Opportunities for psychiatry from genetic findings†

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Background The opportunities for psychiatry deriving from available or likely genetic advances are reviewed.

Method Clinical implications are considered in the context of both the misconceptions and benefits associated with relevant genetic findings.

Results Misconceptions include that: heritability estimates have a 'true' fixed value; a high heritability means that environmental interventions will be ineffective; a high heritability within groups means that environmental conditions that prevail at that particular time, and under heritability apply only to the population studied at that particular time, and under the environmental conditions that prevail at that point. That is not just an academic quibble or caution but is an inherent feature of 'true' fixed value for each trait.

The first misconception is that there is a 'true' figure for the heritability of each trait and disorder that applies generally over time and across populations. That is completely mistaken (Plomin et al, 1997). Estimates of heritability apply only to the population studied at that particular time, and under the environmental conditions that prevail at that point. That is not just an academic quibble or caution but is an inherent feature of what heritabilities mean. They have nothing to say about individuals or fixed features of a disorder. That is, they do not indicate, in any one person, how much of their schizophrenia is genetically determined and how much environmentally determined.
Rather, the heritability estimate indicates, on average, how much of individual variations in the liability to schizophrenia in a particular population at a particular time is due to genetic influences. If circumstances change, the heritabilities will also alter.

The same qualification applies to variations according to when a particular disease or trait is examined. For example, it would make little sense to ask about the heritability of reaching the menopause because all women, if they live long enough, have a menopause. On the other hand, it would make sense to enquire about the extent to which genetic factors play a role in the age at which one reaches the menopause. The same applies to diseases. For example, Alzheimer's disease is infrequent at the age of 70 but it is very common at the age of 90. It is not likely that the role of genetic heritability would be the same at both ages (Blacker et al., 1997), quite apart from the evidence that different genetic factors operate with early onset familial varieties of the disease.

A high heritability means that environmental interventions will be ineffective

A related misconception is that the effects of a genetically determined abnormality cannot be changed by environmental manipulations. Again, that is wrong even with single gene diseases. The example of the inherited metabolic disorder phenylketonuria (PKU) illustrates the point well (Simonoff et al., 1996). The biochemical abnormality, which means that the individual cannot handle the intake of phenylalanine in the diet (a normal substance in all ordinary diets), is indeed fully genetically determined. On the other hand, its effects, in leading to mental retardation, are almost entirely reversible by the simple expedient of keeping the levels of phenylalanine in the diet low. Whether or not the ill effects of genetic mutations can, or cannot, be altered by environmental manipulations entirely depends on how the genes work. With respect to psychiatric disorders, there are good reasons for supposing that many genetic factors operate, at least in part, by creating a vulnerability to environmental risks (Plomin, 1994; Rutter et al., 1997a). That seems to be the case, for example, with respect to both depressive (Kendler et al., 1995a) and antisocial disorders (Cadoret et al., 1995; Bohman, 1996). Accordingly, environmental manipulation may be most beneficial for individuals who have an increased genetic vulnerability.

A high heritability within populations means that differences between populations will also be genetically determined

Another misconception is that when the evidence indicates that a particular characteristic has a strong genetic contribution in two populations, then differences in the mean level of that characteristic between the two populations must be genetically determined. That, too, was the implication of Jensen's 1969 paper and it was wrong (Morton, 1974; Block, 1995). The reasons why populations vary in the mean level of a characteristic may be the same as those causing variations within that population or they may be entirely different (Rutter & Smith, 1995). It is quite invalid to generalise from the findings within one population to assumptions about the reasons for differences between populations.

Genetic effects on disease are unaffected by environmental interventions

A closely related concern is that if there is a strong genetic influence on a behaviour or a disorder, this necessarily requires a denial of free will and of individual responsibility. Clearly, that is not the case. To begin with, no person can be reduced to a mere vehicle of the disorder from which they suffer. Even when the disease is completely genetically determined and associated with
severe disability, as with Down’s syndrome or Huntington’s disease, that does not mean that the disease controls the whole of the individual’s behaviour. That is even more the case with most psychiatric disorders in which the genetic effects are only contributory and operate in indirect ways. It should be added, however, that although we all act on the assumption that we, and others, have free will and individual responsibility, it is an assumption and not a fact open to scientific testing (Glover, 1996). There are good reasons for acting on the basis of that assumption and, if anything, the finding that the vast majority of genetic effects are probabilistic increases the plausibility, rather than detracting from it.

