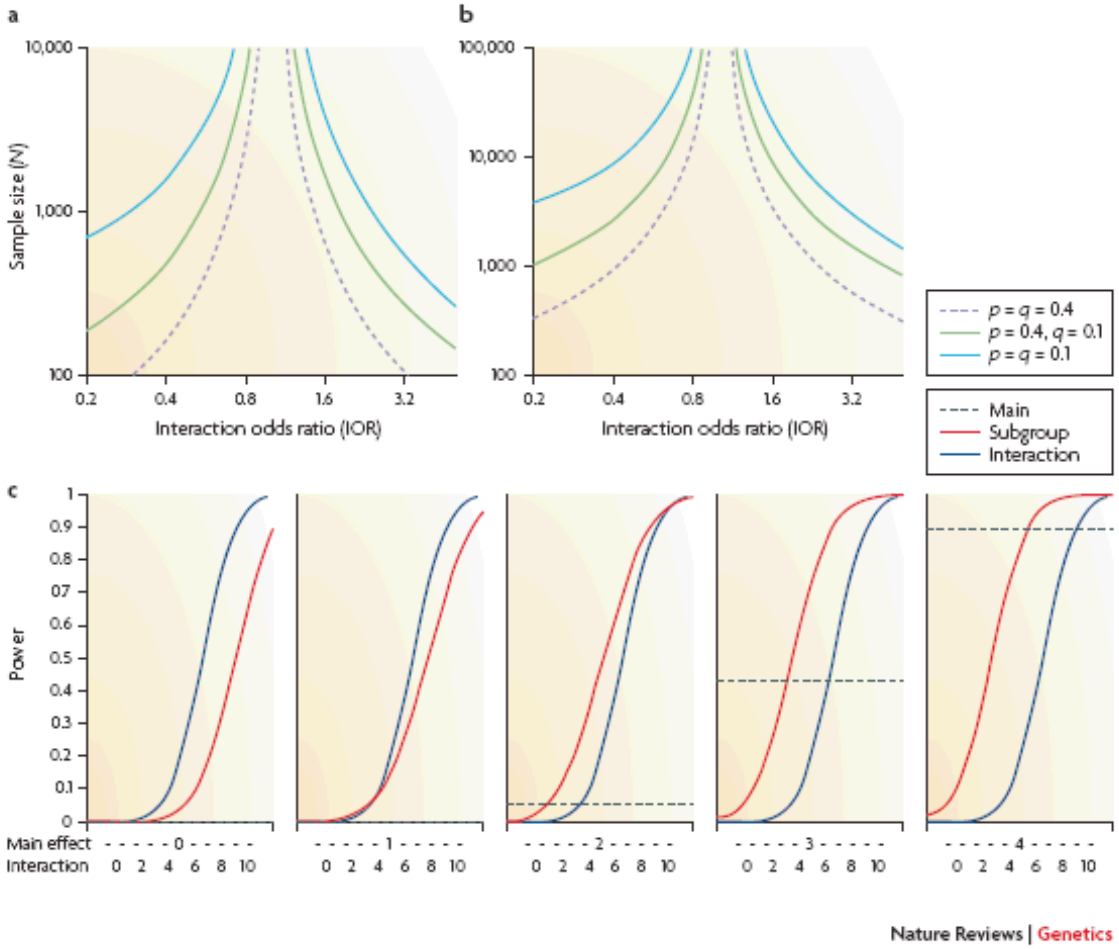

Supplemental Figure 1: Sample size requirements for G×E interactions in candidate gene studies (A) and GWA studies (B,C). In both situations, a case-control design with equal numbers of cases and unrelated controls N, are assumed, varying exposure prevalence p and minor allele frequencies q: dashed, p=q=0.4, q=0.4; dotted (p=0.4, q=0.1) or (p=0.1, q=0.4); solid, p=q=0.1. Panel A is for two-sided significance level $\alpha = 0.05$, panel B for $\alpha = 10^{-7}$; power for both is $1-\beta = 80\%$. Both panels assume a log-additive genetic model with no main effects (calculated using the Quanto program[17]). These panels demonstrate that very large sample sizes are required for detecting modest sized interaction effects, particularly in GWA studies because of the very high significance levels required, Panel C shows the conditional power in a GWA study to detect either a G×E interaction (dotted line) or a genetic effect in either exposure subgroup at significance level $\alpha/2$ (solid line) *given that the main effect* (dashed line) *is not significant*. Each subpanel differs in the noncentrality parameter for the main effect and plots the conditional power as a function of the interaction effect for a fixed p=0.25, q=0.1. The plot demonstrates that there are plausible combinations of main effect and interaction sizes for which the latter would be discoverable even though the former is not. The region where the power to detect interactions in the absence of main effects is greatest in the case of crossing effects (positive in one stratum, negative in the other).