Supplementary Information

Attributable Risk and Exposed Attributable Risk: Relation to heritability

One frequently used concept in risk prediction is Population Attributable Risk (PAR). This is the proportion of the population risk for a disorder that can be attributed to a risk factor. It is not the same as the probability that a person will develop the disorder. If the total population risk of a disorder is 1%, and a polymorphic marker has a PAR of 10%, then 10% of the 1% population risk as attributable to that genetic variation. If all population risk factors were known, the sum of PARs would be 100%. Using standard measures of attributable risk (1, 2), applied to a recently published mega-analysis of 11,977 patients and 51,672 controls (Table 1), the two GWAS SNP markers significantly associated with BD ($p < 5x10^{-8}$) would account for 4.82% of the 1% population risk of illness (3). Between them, these alleles account for 11.87% of the BD PAR (computations per Abrahamson (1)). For SZ, the attributable risks are somewhat higher; all the PARs in the most recent published mega-analysis account for 31.18% of risk of all exposed persons. Once the recent meeting presentation on SZ is published, the PAR may increase only modestly, because the new associated markers have weak effects.

PAR is a function of allele frequency, as is heritability at a given locus, and a rare allele will generally not contribute significantly to either statistic, even though a rare allele can contribute very heavily to the probability that an individual who has the allele will develop disease. In a 2001 article, Risch (4) demonstrated that PAR estimates and heritability estimates can diverge widely on analysis of the same phenotypic data in relatives, in part because of the additive and multifactorial assumptions underlying heritability calculations. He also anticipated the problems that later arose of connecting risk at specific loci to heritability statistics for a disease.

Although we refer to heritability in this paper, the focus is on risk estimates and risk attribution, which are the major questions addressed in counseling. For risk counseling, the Exposed Attributable Risk (EAR) is a very useful statistic: EAR is the proportion of a person's risk of illness that is due to his or her being exposed to a risk factor (in our discussion, having particular genetic marker(s)). It is calculated as

$$\mathrm{EAR} = \frac{\left(P(D) - P(D|\bar{E})\right)}{P\ (D)}$$

Where $\mathrm{P}(D)$ is the probability of disease in the population, and $\mathrm{P}(D|\bar{E})$ is the probability of having the disease for those individuals not exposed to the risk factor.

Bayesian probability of risk of illness given genotype is defined as:

$$P(D|M) = \frac{\left(P(D)\ x\ P(M|D)\right)}{\left(P(D)\ x\ P(M|D)\right)\ +\ \left(1 - P(D)\right)\ x\ P(M|\bar{D})}$$

where $P(D)$ is the probability of the disease in the population (estimated as the observed frequency in the population, 1% for BP and SZ, and 0.6% for Autism). $P(M|D)$ is the probability of an associated SNP or other marker in an individual who has disease (estimated as frequency in cases), and $P(M|\bar{D})$ is the probability of a positive test in an individual not having disease (estimated as frequency of marker in controls). Several major GWAS mega-analyses have been published recently on Bipolar Disorder (5) as well as for Schizophrenia (6, 7), with often overlapping data sources. In this paper, we selected the published papers with the largest aggregated sample size for each disease. The clinician reader of this paper will be repeatedly faced with new reports of genetic associations from mega-analyses of GWAS SNP data, and there are web sites where the reader can do the calculation of this Bayesian probability on new reported associations by entering the frequencies of SNP markers in patients and controls (such as http://psych.fullerton.edu/mbirnbaum/bayes/BayesCalc.htm).

TABLE S1. Attributable Risks for Rare CNVs associated with ASD, SZ or BD

CNV Locus	Type	ASD		SZ		BD	
		EAR	PAR	EAR	PAR	EAR	PAR
1q21.1	deletion			87.7%	0.2%		
	duplication	87.5%	0.2%	76.3%	0.1%		
3q29	deletion			98.4%	0.1%		
7q11.23	duplication	96.7%	0.2%				
15q11.2	deletion			53.2%	0.3%		
15q11.2-13.1	duplication	97.6%	0.5%				
15q13.3	deletion	90.7%	0.2%	90.7%	0.2%		
16p11.2	deletion	89.4%	0.4%				
	duplication	91.5%	0.4%	89.3%	0.3%	74.4%	0.1%
17p12	deletion			82.6%	0.1%		
22q11.21	deletion	97.9%	0.1%	99.5%	0.8%	97.4%	0.1%
22q11.2	duplication	69.5%	0.2%				

EAR: Exposed Attributable Risk in individuals with each rare CNV. PAR: Population Attributable Risk.
EAR and PAR calculations by WINPEPI (1). Data source: Malhotra & Sebat 2012 (8).

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