Supplemental Information

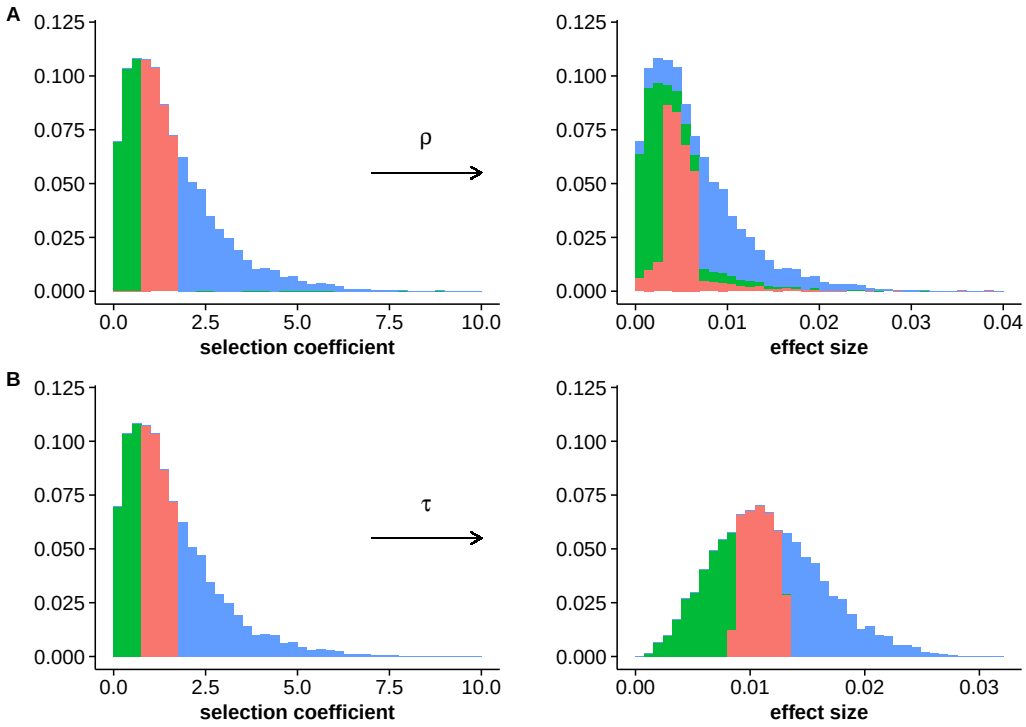

Figure S1: A pictorial representation of our evolutionary model. The left hand panels show a hypothetical distribution of selection coefficients, with weakly deleterious sites colored in green, moderately deleterious sites in red, and strongly deleterious in blue. In the right hand panels, the sites are again colored by selection coefficient, but transformed by either ρ (A) or τ (B) into effect sizes. In (A), the ρ parameter transforms selection coefficients into effect sizes by randomizing the mapping between selection coefficient and effect size, which models pleiotropy (*i.e.*, when $\rho \approx 1$, the majority of weakly deleterious sites also have small effect sizes, but some have large effect sizes). In (B), the τ parameter transforms selection coefficients into effect sizes by altering the shape of the distribution, allowing flexibility with regards to the shape of the effect size distribution.