**‘Genetic’ means single abnormal genes**

A misconception abetted by the media is that evidence for genetic influence means that a single abnormal gene is responsible. When evidence is found for genetic influence on a disorder, the media often translates this to headlines about the gene for the disorder. Although there are thousands of rare disorders that show clear patterns of single-gene inheritance, most common medical and psychiatric disorders show no signs of single-gene or even major gene effects. Evidence from many quarters, including animal models, converges on the conclusion that most genetic influence on common and complex disorders involves multiple genes of varying effect size that contribute probabilistically to risk. Moreover, most of these genes are normal variations and not abnormal mutations. The recognition that complex traits involve multiple ‘susceptibility’ genes, often involving variations on normal dimensions such as temperamental features or physiological reactivity, has led to new conceptions of molecular genetic strategies referred to as ‘qualitative trait loci’ (QTL) (Plomin et al., 1994).

A related misconception is that if a susceptibility gene is discovered for some behaviour, then that necessarily ‘medicalises’ it. The discovery of a susceptibility gene has nothing whatsoever to do with medicine per se. There are susceptibility genes for all forms of human behaviour and not just for those that involve diseases. It would be seriously mistaken to equate the discovery of a susceptibility gene with any implication that the gene is pathological or that the behaviour should now be seen in medical terms. It is a very common misunderstanding, but it represents a serious misconception of what is involved in the operation of genetic influences.

**Genes associated with disease must be bad**

A sixth misconception is that the genes associated with disease are necessarily bad and that, once the genes have been discovered, the next step should be to seek to get rid of them. That too is wrong. In the first place, some genes operate protectively, rather than as a risk factor. For example, that applies to the gene in many Asiatic people that causes a flushing response with alcohol and which serves to protect them to a considerable extent against alcoholism (McGue, 1993). Also, however, the same genetically influenced behaviour may serve as a risk factor for some outcomes but a protective factor for others. For example, behavioural inhibition is a risk factor for anxiety disorders (Biederman et al., 1995) but a protective factor against antisocial behaviour (Lahey et al., 1995). In addition, some genetically influenced behaviours may depend on particular environmental circumstances in order for them to lead to disorder. For example, novelty seeking is an indirect risk factor for antisocial behaviour (Cloninger et al., 1996) but it seems likely that this may be a positive trait in some circumstances, although it is a risk factor in others. In other words, genetic factors associated with disease are neither necessarily good nor bad.

**‘Bad’ genes justify both eugenic programmes and termination of pregnancy**

A further misconception is that when a gene that is undoubtedly bad in most of its effects has been found, the next step will ordinarily be to try to remove the gene from the population. That was the rationale behind eugenics programmes in the past. However, the implication, although it may seem logical, is seriously mistaken. To begin with, some genetic anomalies and mutations are not inherited. Thus, that is usually so with Down’s syndrome and about half the cases of tuberous sclerosis (Simonoff et al., 1996). But, more importantly, the rationale is wrong because most genes are not only probabilistic in their effects but also constitute just one of many risk factors. Almost everybody carries risk genes that they do not realise they have got because they have not led to any particular disease. They have not done so either because the individual has only some of the risk genes that are necessary or because the person has not experienced the risk environments that are necessary along with the risk genes. To get rid of risk genes in the population would mean getting rid of most of the world’s population!

