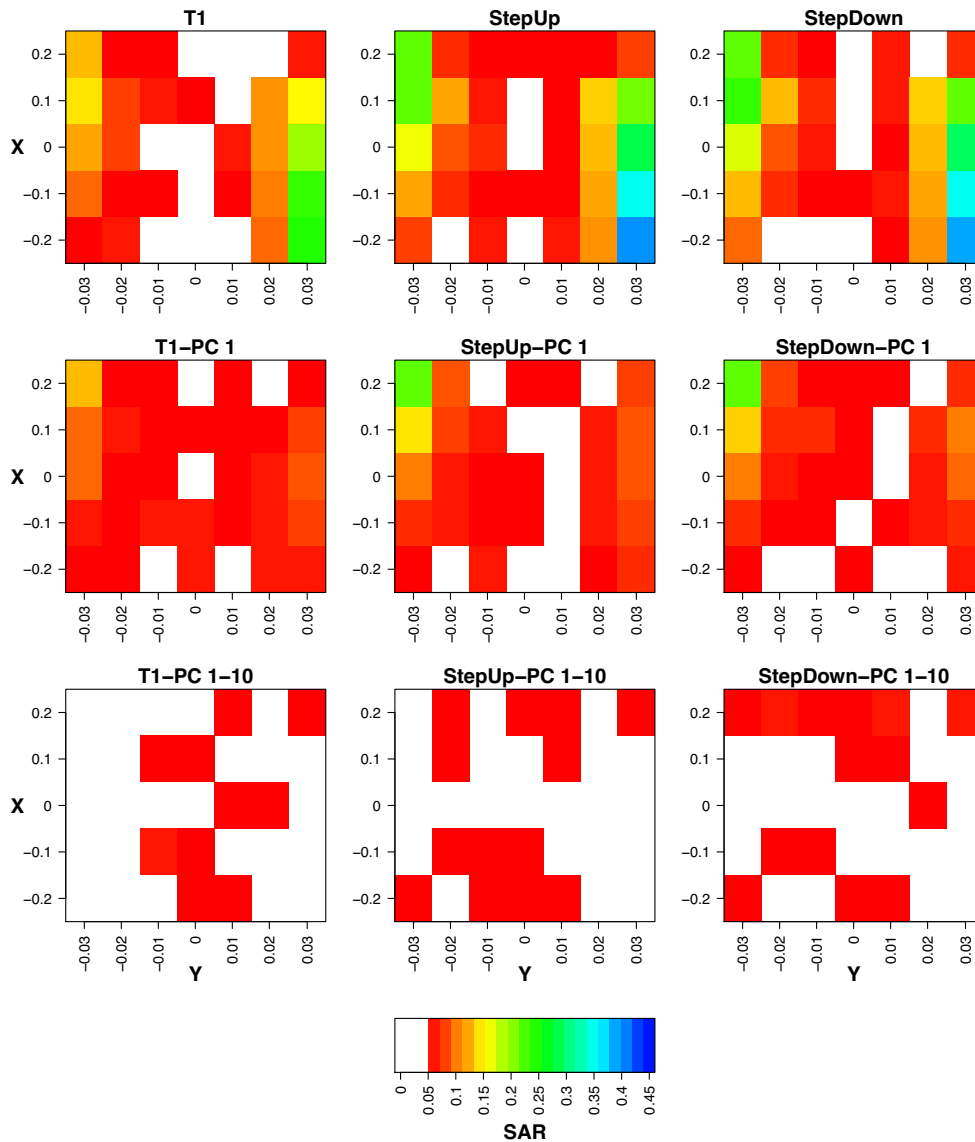


Figure S5: The effects of PCA correction of logistic regression based methods. Similar to the results reported for CMC in Figure 3, these are the results of performance of T1, StepUp, and StepDown on the five population scenario. The first column is T1, then StepUp, and finally StepDown where the first row has no PC correction, the second has one PC as a covariate, and the final row has ten PCs included as covariates. A Spurious association rate (SAR) lower than 5% are represented as white, with other levels signified by sequential coloration with red the lowest and blue the highest.

