Risk counselling for family members in bipolar disorder and schizophrenia

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Abstract
In bipolar disorder (BD) and schizophrenia (SZ) rare and de novo chromosomal microdeletions and microduplications (CNVs) have strong effects on risk. For de novo CNVs, the risk of BD or SZ is 10% and for deletions of the q11 region on chromosome 22, the risk of either of these disorders is 77%. A not-insignificant minority of BD and SZ patients have these types of event (4–6.5%). Psychotherapeutic intervention may be needed for within-family stigma and conflicts over genetic test results. These findings also raise ethical issues on stigma prevention, population screening, and abortion based on genotype.

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It is commonly accepted that bipolar disorder (BD) and schizophrenia (SZ) are inherited disorders. For nearly a century, questions on risks within families of patients have been answered by counsellors presenting statistics on the empirically observed risks in large numbers of families. For example, one could tell the well sister of a patient with SZ that the risk of a child of hers developing SZ is 3%, as against a population risk of approximately 1%. Her own risk would be 10% at birth and less according to the proportion of age of risk she has gone through and remained well. Although the actual reported figures vary among studies, these numbers are sufficiently representative for counselling. There were no predictive tests, except that relatives with prodromal features of illness have may be considered at higher risk.

Even after the era of genome-wide association studies (GWAS) began in the past decade and discoveries were reported of common single nuclear polymorphisms (SNPs) associated with SZ and BD, risk prediction has not changed substantially because the associated SNPs are weak predictors. As an example, the most recently published mega-analysis of BD revealed two markers with genome-wide significance (Psychiatric GWAS Consortium Bipolar Disorder Working Group et al. 2011). The risk of illness for a person with either of these markers can be calculated as a straightforward Bayesian probability. The needed data are marker frequencies in patients and in controls as estimates of the probabilities of marker given illness and non-illness, respectively, and the population frequency of illness. The probability of illness given marker is easily calculable, using the Bayesian calculator website if desired (http://psych.fullerton.edu/mbirnbaum/bayes/BayesCalc.htm). For BD, with a population frequency estimated at 1.0%, the risk of BD for persons with either of the two associated markers is approximately 1.1%; the results for associated markers of SZ are comparable. Such modest predictive power is not usable in counselling or in public health planning, and does not raise the ethical challenges of predictable disorders.

In the past decade, however, chromosomal micro-deletions and microduplications (copy number variants; CNVs) have been identified as major drivers of human genetic diversity (Iafrate et al. 2004; Sebat et al. 2004). Furthermore, there are rare recurrent CNVs and de novo CNV events (mutations) that have major effects on risk of BD and SZ. The rate of de novo CNVs is high enough so that these are common events: 4.3% in BD and 6.1% in SZ, vs. 0.9% in the population (Malhotra et al. 2011; Xu et al. 2008). As for risks, based on data reviewed in Malhotra & Sebat (2012), a person with a rare CNV on chromosome 22 (22q11 deletion syndrome) has 26% risk of BD, 68% risk of SZ and additional risks discussed later.

Overall, these events are not rare and can be expected to introduce ethical challenges into the counselling process for the approximately one in 20 BD and SZ patients with de novo or rare associated CNVs and their families. Since these are markers of predictable illness, the challenges include stigma of being a carrier, family context issues of genetic testing, abortion or pre-implantation procedures and population screening for illness susceptibility.

For risk counselling on genetic disorders such as phenylketonuria, there is little familial context because...
most of the counselling is based on population screening. But for the mental disorders BD and SZ, all of the counselling is currently within a family context. In that context, fears of new illness developing, and fears of additional illness stigma within the family and outside the family based on test results, play a large role. In cultures with arranged marriages, the fears and stigmatizing myths of the prospective spouse’s family play an additional role. Another feature that may complicate the situation of a family seeking risk counselling is that BD and SZ typically develop in adolescence and young adulthood and the symptoms of prodromal illness become conflated with the family conflicts that often accompany these developmental stages. Within these contexts, counselling is best considered a form of short-term psychotherapy, rather than straightforward education on statistical risks.

One ethical issue in genetic testing is whether a relative has a right to genetic test results on someone else in the family and a right to ask for or to interfere with genetic tests of another family member. Interference can be motivated by a desire to ‘protect’ relatives from harmful knowledge and stigma (Doukas & Berg, 2001). A separate issue is whether a physician has a duty to warn relatives of their risks (Doukas & Berg, 2001). Conflicts may arise over these issues and further complicate family relationships.

As technology advances, much of this within-family ethical controversy can be avoided by widespread population screening for all known risks. Population screening, however, can lead to discrimination against and stigmatization of entire ethnic groups (Fulda & Lykens, 2006). This is particularly sensitive for disorders of mental function, including BD, SZ and intellectual disability. Ethnic-targeted screening is now ethically questionable and universal screening has been advocated (Grosse et al. 2010). Also, very rare events may occur in only one family; such ‘private mutations’ might not be detectable as related to illness, even if every member of a population received whole genome sequencing. An efficient and ethically acceptable way of genetic evaluation of families with illness is needed; currently, this is often not feasible.

Concerning abortion and without going into the controversies over abortion in general, there are particular ethical issues in aborting a foetus that will have a period of normal life before becoming ill and (separately) in aborting a foetus that may never have any illness. In the mental disorders, the known risks are highest for the rare (1: 4000) chromosome 22q11 deletion (Vassos et al. 2010). If the compounded risk of SZ and BD are considered, the risk is 77% (calculations not shown) and these are not all of the medical risks of this rare deletion. The 22q11 deletion is also known as the velocardiofacial syndrome, because it includes facial deformities, cardiac illnesses, autism, learning difficulties, hearing loss and immune disorders. It would be unusual for someone with the deletion to escape all these disorders. If this chromosomal abnormality is detected prenatally, it may present the most difficult of ethical challenges for the parents. Historically, involuntary sterilization was carried out for the filthiest of reasons by the eugenics movement in the 19th and 20th centuries and murder of the mentally ill was a Nazi programme to improve the Aryan race. This history casts a shadow over what are now personal decisions about abortion.

As whole genome sequencing becomes commonplace, one may anticipate that more rare variants will be discovered with poten risks for BD and SZ. These clearly will present additional challenges for patients and their relatives. There are, as yet, no counterbalancing therapeutic improvements derived from knowledge about these rare variants, or from knowledge about common variants associated with these illnesses.

References


