What do genetic studies of mental disorders tell us?
Introduction

3.1 Genetic studies of mental disorders attempt to address the following questions:

- Is there an inherited component to mental disorders? If so, to what extent?
- If genetic influences are important for certain mental disorders, can the specific gene variants involved be identified?
- What are the environmental influences that may be important in explaining these mental disorders?
- How do genetic and environmental influences combine and interact?

3.2 This chapter briefly describes the main approaches being used in genetic research, together with their strengths and weaknesses. It illustrates their application to mental disorders and some of the main conclusions that can be drawn. The techniques are described in more detail in Appendix 1.

3.3 Historically, genetic studies of human characteristics and diseases have involved either families or populations. In general, a person’s genes occur in pairs, one inherited from the mother and one from the father. In turn, one or other of each gene pair is passed down to every offspring. Studies of family histories (or pedigrees) have been used to establish whether or not the pattern of occurrence of a disorder within the family is predictable in terms of the inheritance of a single pair of genes (Mendelian inheritance). Such studies may suggest that a disorder is recessive, dominant, or sex linked. Once such a pattern is established, family linkage studies can be used to identify the gene mutation involved. This involves comparing the DNA of unaffected and affected family members. The aim is to find a region of DNA which differs between affected and unaffected individuals. This might contain a gene mutation which contributes to the development of the disorder. The region is narrowed down and, eventually, the gene isolated and different mutations characterised.

3.4 This procedure is now well established and gene mutations causing Mendelian disorders are rapidly being isolated. The genetic mechanisms vary in different diseases. For example, phenylketonuria is a recessive condition in which both copies of the relevant gene need to occur in a mutated form before the condition develops (Box 3.1). In contrast, Huntington’s disease is a dominant condition; it will develop if only one of the two copies of the person’s gene occurs in the mutated form (Box 3.2).

Variable expressivity

3.5 In some disorders, a single major gene is involved but the effect of the mutation varies in different people in terms of timing of onset, severity and manifestation. This phenomenon is called variable expressivity. It occurs, for example, in tuberous sclerosis, a single gene disease in which some people develop seizures and mental retardation whereas others do not, although they usually exhibit other features of the disorder. The reason why the same mutation may have variable effects in different individuals is poorly understood, although it is generally attributed to interaction with other genetic and environmental factors. For some disorders, such as myotonic dystrophy and Huntington’s disease, the molecular basis of variable expression and penetrance is known to be related to lengths of repeated DNA of varying size (Box 3.2). Even in such cases, there is variable age of onset for a given repeat size, so that it is not possible to define phenotypes solely in terms of the gene mutation. Moreover, mutations in single genes for major disorders may sometimes have no discernible effect, a phenomenon termed ‘non-penetrance’.
3.6 Single gene disorders are, however, relatively rare; few mental disorders show such simple patterns of inheritance and few families are affected by each disorder. Many common mental disorders appear to be more complex. Their development is affected by a number of factors (multifactorial), which may include several genes (oligogenic) or perhaps many genes (polygenic) as well as environmental factors. Consequently, such disorders do not have a simple Mendelian pattern of inheritance. Studies of families, of twins and of people who have been adopted away from their birth families are used to estimate heritability. This is a statistic that estimates how much of the variation within a population for a characteristic can be attributed to the influence of genetic factors rather than the environment (Appendix 1, paragraphs 12–17).

Box 3.1 Phenylketonuria (PKU)

1. Clinical features: if people who are affected eat food containing phenylalanine, a component of most proteins, severe mental handicap results. With rigorous dietary control, development can be normal. This demonstrates two important points: first, that even for conditions in which a mutation in a single gene is sufficient to cause the disease, there can be effective treatments or environmental interventions. Second, that genetic information can be useful for identifying when such interventions are needed.

