Genetic counselling for psychiatric disorders

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ABSTRACT

- Family, adoption and twin studies demonstrate that many adult psychiatric disorders, including schizophrenia, major depression and bipolar disorder, have a clear genetic component.
- The aetiology of psychiatric disorders is a complex combination of both genetic and environmental components. While potential susceptibility genes for psychiatric disorders have been identified, interaction with the environment is a crucial component in disease development.
- Pharmacogenetics and genetic testing have the potential to play key roles in the future of clinical psychiatry.
- At present, an increased risk of psychiatric disorders can be identified through a detailed family history. The empirical risk of developing a disorder has been determined for many psychiatric disorders and can be used as a general guide.
- Genetic counselling can extend and enhance patient care by providing information to patients about the complexities of inheriting psychiatric disorders and the associated risks of recurrence.
- The genetic counselling process can facilitate informed decision making, alleviate misconceptions and reduce stigma through an improved understanding of the genetic cause of psychiatric disorders, and offer support to patients and their families.

MJA 2006; 185: 507–510

The number of people affected by mental health problems in Australia is high (an estimated 17.7% of the adult population over a 12-month period) and often their first point of contact is a general practitioner.[1] It is clear from family, twin and adoption studies that genetic factors play an important role in influencing susceptibility to many adult psychiatric disorders. One recent study has found that, while psychiatrists feel that genetic information should be discussed with patients and their families, they do not necessarily feel confident to raise the issue.[2] This finding, combined with the increasing public interest in both mental health and the role of genetics, suggests that referral to and collaboration with genetic services may be a valuable way of augmenting patient care. In this multidisciplinary approach, GPs and psychiatrists provide the expertise for diagnosis and treatment, while genetic counsellors contribute both knowledge of human genetics and skills in risk communication and counselling.[3] Here, we provide an overview of the genetic basis of the major adult psychiatric disorders and examine where current molecular genetic research is leading us. Furthermore, we discuss the potential role of genetic counselling in the care of patients with psychiatric disorders and their families.

The genetic basis of psychiatric disorders

General estimates of heritability — the proportion of phenotypic variance that can be attributed to genetic effects[4] — can be calculated from twin studies. The heritability of psychiatric disorders (Box 1) is high compared with other complex disorders, such as asthma, diabetes and stroke.[16] Importantly, while heritability estimates are high, we also know that environmental factors are critical in determining whether a disorder will develop in a particular individual. For example, the heritability of schizophrenia is estimated to be 82%–85%,[5,6] yet concordance in monozygotic twins is only 40%–48%.[17,18]

The aetiology of psychiatric disorders is complex, with both genetic and environmental components contributing to their development. Our current understanding is that they are polygenic disorders in which multiple genes contribute to susceptibility, and interplay with the environment is crucial. However, a polygenic model may not explain all cases. In some families, a mutation in a single major gene may dramatically increase susceptibility, and single genes may play dominant roles in specific aspects of illness.[19] Moreover, it is thought that different sets of genes may be involved in increasing susceptibility to a particular disorder in various families or populations (genetic heterogeneity).

The search for susceptibility genes for psychiatric disorders

The ongoing search for susceptibility genes has identified promising candidates and homed in on several strong chromosomal linkages for each of the psychiatric disorders. Overall, the results of these studies reflect the complex genetics of these disorders, as potential susceptibility genes have been located on multiple chromosomes, and each disorder has been linked with a number of different candidate genes. Interestingly, some studies suggest an overlap in the genetic aetiology of many psychiatric disorders[19] and challenge the traditional notion that each psychiatric disorder is clinically distinct.

Molecular genetic research is also generating information about how susceptibility genes may interact with the environment. For example, there is mounting evidence to suggest that the risk of depression after multiple adverse life events is associated with variation in the serotonin transporter gene promoter region (5-HTTLPR). First demonstrated by Caspi et al,[20] this association was shown to be reproducible in a number of other studies, including a recent analysis of an Australian cohort.[21] It has also been reported that particular genes can affect a person's response to specific environmental pathogens, such as cannabis.[22] Studies examining the interaction of genetics and the environment have several inherent limitations, and this work will require further replication and analysis.[23,24] Ultimately, these studies not only highlight the complex relationship between genes and the environment, but also suggest why susceptibility genes for psychiatric disorders are not fully penetrant, as environment is such a crucial component in disease development.

Looking to the future

The discovery of susceptibility genes for psychiatric disorders holds the promise of improved understanding of disease, better defined diagnosis, advances in treatment through pharmacogenetics, and the opportunity to assess individuals at risk of these disorders with genetic testing.

