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Familial risks and genetic counselling for common psychiatric disorders

Jane Scourfield & Peter McGuffin

The main aim of genetic counselling is to inform about disorders that may have a genetic basis. The following definition is a helpful starting point:

> "Genetic counselling is the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of this disorder, the probability of developing or transmitting it, and of the ways in which this may be prevented or ameliorated" (Harper, 1993).

Within psychiatry an important element of this work is often the correction of mistaken beliefs, for example that all the offspring of a parent with serious mental illness necessarily have the same 'hereditary taint' or that all disorders with a genetic component are necessarily untreatable. There is, of course, no case for advising individuals with a family history of psychiatric disorder not to have children (McGuffin *et al*, 1994*b*).

The assessment of risk in genetic counselling may be derived from three types of information (Murphy & Chase, 1975):

(a) Empirical information, consisting of estimates based on available research data about the recurrence risk of a disorder in various categories of relatives.
(b) Modular information, which depends on a clear understanding of the mode of inheritance of the disorder.
(c) Particular information, which is a compilation of all the data that can be used in assessing the risks to a particular family including, if appropriate, risks based upon DNA testing.

For most psychiatric disorders the specific mode of inheritance is unknown so in general the information given to service users in genetic counselling will be of the empirical type. The empirical data on which risk estimates are based come from family, twin and adoption studies.

The first step in psychiatric genetic research is to examine whether the disorder of interest clusters in families. If this is true, and relatives of affected probands are at increased risk of the disorder, then the observed clustering of cases may reflect shared genes, shared environment or both. The respective roles of genes and environment can be disentangled by twin and adoption studies. Monozygotic twins share 100% of their genes whereas dizygotic twins share on average 50%, like other siblings. If genes have a role in the disorder of interest, then monozygotic twins must be more alike than dizygotic twins. Adoptees share environment but not genes with their adoptive families so by comparing rates of disorder in their biological and adoptive relatives it is possible to estimate the roles of genes and environment.

An important principle of the counselling process is that it aims to be non-directive, helping individuals and families make their own decisions rather than prescribing a particular course. Any psychiatrist seeing patients who wish to discuss genetic issues surrounding psychiatric disease should have in mind the following goals (from Clarke, 1994):

(a) Listening – find out from the service users what their questions are, if they relate to a specific disease or to an individual within the family who is affected with a particular disorder.

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(b) Be sure that an accurate diagnosis has been made and determine a complete and accurate pedigree; this is fundamental to any counselling process if meaningful information is to be exchanged.
(c) Communicate information in a non-directive way appropriate to the service users' level of knowledge. The estimated risk of recurrence needs to be weighed against the burden of the disorder, a difficult measurement to make. Burden may be considered the cost to a family of recurrence of a disorder (Tsuang, 1978) and once the risk:burden ratio is understood it is for the service user to decide how acceptable this is. It is often useful to summarise in writing the main points which have been raised in a genetic counselling session.

Individuals seeking information from genetic counselling are usually relatives who want to know the risk of developing a disorder themselves or the risk to their children. Less commonly, third parties such as legal representatives or professionals involved in adoption may seek advice.

Paradigm of Huntington's disease

For most psychiatric disorders a vulnerability is inherited and it is assumed that environmental stresses are also required for the disorder to become manifest. However, the 'environment' in complex diseases might include random epigenetic or developmental biological processes, such as changes in gene structure or expression, as well as psychosocial or physical adversity (McGuffin *et al*, 1994*a*). There are, to date, no molecular genetic tests which allow certainty in prediction for psychiatric disorders but future developments should lead to greater predictive accuracy. Currently, Huntington's disease provides the best example of the issues surrounding genetic prediction of late-onset diseases although common psychiatric disorders do not show the Mendelian pattern of inheritance seen in Huntington's disease.

Predictive testing for Huntington's disease has been available for several years, making it possible for individuals at risk to find out whether they will develop the disease. This was initially based on linked DNA markers which allowed individuals at high risk (e.g. offspring) to be classified as very high risk (>95%) or very low risk (<5%). However, since the mutation in the Huntington's disease gene has been identified (Huntington's Disease Collaborative Research Group, 1993) those who will or will not develop the disease can be identified with certainty. Individuals taking the tests undergo careful pre- and post-test counselling which has been well evaluated and has resulted in very few adverse reactions (Quaid, 1993; Harper *et al*, 1996). Despite careful assessment and counselling procedures various unforeseen problems have arisen. These include unintentional risk alteration, for example, testing of offspring resulting in parents knowing their own genetic status without wishing to. Inappropriate referral is another problem with some requests for genetic testing having been received without the consent of the individual at risk. Predictive genetic testing is not an innocuous investigation on a par with other laboratory tests because of its wider implications and its effect on relatives. Personal, family, insurance and career prospects are profoundly affected by a positive test result and the decision whether or not to proceed with testing is one for the individual to make for himself or herself. People should not be referred for testing without their knowledge.

