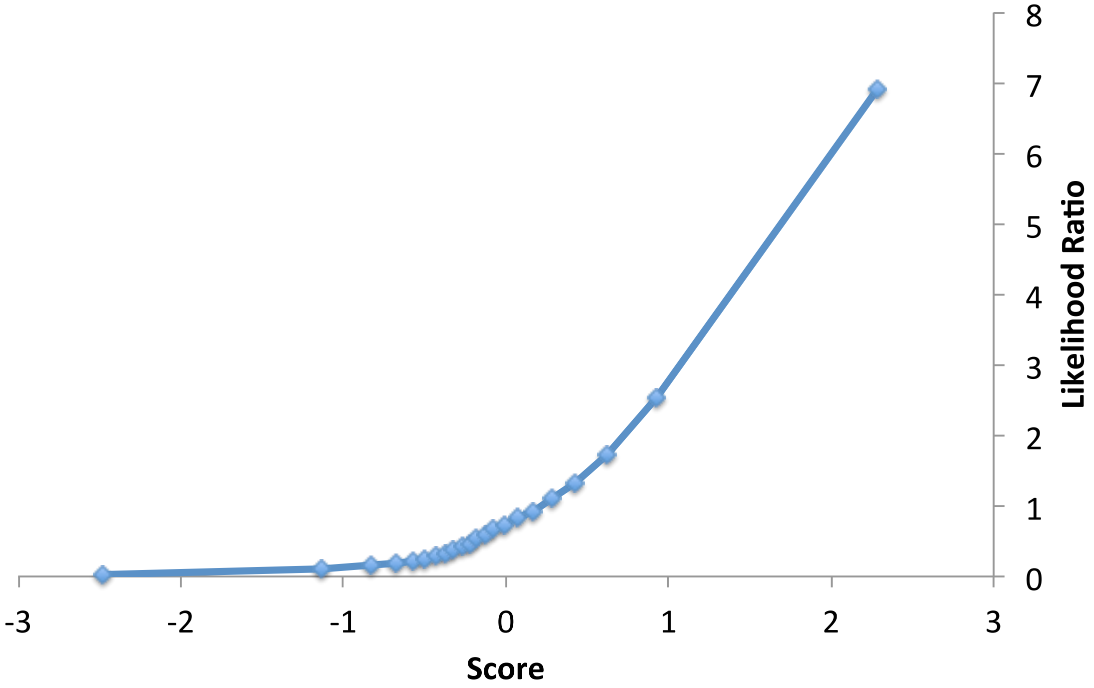
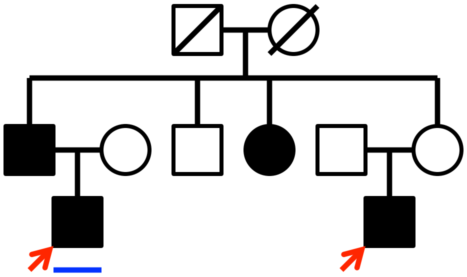


Suppl. Figure S1: Likelihood ratio of the modified InterConnectedness score. The likelihood ratio is calculated as being pathogenic v.s. neutral to the disease of interest. No smoothing algorithm has been applied to this curve, yet the likelihood ratio monotonically and smoothly increases with the modified InterConnectedness score as expected.



Suppl. Figure S2: The pedigree structure used in the simulation of next-generation sequencing studies of complex diseases. Individuals pointed by a red arrow were sequenced and were used in co-segregation analysis. Individual with a blue underscore was used in association analysis.

Suppl. Table S1: Weights for each deleteriousness predictor.

Method	Weight
SiPhy	0.030007
PhyloP	0.123512
GERP	1.27923e-05
FATHMM	0.192933
LRT	0.0327299
MA	0.0989668
MT	0.0418055
SIFT	0.0694245
PP2hvar	0.0737242
PP2hdiv	0.100017
MaxAF	0.236867