2. Genetic mechanism: the PKU gene contains the information needed to produce an enzyme that metabolises the nutrient phenylalanine. Everyone has two copies of the PKU gene in their genetic material. If a person has two defective or mutant copies of the PKU gene, phenylalanine cannot be metabolised and substances build up which damage the activity of the central nervous system. PKU affects about 1/10,000 births in the UK and children are screened for the condition at birth (the Guthrie test).

3. The genetic causes and mechanisms of PKU are well understood: two normal genes and you are unaffected, two mutant genes and you have PKU, one of each and you are a carrier - unaffected but with the potential to pass the mutant gene to your children. The way in which PKU is inherited follows a clear pattern known as Mendelian inheritance (after Mendel who described it). Thus, if the genetic make-up of the parents is known, the chances that any children will inherit the condition can be calculated very accurately. Because the effect of a mutant gene is counteracted by a normal gene, PKU is known as a recessively inherited disorder.

4. This example also illustrates another important point – everyone has two copies of the PKU gene but only certain mutant forms of the gene cause the disease.

3.7 If heritability studies suggest that there is a substantial genetic contribution to a complex mental disorder, the next step is to try and identify the specific gene, or genes, that may be involved. The main approaches used are described in Appendix 1. They include association studies on candidate genes and genome searches using pairs of siblings. These techniques are being used in the study of schizophrenia, manic depression, depression, anxiety disorder, obsessive-compulsive disorder and personality disorder. The search for gene variants associated with complex conditions, however, is characterised by many claims but few confirmations. There are several possible explanations for this. For example, such disorders may involve several interacting genes of varying effects, there may be groups of related disorders (paragraph 3.8), and there are likely to be variations in the way different researchers use diagnostic criteria. These
difficulties are further compounded by the particularly complex developmental processes, often including social and environmental influences, which seem to be typical for mental disorders. Despite these problems, genetic research is beginning to increase our understanding of some mental disorders, as described below.

**Box 3.2**

**Huntington's disease**

1. **Clinical features:** progressive degeneration of the central nervous system leading to involuntary movements, loss of motor control and dementia. Symptoms usually begin to appear when people are between 40 and 50, with death occurring 15–20 years later. At present, the disease cannot be prevented, treated or cured. This is a rare disorder affecting about 1/10,000 people in the UK.

2. **Genetic mechanism:** Huntington’s disease is caused by mutations in the Huntington's gene, on chromosome 4. It is a dominantly inherited condition. That is, if one gene has a mutation, even though the other is normal, the person will develop the condition. If one parent has the Huntington's gene mutation, there is a one in two chance that that parent will pass on that gene to his or her child. This means that even though the other parent is unaffected, there is a one in two chance that any child of that relationship will inherit the condition.

3. The mutation is the expansion of a small region of the gene. This region is called a ‘trinucleotide repeat’ (because the expanded region consists of three base pairs or nucleotides). The size of the repeat correlates with the age of onset of the disorder: large numbers of repeats are associated with earlier onset. Sometimes the repeats increase in size from one generation to the next so that the disease gets more severe in successive generations, a phenomenon known as ‘anticipation’.

4. The function of the Huntington's disease gene when not mutated is not understood. The gene contains the information required to make a protein known as ‘huntingtin’. The trinucleotide repeat region of the huntingtin is able to bind other proteins including an enzyme involved in energy production. The extra repeats in the mutant forms of the gene and, in turn, in the huntingtin protein may promote cell death and/or impair energy production, and it has been suggested that this ultimately leads to neurodegeneration.

**Some mental disorders are a cluster of related disorders**

3.8 Genetic studies indicate that some mental disorders may in fact be groups of related disorders. This appears to be the case for Alzheimer's disease (Box 3.3). In certain rare families which show an earlier age of disease onset, gene mutations have been identified that have a major effect and which are inherited in a Mendelian fashion. Although such mutations may account for only a small fraction of the total number of cases of Alzheimer's disease, studying them has been very informative.