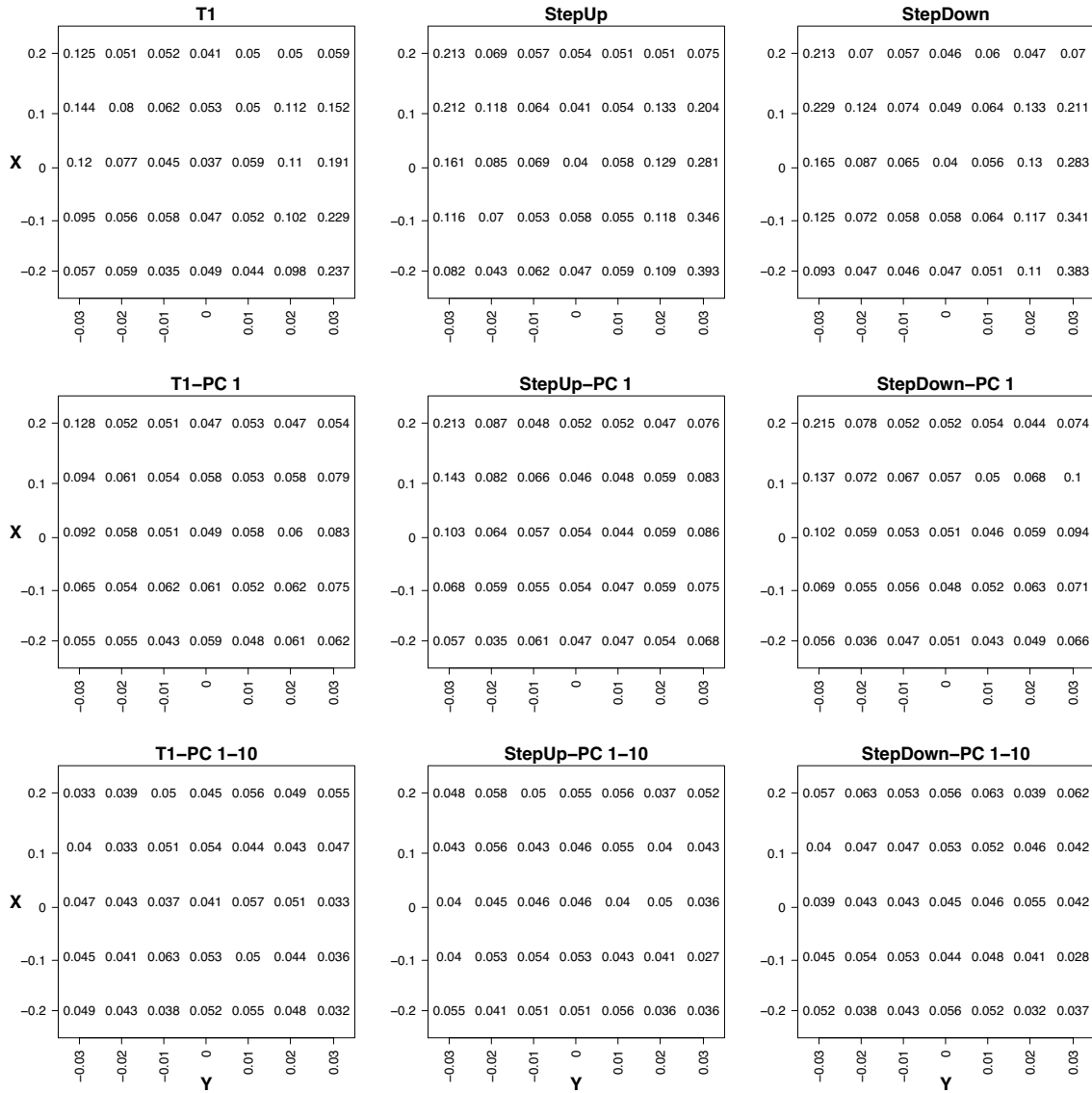


Figure S6: Same as Figure S5, only with the values of the spurious association rate instead of a color spectrum.