Genetic testing of children is another issue raised by Huntington's disease testing programmes. If a child will benefit from the result of a genetic test – for example, if medical treatment will be modified – then the choice is a relatively straightforward one. When predictive tests for an adult-onset disorder are requested in children the results will be of no immediate advantage to the child and, indeed, the child will have lost his or her right to choose not to be tested, as is the case with many adults who prefer not to know their genetic risk status. A child found to be at high risk of a late onset disease will be subject to very different expectations in terms of health, education, career and personal development which may jeopardise personal happiness. There is an international consensus that childhood predictive testing for Huntington's disease is not appropriate and the World Federation of Neurology has advised strongly against it (World Federation of Neurology Research Committee Research Group on Huntington's Disease, 1989). Such issues may be generalised, to some extent, to the future development of predictive genetic tests for other late-onset disorders, such as psychiatric disorders. However, the issues are complicated by the more complex and only partially understood patterns of inheritance.

Risk estimates

In contrast to Huntington's disease where it is possible to provide modular risk estimates for

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patients' relatives and a particular risk once DNA testing has been completed, risk estimates for common psychiatric disorders derive mainly from empirical data based on family studies which examine rates of disorder among various classes of relatives. In genetic counselling for psychiatric disorders it is at present possible only to talk in general terms of risks to relatives and not to estimate precise risks for specific families or individuals.

Schizophrenia

Gottesman (1991) has compiled the data and produced weighted average risk figures from western European studies over six decades that used clinical (rather than operational research-based) criteria. These are summarised in Figure 1 and provide useful risk figures for discussion in genetic counselling.

Siblings and offspring of patients with schizophrenia have about a 10-fold increase in their lifetime risk of developing the disorder compared with the general population, whereas in second-degree relatives (e.g. nephews, nieces, grandchildren) the risk is about 3–4 times the population risk. The risk increases with the number of relatives affected, rising from 9% in a sibling to 16% if a parent and a sibling are affected. Such familial clustering of schizophrenia, while supporting a genetic basis for the disease, does not rule out a shared environmental aetiology. Twin and adoption data provide a method of separating genetic from environmental contributions to the disorder. Meta-analysis of a large number of European twin studies has produced a monozygotic concordance rate of 46% compared with a dizygotic concordance rate of 14%.

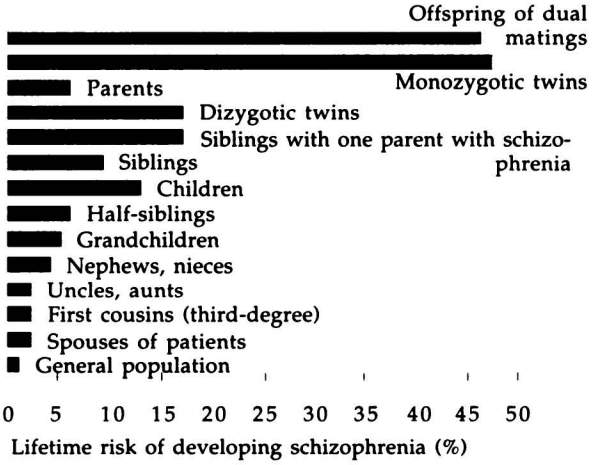

Fig. 1 Average risks for developing schizophrenia, compiled from European studies 1920–1987 (from McGuffin *et al*, 1994*b*)

Such a large monozygotic:dizygotic ratio supports a genetic component in schizophrenia. Further support comes from studies of monozygotic twins reared apart, in whom the concordance rate is 58% (Gottesmann & Shields, 1982). Such twins share genes, but not environment, so any similarity is due to their shared genes. Also, adoption studies have shown that the increased rates of schizophrenia found in the biological relatives of people with schizophrenia are not found in their adoptive relatives or in control adoptees. Both types of study suggest that shared genes rather than shared environment underlie the increased risk of illness in the relatives of people with schizophrenia.

Currently, there is a lot of activity in applying molecular genetic methods of study to schizophrenia, but results so far have not clarified specific genes associated with the disorder. This is not surprising given its non-Mendelian pattern of inheritance and the probable existence of heterogeneous subgroups within the diagnostic category. Nevertheless, promising candidate genes include; the dopamine D_3 receptor gene, a variant of which has been shown to be more often homozygous in people with schizophrenia than control subjects, (Crocq *et al*, 1992); the 5-HT_{2a} receptor gene, one allele of which is more common in people with schizophrenia (Williams *et al*, 1997); and susceptibility loci on chromosomes 22 and 6 which have shown evidence of linkage in several studies (Murphy *et al*, 1996; Cardno *et al*, 1997).