Other mental disorders, such as schizophrenia, may also be groups of related disorders with different causes.

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1 Other forms of dementia, with brain pathology distinct from Alzheimer's disease, largely determined by single genetic loci are being found; for example, frontotemporal dementia and parkinsonism linked to chromosome 17 (McKinnon, Fillmore and Freimer N (1998) Mapping genes for psychiatric disorders and behavioural traits, *Current Opinion in Genetics and Development*, 8:287–292).
Box 3.3

Alzheimer’s disease

1 Clinical features: progressive decline in memory, initiative and intellect, leading to generalised dementia and death usually within five years. At post mortem, the brain shows characteristic features under the microscope.

2 Genetic mechanism: research into Alzheimer’s disease reveals that it is a cluster of dementias, involving different genetic mechanisms.

3 About 1% of cases of Alzheimer’s disease show a Mendelian pattern of inheritance and have an early age of onset. These are due to dominant (autosomal) single gene mutations. Either the amyloid precursor protein (APP) gene, the presenilin 1 gene or the presenilin 2 gene may be defective.

4 The majority of cases of Alzheimer’s disease have a later age of onset and do not show an obvious tendency to run in families. A gene has been identified, called the apoE gene, which occurs in different variants (alleles). A person’s likelihood of developing Alzheimer’s disease depends in part on which apoE alleles they possess (E2, E3 or E4). Each individual possesses two apoE alleles in their genetic material. Studies show that there is an elevated risk of Alzheimer’s disease in groups of people who carry one E4 allele and that the risk is even higher in people who carry two E4 alleles. However, E4 alleles are best thought of as normal variants, not mutations of the Mendelian type which are much rarer. In addition, these alleles are much more weakly associated with the disease than the mutations involved in Mendelian disorders. In fact, about 15% of the general population has at least one E4 allele and many do not develop Alzheimer’s disease, whereas perhaps as many as 50% of people who do develop the disorder do not carry an E4 allele. This indicates that other factors are involved: almost certainly other genes and also environmental factors (for example, diet and head injury).

5 Thus the situation with the apoE gene is very unlike that for single gene disorders in two major respects. First, genetic testing offers an approximate estimate of risk rather than a certain answer because it does not take additional, individual risk factors into account. Second, the apoE4 allele that is associated with increased risk occurs at much higher frequency in the population than the very rare single gene mutations.

6 Genetic studies of Alzheimer’s disease have provided new insights into the underlying causes of the disease. Amyloid precursor protein, the product of the APP gene, is converted into beta-amyloid. Beta-amyloid is the main component of the plaques seen in Alzheimer’s disease and mutations of the APP gene lead to increased levels of beta-amyloid. Understanding these processes offers new possibilities for treatment.

Most common mental disorders probably involve variations of several genes

As already mentioned, most common disorders, and this includes physical diseases as well as psychiatric ones, are probably influenced by variants in several or many genes with each individual gene variant having a comparatively small effect. A good example is so-called type 1 diabetes mellitus, the form of diabetes that starts early in life and responds to insulin treatment.
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The risk of the disorder is about fifteen times higher for the brother or sister of an affected child than for the general population. One of the genes involved is on chromosome 6 in a part called the HLA region. Having a particular HLA variant can increase the risk of diabetes by three- or four-fold. Another is a variant of the insulin gene on chromosome 11. This confers roughly a doubled risk. Other genes have also been reported which confer somewhat smaller increases in risk of type 1 diabetes. A pair of affected siblings, therefore, would have to share several 'high risk' gene variants if the sibling recurrence risk of fifteen-fold over normal were to be explained solely by genetic susceptibility.