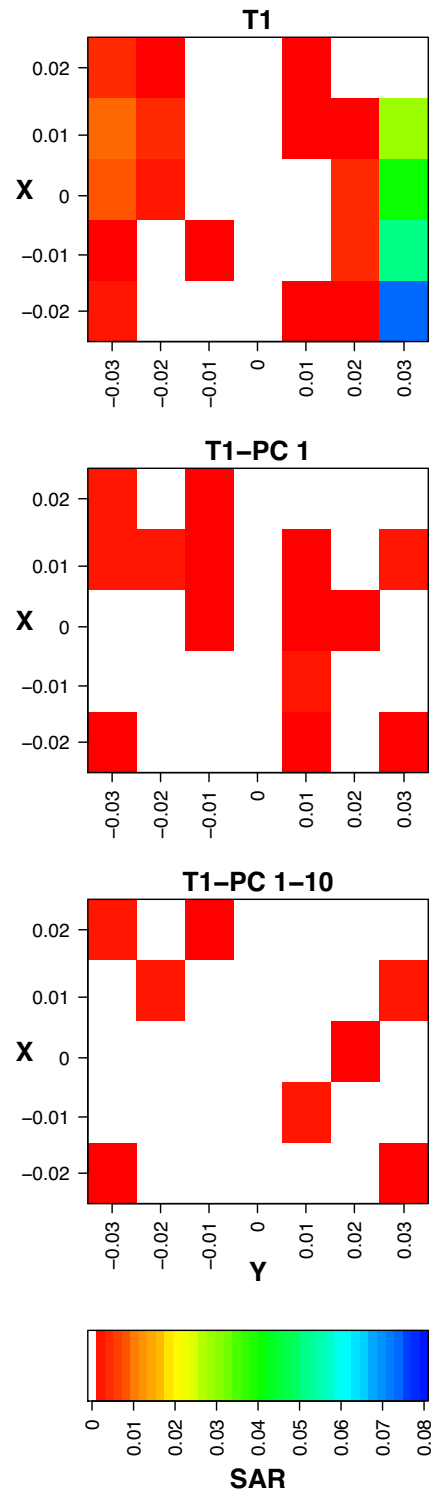


Figure S7: The effects on low P-values of PCA correction in logistic regression based method. Here, we have reperformed the analysis of Figure 2 and Figure S5 for the T1 method, but increased to 100,000 permutations in order to sample low p-values. All of the data is the same as before, including phenotypes, and with 1000 "gene" repetitions the expectation is zero with an  $\alpha = 0.0001$ . A Spurious association rate (SAR) lower than 0.1% are represented as white, with other levels signified by sequential coloration with red the lowest and blue the highest (in this figure 8%).