The precise environmental contributors to schizophrenia are not known with certainty and may include random, unavoidable phenomena (McGuffin *et al*, 1994*a*), but it would seem reasonable to warn individuals at increased risk to avoid drugs such as amphetamines which can precipitate psychosis in those predisposed. Using the known empirical risks it is possible to discuss with patients and relatives what their risk is likely to be, given their particular family history.

When considering the potential usefulness of genetic marker tests in common psychiatric disorders one of the problems is that we do not know how the genes involved combine and interact. One simple solution to this difficulty might be available using a type of mathematical reasoning called Bayesian theory. Taking into account an individual's initial risk of disease (called the prior probability), this allows calculation of a modified risk (called the posterior probability) after a genetic test result is known. For example, the risk of developing schizophrenia if a person has a first-degree relative already affected is about 10%. It has been reported that a variant of the serotonin receptor 5-HT_{2a} gene occurs in about 70% of people with schizophrenia, significantly more often than it is

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found in the general population. What would be the risk of developing schizophrenia for someone who already had an affected brother and who tested positive for the serotonin receptor variant? The answer using the Bayesian method is 12.3%, that is, only a little higher than the known empirical risk figure. This information may, therefore, be of only limited use to the individual at risk. Even if a pair of relatives are alike at all the relevant genetic loci it will still not be possible to predict that if one becomes ill, the other will definitely become ill too. We know this because even in identical twins, who share 100% of their genes, the concordance rates for psychiatric disorder are never 100%. However, it is possible to envisage situations where tests of multiple genes could be carried out and the risk altered by much larger amounts.

Affective disorders

There is no doubt that affective disorders tend to run in families. When the categorisation of bipolar disorder (episodes of mania and depression, or rarely of mania alone) and unipolar disorder (depression alone) is used in family studies, results show that more relatives are affected in the families of probands with bipolar disorders than probands with unipolar disorders. Table 1 shows the results of a review of 12 studies (McGuffin & Katz, 1986) which found weighted average morbid risk of severe affective disorder to be 19.2% (7.8% bipolar plus 11.4% unipolar) in the first-degree relatives of probands with a bipolar disorder and 9.7% in the relatives of probands with a unipolar disorder. Compare this with a population risk of severe affective illness requiring in-patient treatment of about 3% for unipolar and 1% for bipolar disorders.

It is worth noting the large range of risks in Table 1. This is probably the result of various definitions of affective disorder used in different studies and reflects the difficulties of defining clear phenotypes for psychiatric disorders. Bearing in mind these difficulties, first-degree relatives of patients with a bipolar disorder can be told that their risk of developing the disorder is about 8%, compared with a population risk of around 1%, while their risk of unipolar depression is about 11%. Similarly, first-degree relatives of patients with unipolar depression can told their risk of unipolar disorder is about 9% while their risk of bipolar disorders is no greater than the population risk.

Twin studies have the advantage of being more robust with regard to the classification problems mentioned above. Whatever the definition of affective disorder used, higher concordance in monozygotic twins is suggestive of genetic effects. Twin studies have not always made a distinction between bipolar and unipolar disorders, nevertheless, monozygotic concordances are consistently higher than dizygotic concordances although the size of the ratio varies. There is some evidence from the size of the concordance ratios that bipolar disorders have a greater genetic influence than unipolar disorders (Bertelsen *et al*, 1977), a result in keeping with the family studies described above.

The role of genetic factors in unipolar depression is less well established. However, rates of unipolar depression are known to be raised in the relatives of probands (Table 1) and studies estimate population rates of DSM–IV (American Psychiatric Association, 1994) major depression in the UK to be about 8.4% for women and 3.5% for men, with heritability (the amount of population variance explained by genes) varying from 0.48 to 0.75 (McGuffin *et al*, 1996). This indicates an important genetic contribution to this form of depression. The role of genes in less severe depression in the blurred boundaries between disorder and normal distress is much less clear and the available evidence is contradictory (McGuffin *et al*, 1994*b*).