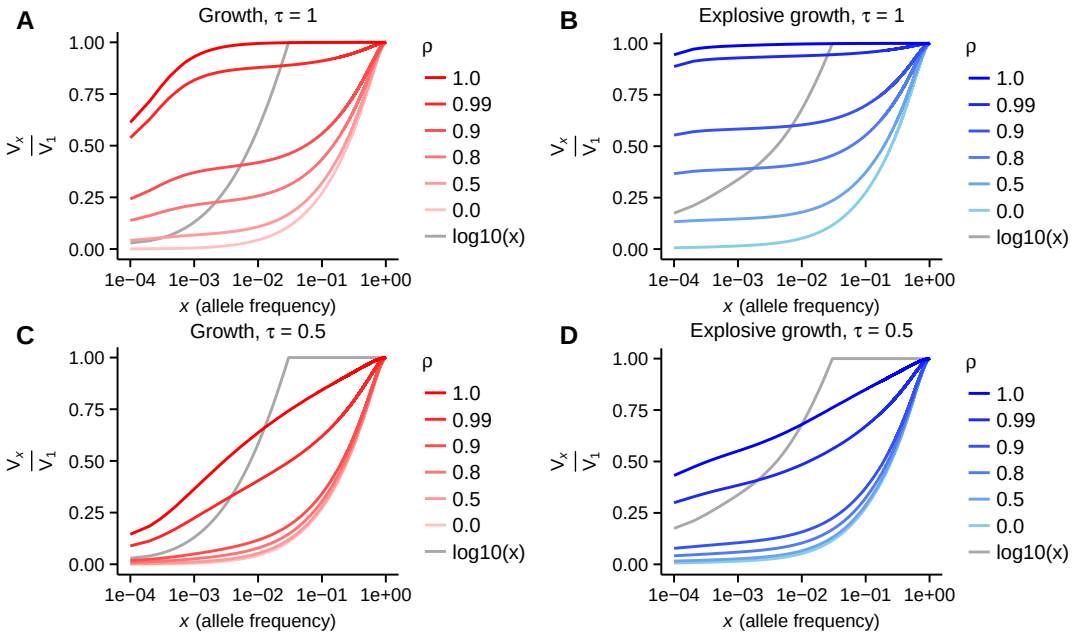

Figure S2: The cumulative proportion of the genetic variance, $^{V_x}/_{V_1}$, explained by variants under allele frequency x for two different models of African demographic history with two different values of τ.

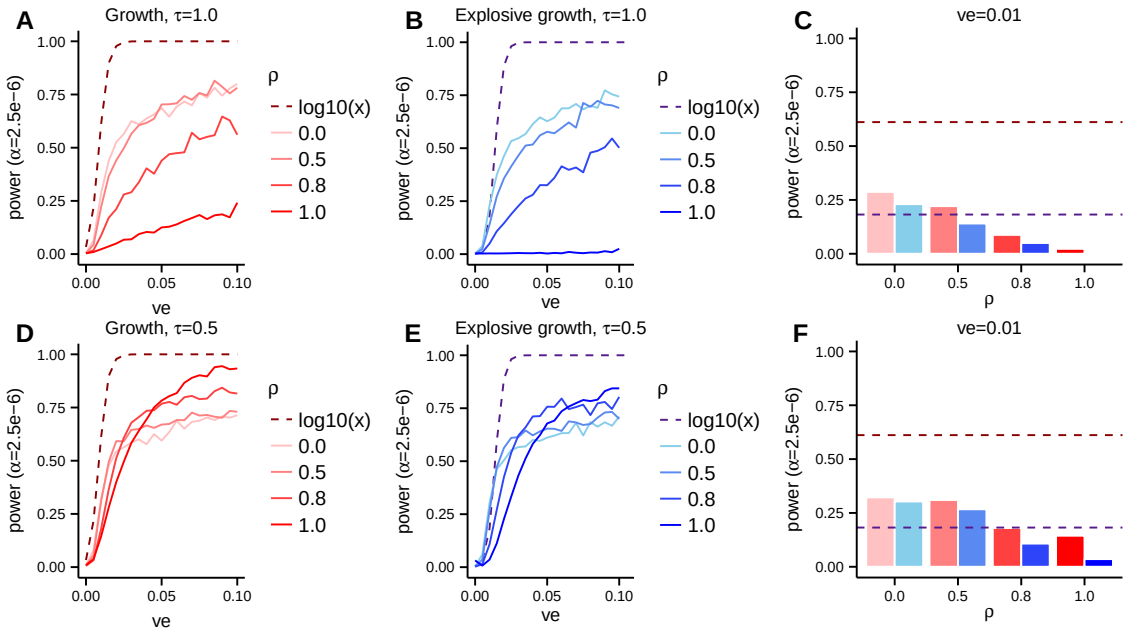

Figure S3: The power of SKAT-O in Africans as a function of the variance explained (ve) by a gene on a phenotype in a sample of size $n = 10^4$ chromosomes under various effect size models. The explosive growth model of Tennessen et al. (2012) is shown in shades of blue, and growth model of Gravel et al. (2011) in shades of red. The dashed lines show the power when the effect sizes are taken to be proportional to $\log_{10}(x)$ for alleles at frequency x, while the solid lines (panels A,B,D,E) and bars (C,F) show results from our phenotype model. Panels C and F aggregate data from the other panels, but specifically for $ve = 0.01$.