3.10 One way of looking at disorders like this is to assume that susceptibility (or liability) to a disorder is variable in the population with some having low susceptibility, some having high susceptibility and most people being somewhere in the middle. It is also assumed that susceptibility results from a combination of predisposing genes and environmental risk factors. Only those individuals with a high susceptibility, which at some point exceeds the threshold for becoming ill, actually show the disorder. This type of model accounts for a number of features of common disorders that would be puzzling if we were to try and explain them with a simpler Mendelian model:

- Common conditions may show a broad range of severity, and in some, for example depressive disorder, the milder forms may shade into normal low mood, with no clear boundaries except that, by definition, a disorder tends to result in impairment.
- The gene variants conferring susceptibility are likely to be common in the population. Many people will carry one or more alleles associated with raised risk (for example the apoE4 risk allele for Alzheimer’s disease) but never develop the disorder.
- A disease may seem to ‘appear from nowhere’. That is, a person may develop the condition even though there is no family history. This may be because an individual’s chance inheritance of a high number of susceptibility genes results in the disorder, even though their parents and other family members carry a combination of these genes that is below the threshold for being affected. Alternatively, it may be that some people with a high susceptibility are not exposed to the relevant environmental factors which also affect the development of the mental disorder.

Some genetic influences affect more than one disorder

3.11 Some psychiatric disorders appear to be genetically distinct from one another. For example, there appears to be no genetic overlap (contrary to what was once thought) between schizophrenia and autism. By contrast, depression and anxiety often occur in the same patients and it has recently been inferred from twin studies that there is a considerable overlap between the genetic factors that confer susceptibility to these two sets of symptoms.

3.12 Such findings again point to a continuum of susceptibility underlying mental disorders and suggest that the same genes that contribute to individual differences in normal personality may be relevant to disease. Thus, genetic studies may reveal information about normal traits which, at the extreme, result in a disorder. Again, this is not confined to psychiatric illness but also is

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2 The theoretical models that are most useful in conceptualising this complicated type of inheritance are known as liability-threshold models. Height or weight are good examples of characteristics that show a bell-shaped normal distribution in a population. The idea that a continuum of liability underlies common diseases suggests that these, like characteristics that are more obviously continuous (e.g. height, weight, personality dimensions), can be regarded as quantitative traits (Appendix 1).
relevant to common physical diseases. For example, the level of cholesterol in the blood is a characteristic which varies throughout the population and high levels at the extreme end of the range may contribute to the development of coronary heart disease. In support of this, it has now been firmly established that lowering cholesterol by the use of drugs in subjects with high cholesterol levels significantly reduces their risk of having a heart attack.

3.13 A recent, and still preliminary, example relevant to mental disorder involves the dopamine receptor DRD4. This gene has different forms, depending on how often a particular region is repeated. The most common forms, or alleles, have four repeats (short allele) and seven repeats (long allele). Two studies have shown that the long allele is associated with significantly higher levels of the personality trait of novelty seeking. Novelty seeking is regarded as a normal personality trait, not a disorder. As both alleles occur at high frequencies in the population, the long allele cannot be thought of as a mutant or defective gene. Rather it is a normal variant or polymorphism. Moreover, the association accounts for only 4% of the normal population variation in scores on a novelty seeking questionnaire, so the gene variant has only a very small effect.

3.14 While novelty seeking is a normal personality trait, subsequent studies have found that the association of DRD4 with novelty seeking may also be correlated with susceptibility to several mental disorders. There is preliminary evidence that the long allele is over-represented in samples of people with attention deficit-hyperactivity disorder (ADHD) and is under-represented in people with major depression. Note, however, that these associations are still controversial and, in any case, so weak that they do not allow useful predictions to be made. Table 3.1 gives further examples of genetic variants (alleles) thought to be associated with different disorders or traits.

Table 3.1:
Some examples of genes thought to be associated with different disorders or traits

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alleles</th>
<th>Associated disorder or trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D4 receptor (DRD4)</td>
<td>Long</td>
<td>ADHD</td>
</tr>
<tr>
<td>Serotonin transporter (5-HTT)</td>
<td>Short</td>
<td>Resistant depression</td>
</tr>
<tr>
<td>Serotonin 2a receptor (5-HT2a)</td>
<td>C polymorphism</td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

What do genetic studies of mental disorders tell us about normal behaviour?