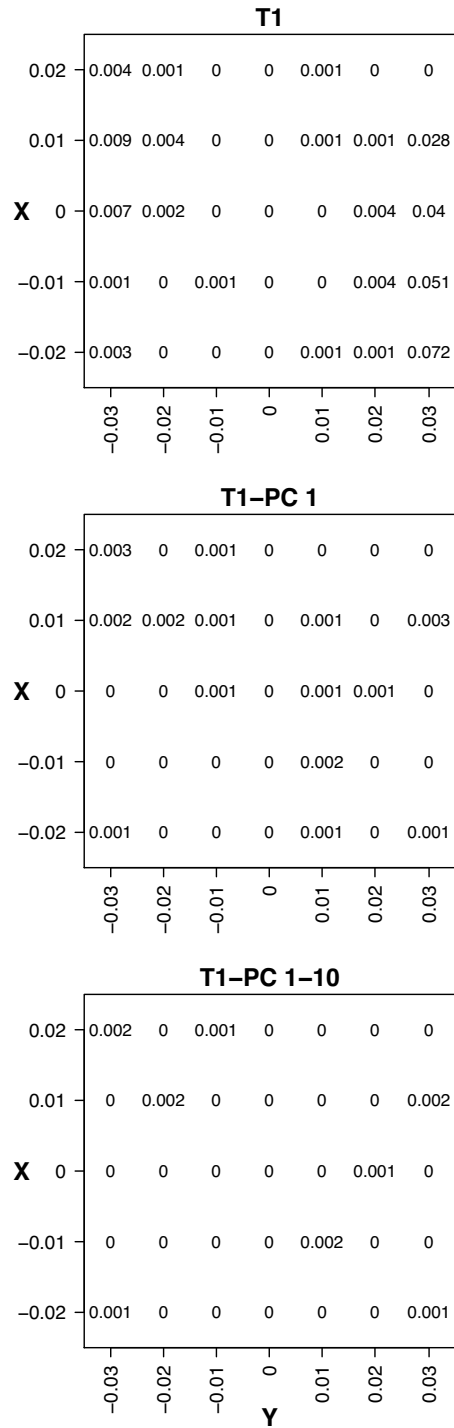


Figure S8: Same as Figure S7, only with the values of the spurious association rate instead of a color spectrum.