The same considerations mean that the discovery of susceptibility genes for mental disorders should not provide the basis for a major expansion of the grounds for termination of pregnancy. Four considerations predominate. First, in the majority of cases, susceptibility genes play only a contributory role in the causative processes. Their presence means that the relative risk for disorder is substantially raised but the absolute probability of the disorder may still be quite small. Second, it is most unlikely to be ethically acceptable to terminate a pregnancy on the basis of a disorder that may leave the person functioning well for much of their life. Thus, for example, for most people, it would not be ethically acceptable to consider termination simply because someone’s risk for having a depressive disorder at some time in their life was increased. The situation is different for lifelong conditions involving major disability (such as severe mental retardation). Third, the genetic liability may lie in a dimensional characteristic on which there is no single point above which the risk arises. Fourth, even when the presence of a mutant gene carries a high level of risk for a major disabling condition, the response may be the development of effective treatments, rather than therapeutic abortion. Thus, the former was the response in the case of PKU.

**Gene therapy will be widely applicable**

Alternatively, there is the possibility of replacing a mutant gene with a normal gene that will correct some basic pathophysiological disturbance. In certain circumstances, gene therapy will prove useful (Birnstiel, 1996), although there are still very considerable practical problems to be overcome if it is to prove clinically feasible and effective (Crystal, 1995). Thus, for example, clinical trials are underway with the monogenic disorder cystic fibrosis (Knowles et al., 1995). It may also have a place in the treatment of some of the single gene disorders associated with severe learning disability (Fletcher, 1995; Moser, 1995). It is much more doubtful, however, whether gene therapy will have any significant place in the treatment of most multifactorial...
psychiatric disorders in which several genes, each of small effect, are implicated. Not only would gene replacement be unlikely to be effective in such a situation, but also genetic findings may well lead to effective (and less heroic) interventions of other kinds. Although it would be wrong to assume that gene therapy could have no place in the treatment of psychiatric disorders, it seems a rather distant prospect of uncertain value.

**Genetic screening**

The last major misconception is that the prime purpose of molecular genetic findings will be the development of genetic screening of the general population. This prospect raises serious ethical issues (Nuffield Council on Bioethics, 1993; Andrews et al, 1994), including the possible misuses for denial of health insurance or for discrimination in employment. Even in the medical arena, there are quite tricky ethical, as well as practical, dilemmas (for example, with respect to screening children for disorders with an onset in adult life, or screening at any age for diseases that are currently untreatable).

In some respects the situation with respect to susceptibility genes for multifactorial disorders is more straightforward in that the predictions at an individual level are so much weaker that, if dealt with rationally, they should be less open to misuse. Nevertheless, in practice, the problems may be greater simply because of the lack of appreciation that this is so. As already discussed, it is likely that virtually everyone in the general population has genes that are involved in the liability to some multifactorial disorder. That is both because some are extremely common (such as short sight or hay fever in the domain of somatic diseases and depression or anxiety in the domain of mental disorders) but it is also because most multifactorial disorders will involve the operation of several susceptibility genes. Sometimes these may be required in combination for the disease or disorder to develop and in other cases a varied assortment of genes may suffice. Either way, all of us will have quite a complex set of varied genetic risk and protective factors. But, most of all, genetic screening in the field of multifactorial disorders cannot have quite the same meaning as with monogenic disorders because the risks are probabilistic and often they may be contingent on the occurrence of some parallel set of environmental risk factors. All of these considerations mean that there are very severe constraints on both the practicality and the utility of genetic screening.

There is one further point that requires emphasis with respect to actuarial predictions based on genetic screening for either insurance purposes or genetic counselling (Masood, 1996). The initial findings on the risks associated with a particular susceptibility gene are likely to stem from unusual samples (chosen deliberately for their advantages in localising genes). Thus, they may derive from families with an unusually heavy concentration of affected members or from clinical samples in which the patients have severe typical disorders. The risks associated with susceptibility genes may be substantially lower in other samples. Also, it is important to bear in mind that the risks may vary by racial group, by environmental circumstances, or by associations with other genes. It is necessary to exercise considerable caution in estimating genetic risks and to appreciate that they are relative, and not absolute.

**THE VALUE OF QUANTITATIVE GENETICS**

Given all these misconceptions, it might be thought that the use of quantitative genetics to determine the relative importance of genetic and environmental influences on particular behaviour or particular diseases has been a waste of time. That is clearly not the case, however. To the contrary, it has been hugely important in at least five different ways.