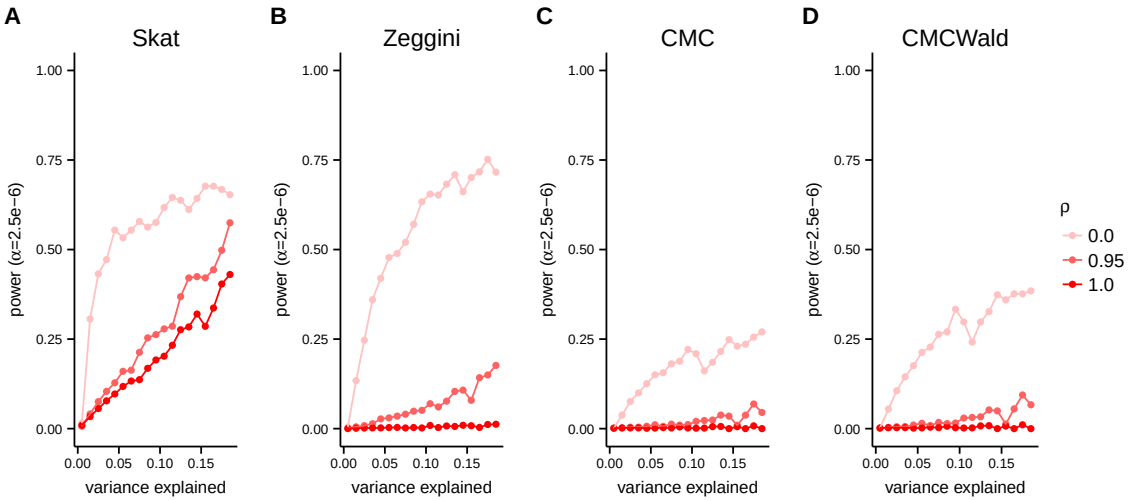

Figure S4: Power as a function of the variance in the phenotype that is explained by the test sequence for four different rare-variant association methods in rvtests (`http://zhanxw.github.io/rvtests/`), in a sample size of $n = 10^4$ European chromosomes. Simulations were performed under the demographic model of Gravel et al. (2011).