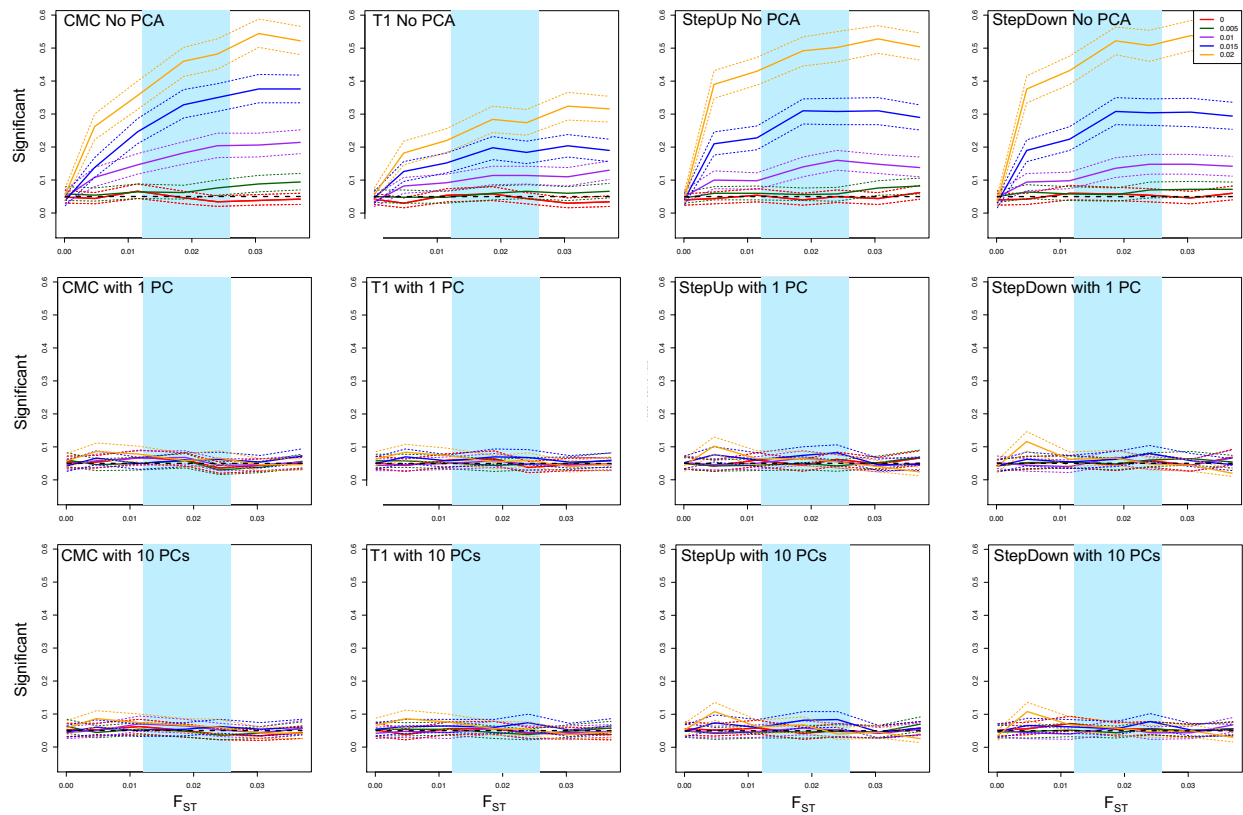


Figure S9: The effects of PCA correction of logistic regression based methods in the two population scenario. The first column is CMC, then T1, then StepUp, and finally StepDown where the first row has no PC correction, the second has one PC as a covariate, and the final row has ten PCs included as covariates. The dashed black line represents the 0.05  $\alpha$  value used to determine significance and the dotted lines represent the 95% confidence intervals calculated by bootstrapping.

