

Risk:Non-risk variants	Proportion of risk variants (f)	Number of risk variants per individual (r)	Number of non-risk variants per individual ($v = r/f - r$)	Number of variants per individual ($q = r + v$)
1:5	0.2	0.00498	0.01992	0.0249
1:10	0.1	0.00498	0.04482	0.0498
1:20	0.05	0.00498	0.09462	0.0996
1:50	0.02	0.00498	0.24402	0.249
1:100	0.01	0.00498	0.49302	0.498
1:200	0.005	0.00498	0.99102	0.996
1:500	0.002	0.00498	2.48502	2.49

Supplementary Table 1. Number of variants and proportion of risk variants for *de novo* analysis.

Risk:Non-risk variants	Proportion of risk variants (f)	Number of risk variants per individual (r)	Number of non-risk variants per individual ($v = r/f - r$)	Number of variants per individual ($q = r + v$)	Number of possible functional variants per gene (f_{gene})	Number of possible variants per gene ($s = f_{gene}/f$)
1:5	0.2	0.252	1.008	1.26	123	615
1:10	0.1	0.252	2.268	2.52	123	1230
1:20	0.05	0.252	4.788	5.04	123	2460
1:50	0.02	0.252	12.348	12.6	123	6150
1:100	0.01	0.252	24.948	25.2	123	12300
1:200	0.005	0.252	50.148	50.4	123	24600
1:500	0.002	0.252	125.748	126	123	61500

Supplementary Table 2. Number of variants and proportion of risk variants for case-control analysis.

Risk:Non-risk variants	Number of variants (kbp)	Percent of genome	Approximate equivalent for detecting coding variants
1:0	123	0.004%	PTV in disorder associated genes
1:1	245	0.008%	
1:2	368	0.012%	PTV in loss-of-function intolerant (pLI) genes
1:5	735	0.02%	
1:10	1,348	0.04%	All coding variants in disorder associated genes
1:20	2,573	0.08%	PTV in all genes
1:50	6,248	0.2%	All coding variants in loss-of-function intolerant (pLI) genes
1:100	12,373	0.4%	
1:200	24,623	0.8%	All coding variants in all genes
1:500	61,373	2%	
1:1000	122,623	4%	All variants in evolutionary conserved regions (GERP)
1:2000	245,123	8%	
1:5000	612,623	20%	

Supplementary Table 3. Ratio of risk to non-risk variants and number of variants considered.

Reference Cohort Size (n)	Minimum heterozygote allele frequency ($AF_{het} = 1/2n$)	Minimum homozygote allele frequency ($AF_{homo} = (AF_{het})^2 / 4$)	Example
2,000	2.5×10^{-4}	1.6×10^{-8}	1000 Genomes
5,000	1.0×10^{-4}	2.5×10^{-9}	
20,000	2.5×10^{-5}	1.6×10^{-10}	WGSPD
50,000	1.0×10^{-5}	2.5×10^{-11}	
200,000	2.5×10^{-6}	1.6×10^{-12}	ExAC
500,000	1.0×10^{-6}	2.5×10^{-13}	
2,000,000	2.5×10^{-7}	1.6×10^{-14}	
5,000,000	1.0×10^{-7}	2.5×10^{-15}	
20,000,000	2.5×10^{-8}	1.6×10^{-16}	
50,000,000	1.0×10^{-8}	2.5×10^{-17}	

Supplementary Table 4. Lowest allele frequency distinguishable from a population cohort.