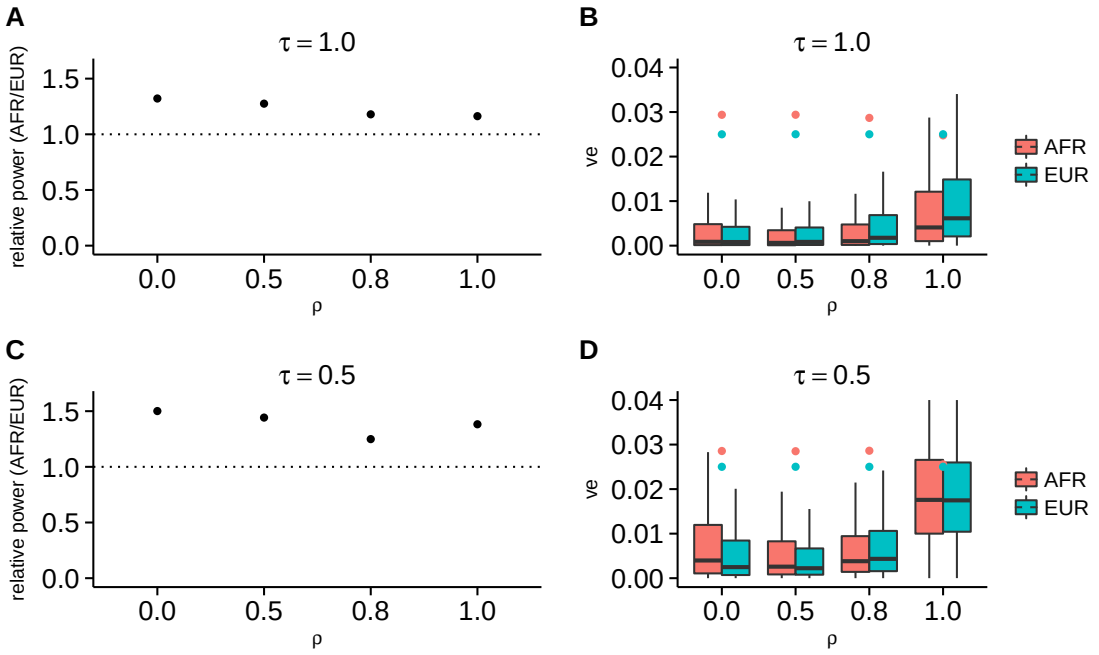

Figure S5: We find higher power in Africans, which is likely to reflect a combination of genetic architecture and increased genetic variance relative to Europeans. Note that in this Figure we have not conditioned on variance explained to compute power, so power differences may reflect a combination of changes in overall heritability and changes in genetic architecture. The points in the right hand panel show the mean variance explained per gene, while the black bar in each box plot shows the median variance explained. Note that we have fixed total variance explained in each simulation at 0.5 in Europeans for 20 genes, so the mean variance explained per gene in Europeans is 0.025 is by definition.

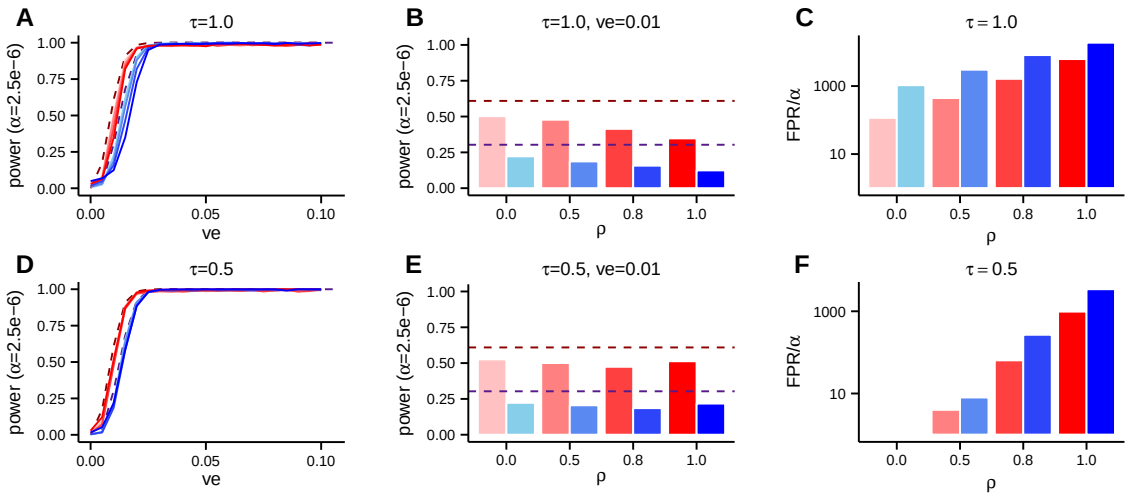

Figure S6: The power and false positive rate of SKAT-O in Africans with the weights of SKAT-O adjusted to $\beta[0.5, 0.5]$, in a sample size of $n = 10^4$ chromosomes. The explosive growth model of Tennessen et al. (2012) is shown in shades of blue, and growth model of Gravel et al. (2011) in shades of red. The dashed lines show the power when the effect sizes are taken to be proportional to $\log_{10}(x)$ for alleles at frequency x, while the solid lines (A,D) and bars (B,E) show results from our phenotype model. Each solid line in A and B corresponds to a different value of ρ (and the same color scheme as in the other panels). Panels B and E aggregate data from A and D, but specifically for variance explained (ve) equal to 0.01. In C and F, we plot the FPR divided by 2.5×10^{-6} (α), which represents the fold increase in the FPR.