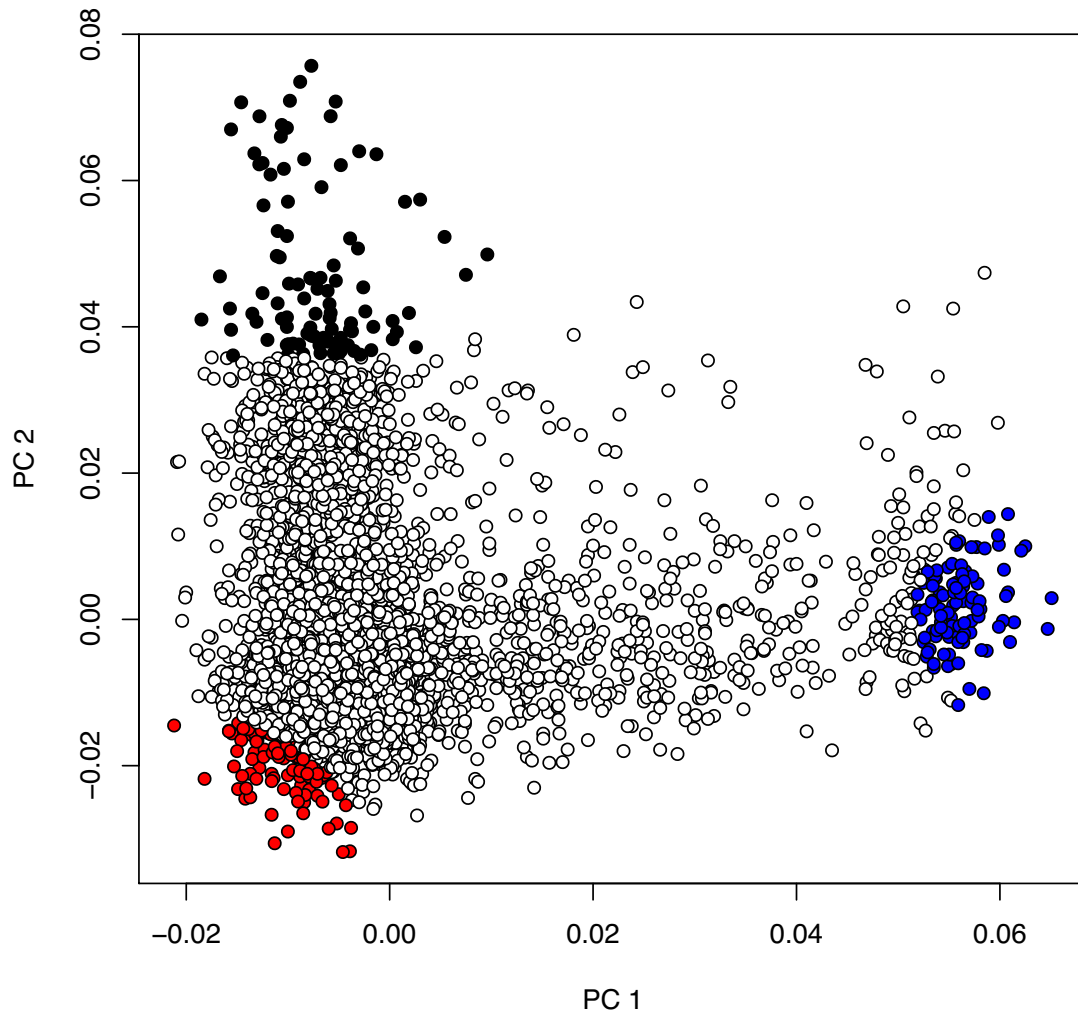


Figure S10: Individuals selected at the extreme of the PCA plot to form three discrete groups.  $N=100$  per group.  $F_{ST}$  was evaluated between the three groups on SNPs with  $MAF > 0.05$ . The average  $F_{ST}$  values were: blue-black = 0.01131, blue-red = 0.01098, red-black = 0.00391, which are all less than the minimal HGDP average of 0.01211.

# Tables

Table S1: List and detailed description of the nine rare variant association methods tested.

Test	Description
$\chi^2$ test of independence	a contingency table of cases or controls vs individuals with or without any rare variant in a region.
Fisher's Exact Test	again on a contingency table of cases/controls vs variant/invariant.
<i>Trare</i> (e.g. T1)	a logistic regression test predicting on the presence or absence of any rare variant ( $\leq rare$ ) in a region (for example if <i>rare</i> is defined as 1% then it is the common T1 test) [1–3].
Combined Multivariate and Collapsed Test (CMC)	based on a logistic regression all variants are collapsed into an aggregate like T( <i>rare</i> ), but the common variants (defined as $> rare$ ) are each included as a separate predictor on the phenotype, thus the model is $logit(Y) = \alpha + \beta_a * X_a + \beta_1 * X_1 + \dots + \beta_N * X_N$ [1] where $X_a$ is the aggregate variable and $N$ common variants.
Madsen-Browning Weight Test	as implemented in Madsen and Browning (2009) [4], which is based on a rank statistic of variants, weighted by allele frequency in unaffected individuals (e.g. $1/[n_i * p_i * q_i]$ ). Significance is assessed as a one tailed test by either normal approximation by permutation or standard permutation.
Variable Threshold Test	a one tailed Z statistic, which is optimized by assessing the frequency of alleles that should be included [3].
RareCover	as implemented by Bhatia et al. (2010) [5] it is a $\chi^2$ that selects and collapses rare variants with a greedy optimization algorithm.
StepUp	similar to RareCover only based on logistic regression [6, 7]. Initially the model fits each variant separately to estimate relative coefficients (negative equals protective, positive equals detrimental). Then each variant is added to the appropriate aggregate variable one at a time optimizing for the highest likelihood. The model is $logit(Y) = \alpha + \beta_p * X_p + \beta_n * X_n$ where 'p' signifies positive and 'n' signifies negative.
StepDown	is a variant of StepUp's optimization procedure. Instead of starting with no variants and adding them one at a time, it starts with all variants in their aggregate variable and tests each one by sequential deletion. If there is no reduction in likelihood they are restored. It only cycles through the variants once and is faster than StepUp.

Table S2: These are the parameter values estimated from the data from the arbitrary model presented in Figure 1. They are rescaled from 1MB to 45KB as per the average gene genomic length (i.e. including introns) and the values used in our simulation tests.