3.15 It is apparent from some of the above examples that genetic studies of mental disorders may reveal information about normal traits if the disorders blend into the extreme end of the normal population. This carries an implication that susceptibility genes which predispose to mental disorder may also confer identifiable advantages for the individual. For example, it has been suggested that manic depression (bipolar affective disorder) arises at the extreme end of variation in a trait associated with energy and creativity. This adds a further dimension to the debate about whether it is possible to draw a line between disorders regarded as pathological and legitimate territory for medical interventions and those behaviours within the normal range that are not.

Many mental disorders involve genetic and environmental factors

3.16 Considerable energy continues to be expended on trying to demonstrate that either biological or environmental factors are of prime importance in the development of mental disorders. Some diseases are indeed due largely to one or other of these factors. For example, the eating disorder bulimia nervosa is familial but there appears to be a negligible genetic contribution to bulimia symptoms, suggesting that environmental influences are of prime importance. Conversely, in Huntington’s disease, inheriting the genetic defect is necessary and sufficient for development of the condition. Even for this condition, however, there is considerable variation in severity and age of onset, some of which is likely to be due to environmental factors.

3.17 Epidemiological studies suggest that, for most of the common mental disorders, both genetic and environmental influences are likely to be important. This concept is familiar from studies of familial hypercholesterolaemia, a genetic disorder present in one in 500 individuals that causes high cholesterol in the blood. The extent to which this predisposes to illness (heart attack) is raised if a person smokes, and is lower in women than men because hormonal influences protect women from hardened arteries until after the menopause.

3.18 A drawback of many studies, however, is that they tend to treat genetic and environmental influences as independent factors. But in the more complex mental disorders, genetic and environmental factors interact to a great extent and so are difficult to separate. For example, at first glance, traumatic life events might seem to be environmental occurrences over which individuals have little control. Studies have suggested, however, that genetic differences between individuals affect whether particular events have a traumatic effect. In other words, people differ in their vulnerability to life events. One way of viewing this finding is that genetic susceptibility influences the way in which a person reacts to the environment. In spite of having similar experiences individuals might, or might not, become mentally ill.

3.19 Moreover, the occurrence of events is not always randomly distributed across the population. This has led some to suggest that genetic differences between individuals may affect their behaviour.

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12 Put another way, differences in individual genetic make-up may lead them to experience the same environment differently. For example, it has been suggested that neuroticism is influenced by genetic factors and that neurotic individuals are more susceptible to environmental stress and depression than others.
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and hence the events they experience. Factors often thought of as environmental, including parenting, may also reflect genetic influences. If there is a family history of mental illness, for example, a child’s susceptibility may be influenced by an affected parent in two ways. First, the child may also have an increased genetic risk. But second, the parent’s mental disorder may also produce a more high-risk environment for the child.

3.20 There are important practical implications of evidence that genetic and environmental influences contribute to development in a mutual and interconnected fashion:

- Research studies need to be able to study variation in a number of different genes that are involved in susceptibility to the disease, as well as measuring, with as much accuracy as possible, a number of different environmental risk factors which might be important in contributing to the development of the disease. Measuring such risk factors might be carried out, for example, by detailed questionnaires of life history and lifestyle.

- Even if the genetic influences affecting a disorder are well understood, there is likely to be a degree of variability in the symptoms and outcomes observed.

- Even if the genetic contribution to the development of a disorder is substantial, environmental interventions may still be effective. For example, height is estimated to have a high heritability of 90% but there have been big increases in average height this century due, probably, to improved nutrition. Another example is that of phenylketonuria, in which the consequent neurodevelopmental defects can be overcome by modifying the diet (Box 3.1). This illustrates the point that people with certain single gene disorders can do well if the environment is changed. Thus even strong genetic effects can be environmentally dependent.