**Ubiquitous influence of both genes and environment**

The first important finding from quantitative genetics that has a pervasive influence on how we think about the role of genetic factors is that there is a genetic contribution to virtually all complex human traits and behaviours (Plomin et al, 1997). The same evidence, however, also shows that environmental factors are similarly ubiquitous in their effects. Although both conclusions would now be generally accepted by almost everyone, it is necessary to note that it does represent a marked departure from the past in which much time was spent in sorting out behaviours that were supposedly due to nature and those that were supposedly due to nurture. The finding that genetic influences are ubiquitous is, of course, not really a surprise to anyone who approaches the matter from a biological perspective. The workings of the mind have to be based on the functioning of the brain and all human structures and functions exhibit individual variation that is, at least in part, subject to genetic influences. It would be very surprising indeed if human behaviour constituted an exception to this general tendency. There are, however, three very important consequences of this first finding.

First, it is necessary that we get away from thinking that genetic factors apply only to diseases and, instead, take on board the fact that they apply to all aspects of human functioning. Second, it is necessary to appreciate that it is likely that many genetically influenced dimensional characteristics will play a role in the risk for diseases. That is to say, the risks may derive from someone’s level on some perfectly normal dimensional attribute rather than their possession of some abnormal trait. For example, in the field of somatic medicine, cholesterol levels are systematically related to the risk of coronary artery disease at all points on the distribution, and not just at the so-called ‘pathological’ end of the scale (Chen et al, 1991). It is virtually certain that the same will apply to psychological characteristics such as temperamental variations, or reactivity to stress, or cognitive skills (Plomin et al, 1991). Third, genetic influences extend to what seem to be environmental risk factors (Plomin & Berge- man, 1991; Plomin, 1994; Kendler, 1996; Plomin et al, 1997). At first sight that sounds counter-intuitive in that, for obvious reasons, there cannot be DNA in the environment. Nevertheless, the finding is both real and important and it arises in three main ways. To begin with, many measures of the environment rely on people’s perceptions of their experiences. This would be so, for example, with family members’ ratings of discord or warmth or hostility. In so far as such ratings derive from their own attitudes and biases and perceptions, the measures may say more about the people making the ratings than about the events, experiences or circumstances that the measures are meant to reflect. When that is the case, the ‘environmental measure’ is not a measure of the environment at all.

An alternative way in which environments reflect a genetic influence arises from the fact that environments are not randomly distributed (Rutter et al, 1995). Whether or not someone experiences divorce or a breakup of a longstanding friendship, or a lack of
social support, will be in part determined by their own ways of behaving. In this case, the measures truly reflect the environment but individual differences in the likelihood of experiencing those risk environments are influenced, in part, by genetic factors.

The third possibility is that although the environmental risk is real, the main impact arises from its association with genetic risk. For example, many studies have shown that parental mental disorder is accompanied by an increased likelihood of many different sorts of risk experiences (Rutter, 1989). Nevertheless, it remains an important empirical question whether the risks associated with parental mental disorder reflect the risk environments engendered by that disorder or rather a direct passing on of genes.

**Some prevailing diagnostic conventions are mistaken**

Genetic findings have also been important in showing that, not only does the strength of genetic influence vary according to the type of psychiatric disorder, but so also does the degree of diagnosis-specificity. Thus, for example, genetic factors predominate in accounting for population variance in the underlying liability to such psychiatric disorders as autism (Rutter et al., 1997a), schizophrenia (McGuffin et al., 1994), and bipolar affective disorder (McGuffin & Sargeant, 1991), as well as hyperkinetic disorder symptoms (Silberg et al., 1996a,b). In each of these cases, too, there is a degree of diagnostic specificity for the genetic contribution. The strength and relative specificity of the genetic contribution makes these strong candidates for molecular genetic studies. By contrast, there are other psychiatric disorders where the effects seem more indirect and not diagnosis-specific. It is important to appreciate that many genetic factors have quite diverse, pleiotropic effects (Plomin, 1991). For example, the genetic contribution to anxiety disorders and depressive disorders seems to be the same in large part (Kendler et al., 1995a). Possibly, it is mediated, to a considerable extent, through genetic effects on the temperamental characteristic of neuroticism or emotionality. Because this temperamental feature itself shows very substantial heritability, it, too, provides a good candidate for molecular genetic studies.

