

Description of Additional Supplementary Files

Supplementary Data 1: Polygenic burden comparison (t-test) between simulated cases and controls

A two-sample t-test was used to test if the polygenic burden is higher in cases than in controls (one-sided test). We assumed polygenic genetic architecture and varied other parameters including the heritability due to polygenic burden (h^2_{PB}), the heritability due to large-effect variant (h^2_{LEV}), the minor allele frequency of LEV ($freq_{LEV}$), the prevalence, sample size, and the disease model.

Supplementary Data 2: Summary-statistics and prediction results from the UK Biobank

In columns A-R, we summarized the empirical data from multiple UK Biobank-based sources. Based on the parameters estimated from the UK Biobank, we estimated the utility for observing lower polygenic burden (PB) in large-effect variant (LEV) carriers than non-carriers, among cases (column S). We also estimated the number of LEV carriers per 1000 cases for different PB percentiles (columns T-AM).