In the context of more common mental disorders it has been suggested that genetic influences may increase a person’s vulnerability to environmental risks. An important question, then, is whether these are risks that it will be practical for people to avoid.

Criticisms of the genetic study of mental disorder

3.21 Given the strong evidence for a genetic contribution to many mental disorders (see Appendix 1), the difficulty of identifying specific susceptibility genes came as a surprise to many. Early results, highly publicised, of linkages of schizophrenia to chromosome 5 and bipolar disorder to chromosomes 11 and X, were followed by numerous failures of confirmation in independent samples. Conventional scientific explanations for these problems revolve around issues such as sample size, diagnostic criteria and statistical interpretation.\(^1\)\(^2\) Theoretically, all of these problems can be overcome by collecting more data or employing association studies.

3.22 2 An alternative interpretation is that there is something fundamentally wrong with the methodology of the statistical approach to genetics involving the calculation of heritabilities. It has been argued that the conceptualisation of factors predisposing to illness into two categories - genes and environment - is not a helpful model of biological and social development. Critics have put forward alternative models\(^1\)\(^4\) accommodating multiple interconnections and hierarchical organisation from societies through individuals to cells and their chemical constituents. As Gray

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(1992) states, "the effects of both genetic and environmental differences are contingent on the context in which they occur . . . The impact of an environmental factor will vary depending on the developmental state of the organism and, reciprocally, the effect of a gene being activated will depend on the state of the rest of the developmental system". 14

3.23 As with many other accounts drawing upon a large number and wide range of factors, the construction and testing of such a hypothesis is liable to be complicated. For this reason, some would argue that, while the traditional model is undoubtedly an oversimplification, approaches such as partitioning of variance are undoubtedly useful and similar to the study of human beings in terms of their nervous, cardiovascular and gastrointestinal systems.

3.24 That said, the widely used short-hand of 'genes for' so-called traits such as schizophrenia, intelligence, criminality, or even divorce, by some scientists and some elements of the media, is both inaccurate and unhelpful. Critics argue that speaking of a 'gene for' something suggests a deterministic one-to-one relationship between the gene and the characteristic: between genotype and phenotype. We agree that such oversimplifications have great potential to do harm and are to be discouraged.

Conclusions

3.25 Because of its inaccessibility, the brain is not an easy organ to investigate and our understanding of normal brain function is still quite limited. Therefore it is not surprising that it has been very difficult to study the abnormal function of the brain in mental disorders. One great attraction of a genetic approach (and this is well established in other fields of medicine) is that it allows indirect access to processes that are otherwise difficult to study in living people. Thus genetics allows the possibility of inferring the biochemical and functional abnormalities that lead to disease once the underlying changes in DNA have been identified.

3.26 Despite considerable effort to date, genetic research has so far yielded little practical help in limiting the suffering of those with mental disorder. Almost every susceptibility locus identified for the complex disorders listed in Chapter 1 (paragraph 1.3) is still the subject of scientific controversy. However, the difficulty of reproducibly identifying gene loci in common mental disorders represents a key scientific discovery in its own right. It indicates that disorders such as schizophrenia and manic depression are rarely, if ever, caused by simple dominant or recessive mutations analogous to those in rarer disorders such as Huntington's disease or phenylketonuria. 15 This has important implications for application to clinical practice, as outlined in Chapter 4.

3.27 Methodology for genetic research is progressing rapidly due, in part, to the impact of the Human Genome Project. There seems little doubt that, over the next ten years, susceptibility loci will be identified and some of these will hold up to robust scientific scrutiny. These discoveries will certainly improve understanding of the causes of mental disorder, probably more by small incremental steps than major revolutions. The full potential of these discoveries can only be realised if accompanied by a well-integrated and rigorous research programme covering social, developmental and other biological approaches to the understanding of mental disorder.