Twin, adoptee, and family studies have been crucially informative in their indication that some of the prevailing diagnostic assumptions in psychiatry are, at least partially, mistaken. For example, many clinicians have tended to assume that schizophrenia constituted a qualitatively distinct abnormal disease or disorder category that had no continuity with normal variations. Quantitative genetic studies have, however, shown that the genetic liability to schizophrenia also extends to a liability to schizotypal personality disorders and other conditions that are now conceptualised as part of a broader ‘schizophrenic spectrum’ (Kendler et al., 1993, 1995b; Erlenmeyer-Kimling et al., 1995). It remains unclear whether this means that the liability to schizophrenia operates through normal dimensions of personality or whether, by contrast, it is simply that the diagnostic concept needs to be very much broadened, although not extended into normal variations. Exactly comparable issues arise with respect to autism and the extension of the genetic liability to related social and communicative abnormalities occurring in individuals of normal intelligence (Bailey et al., 1996). In much the same way, the genetic liability for oppositional defiant disorder and conduct disorder seems to be the same (Eaves et al., 1997). There is also substantial overlap with the genetic liability for hyperkinetic disorder (Silberg et al., 1996a,b). Although the evidence is not quite perhaps as clear-cut, it has been generally supposed that the genetic liability to Tourette’s syndrome incorporates at least some forms of multiple tics and obsessive-compulsive disorder (Pauls et al., 1991, 1995; Simonoff & Rutter, 1996). Molecular genetic research will obviously take us very much further in understanding the patterning of disorders (see below) but it is already clear that there needs to be something of a rethink on diagnostic conventions and psychiatric classification.

Just as genetic findings have indicated that some disorders are more broadly based than previously appreciated and that some of the finer diagnostic distinctions may not be justifiable, so also genetic findings have indicated that some broadly based psychiatric diagnostic categories may need to be subdivided. For example, it is clear that the genetic contribution to bipolar affective disorder and to the most severe unipolar disorders is very substantial, whereas environmental factors seem to predominate in the liability to the much more common milder varieties of depression (McGuffin & Katz, 1986). Similarly, it is clear that antisocial behaviour includes varieties (such as those associated with hyperactivity) that have a very strong genetic contribution, and varieties (such as the milder forms of antisocial behaviour that so frequently constitute a temporary phase in adolescence) that are largely environmental in origin (Silberg et al., 1996a).

**Genes influence the course of development**

Because all the genes are in place at the time of birth, sometimes it is assumed that all genetic effects must also be operative then. A moment’s thought makes it clear that this cannot be the case. Not only do some genetic diseases (such as Huntington’s) not have an onset until mid-life, but also genetic effects on the timing of maturational transitions such as puberty are strong (see Rutter & Rutter, 1993). Genetic factors play a role, too, in the ups and downs of normal development – that is in the patterning and course of psychological growth (Matheny, 1989, 1990). The effects of genes are dynamic, not static.

The same wrong assumption has led to the expectation that genetic effects should be maximal at birth and decrease progressively thereafter as environmental influences progressively exert their power. In fact, the evidence suggests that the reverse tends to be the case, at least for some traits (Plomin, 1986). This, at first-sight counter-intuitive finding, probably arises through several different mechanisms (Rutter et al., 1997a). For example, genetic effects on the same behaviours as shown at different ages tend to be the same, whereas the environmental effects are often different; as a consequence, there is more opportunity for genetic effects to be cumulative. Also, insofar as genetic effects shape either individual differences in environmental risk exposure or sensitivities to environmental risks (see below) their input will tend to increase over time. This may be relevant, for example, in relation to the rise in depressive disorders in females over the period of adolescence, and to the suggestion that this is associated with an increasing genetic influence (Thapar & McGuffin, 1994).

