

Detailed description of simulations

Deterministic simulation (direct numerical analysis)

For each model we evaluated the probability of disease (g_x) as described in the main paper using direct numerical evaluation, calculating the probability (q_x) of an individual having (or equally the proportion of the population with) $x = 0, 1.. 2n$ risk loci, since $x \sim B(2n, p)$. In the Odds model $\gamma = \tau(1-f_n)/(1-\tau f_n)$.

Stochastic simulation

We use stochastic simulation to allow comparison models on the measures of risk rates in relatives and narrow sense heritability on the risk scale (h_{01}^2). Input parameters are K , n , p and h_L^2 or τ , but based on the results from the deterministic simulation we consider only $n = 1000$ and $p = 0.3$. For the Risch and Odds models we simulate the alleles at each locus for individuals over three generations for $N = 10^6$ families. Alleles of founders are sampled as $B(2, p)$. Each child receives one allele sampled at random from each parent. For each individual the number of risk alleles x is calculated. The probability of disease for the Risch model is: $g_x = f_n \tau^x$, and Odds model: $g_x = K c_n \gamma^x / [1 + K(c_n \gamma^x - 1)]$ with f_n and c_n derived iteratively as in the deterministic simulation. For each individual, we sampled $w \sim U(0,1)$ and if $g > w$, the individual was considered affected, otherwise not affected. The disease status of an MZ twin was calculated in the same way by drawing a second random number from the uniform distribution.

For the Probit model, the input parameters were K and h_L^2 calculated as for the deterministic model and assumed a normal distribution of genetic effects on the underlying liability scale. The results from the deterministic simulations had shown that the results were independent of n and p and the variance contributed by each

locus, but were dependent only on the total variance contributed by all loci, parameterised through h_L^2 . The genetic (u) and phenotypic (y) risk of disease on the liability scale was simulated as $y = u + e$ where $u \sim N(0, h_L^2)$ for founders and $u = \frac{1}{2}u_{dad} + \frac{1}{2}u_{mum} + u_{mend}$ for children where the mendelian segregation term $u_{mend} \sim N(0, \frac{1}{2}h_L^2)$. The environmental effect $e \sim N(0, 1-h_L^2)$. The underlying risk phenotype of an MZ twin was simulated by drawing a new e for an individual. Individuals were considered affected if $y > \Phi^{-1}(1-K) = t$.

From these simulations we could calculate λ_{MZ} , λ_{Sib} , λ_{OP} and the recurrence risk of disease in grandchildren of affected grandparents, λ_{OG} . From these we calculate H_{01}^2 (equation 1) and $h_{01}^2 \approx 4(\lambda_{OG} - 1)K / (1 - K)$ which is an estimate of narrow sense heritability that is less contaminated by non-additive variance than the estimate $2(\lambda_{OP} - 1)K / (1 - K)$. We used the results from the deterministic simulation to check results from the stochastic simulation (the deterministic results are a subset of the stochastic results) and in the Results section we do not distinguish between them.