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-N 100000 20000 10	
-t ( $\mu_i = 1.587 + (((21 - 1)/2) - i) \times 0.09078$ )	estimated $\mu$ and $\delta$
-r 40.123 41000	estimated recombination rate
-l 7 4000 4000 4000 4000 4000 0 0 0	fixed
-ej 0.005 7 1	fixed
-ej 0.00875 1 6	fixed
-en 0.008625 1 0.077000	fixed
-en 0.008500 1 0.005880	fixed
-en 0.004875 1 0.077000	fixed
-en 0.00475 1 0.007460	fixed
-en 0.00125 1 0.077000	estimated expansion time
-en 0.00125 2 0.077000	same
-en 0.00125 3 0.077000	same
-en 0.00125 4 0.077000	same
-en 0.00125 5 0.077000	same
-en 0.004875 7 0.077000	fixed
-en 0.004750 7 0.007460	fixed
-en 0.001000 7 0.077000	fixed
-en 0.042500 6 0.125000	fixed
-en 0.007625 6 0.240000	fixed
-en 0.007500 6 0.062500	fixed
-en 0.000500 6 0.240000	fixed
-ej 0.001297 5 4	estimated divergence time
-ej 0.001399 4 3	estimated divergence time
-ej 0.001888 3 2	estimated divergence time
-ej 0.004136 2 1	estimated divergence time
-ma X 0.08733 0.08733 0.08733 0.08733 0 0	estimated single migration value
0.08733 X 0.08733 0.08733 0.08733 0 0	
0.08733 0.08733 X 0.08733 0.08733 0 0	
0.08733 0.08733 0.08733 X 0.08733 0 0	
0.08733 0.08733 0.08733 0.08733 X 0 0	
0 0 0 0 0 X 0	
0 0 0 0 0 0 X	
-eM 0.001287 7 X 0 0 0 0 0 0 0 X 0 0 0 0 0 0 X 0 0 0 0	estimated as
0 0 0 X 0 0 0 0 0 0 0 X 0 0 0 0 0 0 0 X 0 0 0 0 0 0 X	final divergence time
	- $1.0 \times 10^{-5}$

## References

- [1] Li, B. and Leal, S. M. (2008). Methods for detecting associations with rare variants for common diseases: application to analysis of sequence data. *The American Journal of Human Genetics* *83*, 311–321.
- [2] Morris, A. P. and Zeggini, E. (2010). An evaluation of statistical approaches to rare variant analysis in genetic association studies. *Genetic Epidemiology* *34*, 188–193.
- [3] Price, A. L., Kryukov, G. V., de Bakker, P. I., Purcell, S. M., Staples, J., Wei, L. J., and Sunyaev, S. R. (2010). Pooled Association Tests for Rare Variants in Exon-Resequencing Studies. *The American Journal of Human Genetics* *86*, 832–838.
- [4] Madsen, B. E. and Browning, S. R. (2009). A groupwise association test for rare mutations using a weighted sum statistic. *PLoS Genetics* *5*, e1000384.
- [5] Bhatia, G., Bansal, V., Harismendy, O., Schork, N. J., Topol, E. J., Frazer, K., and Bafna, V. (2010). A covering method for detecting genetic associations between rare variants and common phenotypes. *PLoS Computational Biology* *6*, e1000954.
- [6] Han, F. and Pan, W. (2010). A Data-Adaptive Sum Test for Disease Association with Multiple Common or Rare Variants. *Human Heredity* *70*, 42–54.
- [7] Hoffmann, T. J., Marini, N. J., Witte, J. S., and Lewin, A. (2010). Comprehensive Approach to Analyzing Rare Genetic Variants. *PloS One* *5*, 124–137.

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<sup>21</sup>Acute Lung Injury (ALI), <sup>22</sup>Atherosclerosis Risk in Communities (ARIC), <sup>23</sup>Cardiovascular Health Study (CHS), <sup>24</sup>Chronic Obstructive Pulmonary Disease (COPDGene), <sup>25</sup>Coronary Artery Risk Development in Young Adults (CARDIA), <sup>26</sup>Cystic Fibrosis (CF), <sup>27</sup>Early Pseudomonas Infection Control (EPIC), <sup>28</sup>Framingham Heart Study (FHS), <sup>29</sup>Jackson Heart Study (JHS), <sup>30</sup>Lung Health Study (LHS), <sup>31</sup>Multi-Ethnic Study of Atherosclerosis (MESA), <sup>32</sup>Pulmonary Arterial Hypertension (PAH), <sup>33</sup>Severe Asthma Research Program (SARP), <sup>34</sup>Women's Health Initiative (WHI)

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[http://www.whiscience.org/publications/WHI\\_investigators\\_shortlist.pdf](http://www.whiscience.org/publications/WHI_investigators_shortlist.pdf)