Alzheimer's disease

Fifty per cent of cases of severe dementia are due to Alzheimer's disease, 20% to multi-infarct dementia and 20% to mixed Alzheimer's/multi-infarct. The remainder are due to a variety of rarer causes. There is relatively little genetic research into common forms of multi-infarct dementia so the remainder of this section will be confined to a discussion of

Table 1 Affective illness in first-degree relatives of probands with bipolar or unipolar disorder (data from McGuffin & Katz, 1986)

Proband type	No. of studies	Age-corrected number at risk	Relatives Morbid risk % (range) Bipolar	Unipolar
Bipolar disorder	12	3710	7.8 (1.5–17.9)	–
		3648	–	11.4 (0.5–22.4)
Unipolar disorder	7	2319	0.6 (0.3–2.1)	9.1 (5.9–18.4)

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genetic factors in Alzheimer's disease which can be divided into an early-onset, strongly familial type and a more common late-onset type.

Genetic studies of Alzheimer's disease face a number of difficulties; first, there is a lack of clear diagnostic criteria in early studies; second, Alzheimer's disease has a late onset and it can be assumed that many individuals who might be genetically predisposed will die from other causes before developing the disease. Relatives participating in family studies might not yet have developed the disease and these last two points will tend to reduce familial clustering and therefore underestimate genetic contributions. This can be overcome by statistical techniques which adjust for age at onset, but nevertheless surprisingly little is known about the quantitative genetics of Alzheimer's disease. Recent family studies have estimated the risk of dementia in first-degree relatives of probands with Alzheimer's disease to be nearly 50% by age 85–90 years (McGuffin *et al*, 1994*b*). This should not be interpreted, as it has sometimes been, as indicating autosomal dominant inheritance, since 20% of the general population in this age group will also show signs of dementia.

Genes on chromosome 14 (presenilin 1), chromosome 1 (presenilin 2) and chromosome 21 (the amyloid precursor protein or APP gene) have been identified as contributing to early-onset Alzheimer's disease, defined as having an onset before the age of 60 years. Families with genetic mutations associated with early-onset Alzheimer's disease are rare, accounting for less than 5% of cases, but offspring of cases are at 50% risk of expressing the disease if they live long enough. Genetic testing for such families is not generally available, although it has been done in a few specialist centres. The issues surrounding such tests are similar to those in Huntington's disease.

The apolipoprotein ε (Apo ε) gene on chromosome 19 is a 'susceptibility' gene which affects risk and age of onset of Alzheimer's disease and was identified from studies of individuals with late onsets. Three forms of allele are known, ε2, ε3 and ε4, of which the Apo ε4 allele has been shown to have strong association with Alzheimer's disease in late-onset cases. Individuals with two ε4 alleles have a risk of Alzheimer's disease which is increased 16 times. However, the relationship between ε4 and Alzheimer's disease is complex and only 25–40% of subjects with one ε4 allele will develop Alzheimer's disease. Those without the ε4 allele are still at risk of Alzheimer's disease, as about 50% of Alzheimer's disease is not associated with the ε4 allele. The presence of the allele does not allow prediction of the age of onset of Alzheimer's disease for cognitively normal individuals. It does not follow a Mendelian pattern of inheritance and its presence is neither necessary nor sufficient for the development of Alzheimer's disease. In light of these findings the American College of Medical Genetics/American Society of Human Genetics Working Group on Apo ε and Alzheimer's disease has published a consensus statement (1995) to the effect that Apo ε genotyping for diagnostic or predictive testing of Alzheimer's disease is not recommended.

Alcohol dependency

There are many studies showing an increased risk of alcohol dependency in the relatives of people with alcohol dependency, but relatively few meet modern standards of methodological rigour. Studies using standardised diagnoses have shown that more male than female relatives of people with alcohol dependency are affected, as summarised in Table 2. These rates are based on Feighner diagnostic criteria (Reich & Cloninger, 1990) and can be helpful in genetic counselling sessions. However, bear in mind that the Feighner criteria emphasise harm and disability associated with alcohol consumption so may be defining a particular subgroup. Rates are generally similar in relatives of male and female probands, suggesting that the gender of the proband does not have a significant effect.

Table 2 Frequency of alcohol dependency in spouses and first-degree relatives of 300 patients with alcohol dependency(from McGuffin *et al*, 1994*b*; data from Reich & Cloninger, 1990)

	Male probands			Female probands		
	n	% affected	Mean age	*n*	% affected	Mean age
Fathers	80	37.5	54.1	13	38.5	61.2
Mothers	125	20.8	51.2	27	3.7	59.3
Brothers	192	56.8	29.3	36	52.8	36.7
Sisters	196	14.8	31.3	49	20.4	35.3
Sons	28	32.1	23.8	20	50.0	26.3
Daughters	47	19.1	23.1	18	16.7	24.9
Spouses	100	13.0	35.9	25	56.0	41.0

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The extent to which such familial clustering is due to genes or environment has been explored in twin and adoption studies. In summarising the results of twin studies, varying diagnostic criteria (alcohol dependence, misuse or both) have to be taken into account along with the different populations studied. Reported heritabilities have been as low as zero (Gurling *et al*, 1981), but increase to 60% in men and 42% in women when narrow diagnostic criteria requiring alcohol dependence have been used (Pickens *et al*, 1991). A recent twin study found a heritability of 60% for both men and women (Heath *et al*, 1997).