Pharmacogenetics in clinical psychiatry

The interaction between genetic factors and therapeutic drugs is commonly referred to as either pharmacogenetics or pharmacogenomics. Generally, "pharmacogenetics" is the term used to describe the study of the genetic basis for individual responses to drugs, while the term "pharmacogenomics" applies more broadly to the study of variability in the genetic basis of disease susceptibility and drug responses at a population level.

Psychiatric pharmacogenetics is a burgeoning area, which constitutes a major arm of current psychiatric research. Ultimately, the goal is to use the patient's genotype to predict both the response to treatment and the development of side effects. Specific genes linked to the efficacy of psychotropic drugs have already been identified; however, these studies still need to be replicated in different populations.[25]

1 Heritability estimates for common psychiatric disorders

Psychiatric disorder	Estimate of heritability
Schizophrenia	82%–85%[5,6]
Bipolar disorder	79%–93%[7-9]
Major depression	33%–48%[10-12]
Obsessive compulsive disorder	26%–47%[13,14]
Panic disorder	44%[15]

2 Empirical risks of developing schizophrenia for relatives of a person with schizophrenia[17,18]

Relationship to person with schizophrenia	Lifetime risk
General population	1%
First-degree relative	
Identical twin	40%–48%
Fraternal twin	10%–17%
Sibling	9%
Parent	6%–13%
Offspring	13%
Second-degree relative	
Aunt/uncle	2%
Niece/nephew	4%
Grandchild	5%
Third-degree relative	
First cousin	2%

Genetic testing

Ideally, genetic testing for psychiatric disorders should facilitate effective treatment and management of illness through early detection and prevention strategies.[26] Genetic testing could also help with decisions about a person's future and family planning. However, due to the crucial role of the environment, a positive test for a given susceptibility gene will not tell us whether a person will develop the disorder, nor the severity of the disorder. As a result, genetic testing may in fact bring greater confusion, uncertainty and psychological stress.[27]

There are also several ethical issues to consider. Questions of ethics in genetic testing most commonly centre on whether there is a clear clinical benefit to be gained from learning one's genetic status. This question is particularly important because the onset of many adult psychiatric disorders commonly occurs during adolescence, and the appropriateness of genetic testing of children must be considered.

Several studies of attitudes towards genetic testing for bipolar disorder or schizophrenia have found positive attitudes and a high hypothetical demand for genetic testing.[26,28-31] Interest in prenatal testing and selective termination of an affected pregnancy was more limited.[26,28,30] These studies indicate that if a genetic test for bipolar disorder or schizophrenia were available, there would be a great demand for genetic testing. However, it is important to keep in mind that the current uptake of presymptomatic genetic testing for Huntington disease is significantly lower than predicted by surveys taken before testing became available.[32]

Genetic counselling for psychiatric disorders

The Human Genetics Society of Australasia defines genetic counselling as "a communication process which involves making or discussing a diagnosis, providing accurate information about the disorder and options available to the client, and considering the impact the information has on clients and their families".[33] Genetic counselling aims to address the individual needs, questions and concerns of the patient in the particular context of his or her family and society. Genetic counselling for psychiatric disorders has advanced alongside the growing field of psychiatric genetics.[3,27,34-36] This is, however, a relatively new discipline, and studies assessing the process and best practice are limited.[36] A single pilot study conducted in the United States suggested that genetic counsellors had some concerns about the depth of their knowledge of research in psychiatric genetics and their understanding of psychiatric diagnosis.[37] These concerns are being addressed, and a number of educational resources have been developed for counsellors (for example, at http://www.nchpeg.org/cdrom/index.html).

The genetic counselling process

It is anticipated that genetic counselling for psychiatric disorders will extend and enhance patient care by informing patients about the disorder, the role of genetics and the impact of environmental factors. Moreover, the genetic counselling process can examine risks of recurrence in a balanced manner, clarify misunderstandings, facilitate informed decision making and offer support to patients and their families. The genetic counsellor is aware of the most appropriate and relevant resources and can facilitate referral to other health professionals or community-based support groups. People who may particularly benefit include those concerned about the genetic risk to themselves or their family members, and couples with a history of psychiatric disorders who are considering having children.

Risks of recurrence

The estimation and discussion of risk is a critical component of the genetic counselling process. An increased risk of psychiatric disorders can be identified through family history information. The empirical risk of developing a disorder has been determined for many psychiatric disorders (Box 2 and Box 3) and can be used as a general guide. The genetic counsellor collects detailed information about family history and constructs a family tree (pedigree), which may be useful in determining an individualised risk estimate. The pedigree may in fact reveal a clear pattern of inheritance. Although rare, some families do exhibit Mendelian-like inheritance patterns.