Adoption studies have shown that male adoptees with a biological parent with alcohol dependency are at increased risk of alcohol dependency, as are female adoptees – although one study found that alcohol dependency was increased only in the daughters of women with alcohol dependency (Bohman *et al*, 1981). A further complication in this area is the possibility of subtypes of alcohol dependency, a question which remains unresolved. Cloninger *et al* (1981) proposed two subtypes: Type 1 'milieu-limited' occurs in men and women and is characterised by mild, adult-onset misuse influenced by both genetic and environmental factors; Type 2 'male-limited' is characterised by severe misuse with a teenage onset in men, associated with criminality in their biological fathers, and is strongly influenced by genes. This subdivision is not universally supported. Overall, there is evidence to support a modest genetic contribution to broadly defined alcohol misuse/dependence and a greater genetic contribution to more narrowly defined alcohol dependence. For genetic counselling the empirical risks to relatives in Table 2 can be useful. Alcohol dependency differs from the other common psychiatric disorders discussed above as the aetiology of the environmental component (drinking alcohol) can be completely avoided, something which is seen in the increased rate of total abstention among relatives of people with alcohol dependency.

Conclusions

With regular media attention directed at genetic research the public is increasingly aware of genetic factors in disease and more likely to seek genetic counselling for psychiatric disorders. Practising psychiatrists need to be aware of the available evidence with regard to risk of common psychiatric disorders among different groups of relatives with a positive family history. These risks, where available, have been discussed above and tables presented to summarise data which can be used in discussion with patients. Molecular genetic research in psychiatry is advancing rapidly but with complex patterns of inheritance it is unlikely that any form of genetic testing will be available in the near future. Even if susceptibility genes are reliably detected, which seems likely, they may play only a modest role in risk prediction. This has been discussed in the context of schizophrenia and the recently reported allelic association with a 5-HT_{2a} receptor gene variant. However, based on the empirical data already available it is possible to have informed discussion with patients and their families regarding the risk to different groups of relatives. For most psychiatric disorders an inherited vulnerability is probably insufficient to manifest the disorder without the presence of necessary environmental stresses. Those identified as being at increased risk could be advised, where possible, to avoid environmental stresses to which they would be particularly susceptible. Clearly, threatening life events cannot be avoided by those at increased risk of depression but an individual with a strong family history of schizophrenia could be advised not to experiment with stimulant drugs like amphetamines, LSD or cocaine because these drugs can precipitate psychosis in people who are genetically predisposed. Similarly, the son of a father with alcohol dependency could be advised that he would be more than usually susceptible to moderate drinking becoming immoderate (McGuffin *et al*, 1994*b*).

Huntington's disease testing has shown us that in fact the majority of 'at-risk' adults prefer to live with uncertainty. Despite up to 84% of indivduals at risk having expressed interest in a test prior to its development, the numbers actually coming forward have been much lower than expected (only 9% of those at risk in South Wales; Harper *et al*, 1996). Any genetic testing in complex disorders, such as common psychiatric disorders, could not give the precise predictions possible in Huntington's disease testing programmes, so although there is a perception that individuals who are at risk are thirsty for knowledge, experience to date suggests that those coming forward for testing would be a minority.

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Multiple choice questions

1. The risk of schizophrenia in a first-degree relative of a person with schizophrenia is:
   a 10%
   b 2%
   c 20%
   d 50%.

2. The average risk of severe affective disorder in the relatives of probands with a bipolar disorder is:
   a 40%
   b 19%
   c 5%
   d 2%.

3. The following chromosomes carry genes which cause early-onset familial Alzheimer's disease:
   a chromosome 14
   b chromosome 21
   c chromosome 1
   d chromosome 19.

4. In general, the nature of the information on which genetic counselling for psychiatric disorders is based is:
   a molecular
   b empirical
   c modular
   d particular.

5. A recent twin study found the heritability of alcohol dependency to be:
   a 0%
   b 20%
   c 60%
   d 80%.

MCQ answers

1	2	3	4	5
a T	a F	a T	a F	a F
b F	b T	b T	b T	b F
c F	c F	c T	c F	c T
d F	d F	d F	d F	d F

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