Age of onset also needs to be taken into account when looking at risk. In many adult psychiatric disorders, early onset of symptoms is thought to be indicative of a more heritable form of the disorder.[38] There is also evidence to suggest that in schizophrenia, a more severe illness could mean relatives are at greater risk of also having the condition.[39] Differences in the development of psychiatric disorders between the sexes should also be taken into account. For

3 Estimated lifetime risks for common adult psychiatric disorders

Psychiatric disorder	General population	First-degree relative
Schizophrenia	1%	5%–16%
Bipolar disorder	1%–5%	4%–18% (BPD) 9%–25% (UPD)
Major depression	5%–35% (females) 5%–15% (males)	10%–25%
Obsessive compulsive disorder	1%–3%	10%
Panic disorder	2%–6%	8%–31%

Adapted from: Finn CT, Smoller JW.[36]
BPD = bipolar disorder; UPD = unipolar depression. ◆

example, depression occurs twice as often in women as in men; while schizophrenia is not only more common in men, but the age of onset differs between men and women (early twenties for men, late twenties for women). Finally, the presence of related psychiatric disorders within a given family may be evidence that the risks to an individual are altered. However, at this stage the specific research data required to calculate an accurate risk are not available.[27]

Different people's perceptions of risk can vary dramatically and it is important that the discussion of risk be presented in an unbiased manner and in a number of different formats. It is also important that the patient understands the limitations of risk estimates.[34] Notably, a survey of patients with bipolar disorder found that they characteristically overestimated the risk of developing bipolar disorder.[40] Similarly, as family members of people with psychiatric disorders have commonly been found to be keen to have genetic testing, it seems likely that they too are overestimating their risk of developing the disorder.[31] This tendency for both patients and their families to overestimate the risks suggests that genetic counselling may help people to frame risks differently.[40]

Emotional responses and implications for the individual and their family

Families with a history of mental health problems may already be confronted with guilt, shame and stigma. An improved understanding of the genetic cause of these disorders may help to decrease these experiences, if the information is presented in a balanced manner.[35] A recent Australian study of families with bipolar disorder found that one of the perceived benefits of genetic testing was that knowing there was a genetic basis for the disorder would decrease stigma within the family and community.[26] Consequently, it seems likely that gaining an understanding of the genetic basis of these disorders through genetic counselling may help many patients and their families cope with the associated stigma.

The opportunities for family members to discuss their experiences and concerns surrounding mental illness are at best infrequent, and genetic counselling may provide a welcome forum.[36] Similarly, support for caregivers can be addressed, and the session may also provide an opening to talk about the importance of family support to the patient, and the strain this can put on family members.

If a patient or family member is at increased risk of a particular disorder, it may be helpful to discuss early signs and symptoms and encourage an early psychiatric assessment. Environmental risk factors and prevention strategies can also be discussed. For example, stress plays a pivotal role in the triggering of psychiatric disorders, and the session could examine the individual's approach to avoiding high stress levels.[35] For some patients, genetic counselling could improve treatment adherence, as the individual gains a better understanding of the biological basis of the disorder.

A genetic counselling session may also address concerns about family planning and provide support for reproductive decisions. This may involve a discussion of the risks to children, the support available and ongoing consequences. There may also be issues specific to family planning and pregnancy; for example, schizophrenia is linked to environmental risks, such as obstetric complications.[41] Ideally, both partners should be included in these discussions and the dialogue should be in the context of their own family, their experience with mental illness, and what having or not having children might mean for them.

Genetic information may be difficult to discuss within families; it may be unfamiliar and complicated. Other family members may react to the information in a negative or angry manner — they may not want to know. Genetic counsellors routinely talk with people about the impact of telling others about the genetic basis of their particular condition, providing some advice about communication and common reactions to expect. Follow-up to the genetic counselling session routinely involves a letter summarising the key points of the session. Providing written information may be especially helpful if the patient was affected and having difficulty concentrating or making decisions during the session. The follow-up letter can be shared with the patient's physician and may be used to provide information for family members.

Conclusions

Genetic factors are crucial in determining susceptibility to psychiatric disorders. Ultimately, research in psychiatric genetics will advance our understanding of psychiatric disorders and present an opportunity for improved treatment and prevention strategies that may encompass genetic testing. At present, an increased risk of psychiatric disorders can be identified through a detailed family history. GPs and psychiatrists can extend and enhance patient care through referral to or interaction with clinical genetic services that provide genetic counselling. From genetic counselling, patients can learn about the complexities of inheriting psychiatric disorders and the associated risks of recurrence. Moreover, the genetic counselling process can facilitate informed decision making and offer support to patients and their families.

Acknowledgements

We thank MaryAnne Aitken and Martin Delatycki for critical review of the manuscript.

Competing interests

None identified.

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(Received 11 Apr 2006, accepted 24 Aug 2006) ❑