**The effects of nature and nurture are not separate**

In some respects, one of the most fundamental contributions of quantitative genetics has been the demonstration that nature and nurture are no way near so separate as once used to be assumed (Scarr, 1992; Plomin et al., 1997; Rutter et al., 1997a).
The evidence is clear that there are important, and sometimes quite strong, associations between genetic risks and environmental risks (gene-environment correlations). For example, the forms of parental mental disorder or psychopathology that entail the passing on of genes creating a liability to the same disorders in the offspring, are also ones that are associated with a much increased likelihood of environments carrying psychiatric risk (because of the increased rate of family discord, divorce and separation, impaired parenting, etc.—see Rutter, 1989). Also, people's own characteristics play a substantial role in eliciting particular behaviours in other people (evocative gene-environment correlations). Thus, the work of Patterson (1982) and his colleagues showed the extent to which aversive behaviour by children (which is likely to be genetically influenced to some degree) tends to evoke coercive negative responses from other family members. Also, people's own characteristics will play a substantial role in their selection and shaping of their own environments and experiences (active gene-environment correlations). Finally, some genetic effects operate through rendering individuals more vulnerable than other people to risk environments (gene-environment interactions). These features appear to be particularly important in the field of antisocial behaviour (Rutter, 1997), mild learning disability (Rutter et al., 1996), unipolar depression (Rutter et al., 1997b) and possibly schizophrenia (Tienari et al., 1994). At present, the best data are available on person-environment interplay rather than on the specific role of genetic factors in such interplay. Nevertheless, this body of work has already been important in emphasising various indirect ways in which many genetic factors operate. That necessarily has an impact on how we need to think about genetic risk and on what we do with findings about the importance of genetic factors.

**Environmental effects tend to be person-specific**

Finally, genetic findings have been influential in forcing a major change in the ways in which we have to think about environmental influences (Plomin & Daniels, 1987; Dunn & Plomin, 1990). The key finding is that, in general (but with some important exceptions) most environmental influences tend to serve to make children growing up in the same family different rather than similar in their characteristics. The strong implication is that the study of environmental risk factors needs to pay much more attention to person-specific features than has been the case in the past. That is to say, for example, we need to determine the extent to which family conflict actually impinges on each child in the family rather than relying on global measures of the extent to which the family as a whole is characterised by discord (Reiss et al., 1995; Rutter et al., 1997c). This relative specificity of the impact of environmental risks does not, of course, mean that family-wide risk features (such as discord or divorce or poverty or overcrowding) do not create any significant risk. Rather, what the findings mean is that the extent to which children are embroiled in these family-wide risks shows considerable individual variation; the impact will also be influenced by the ways in which they think and feel about their experiences; the impact may also vary according to their age, gender, or particular environmental risks (as a result of past experiences or constitutional features).

**Implications for the future**

It is sometimes assumed by enthusiasts for the new opportunities of molecular genetics that the field of quantitative genetics is strictly for the past and not for the future. As is explicit in this discussion of the contributions of quantitative genetics, new areas are still being opened up in which quantitative genetics has a lot to offer. It is true that there is now limited scope for studies primarily concerned with quantifying the genetic contribution to yet another human trait or disorder (although there are still some conditions where this information is needed because we know so little). The greatest potential is in terms of the specifics outlined above and, especially, in the various complex mechanisms involved in the interplay between nature and nurture. Molecular genetics will take these matters further forward (see below) but there is still a very considerable need for quantitative genetics and, most particularly, for the integration of quantitative and molecular genetic strategies with epidemiological and developmental perspectives. The crucial qualification that needs to be added, however, is that such research will only fulfil its potential if genetic designs include high quality, discriminating, measures of putative environmental risk factors. That has been a most notable lack in most genetic studies that have been undertaken up to now.

**THE VALUE OF MOLECULAR GENETICS**

Most of the issues raised with respect to quantitative genetics can be tackled better if specific susceptibility genes can be identified (Plomin & Rutter, 1997). The most important contribution of molecular genetics, however, is novel in that it opens the way for a more direct study of causal processes. Because the contribution of molecular genetics to psychiatry is only just beginning to be evident, it is inevitable that this section is more of a promissory note than an account of accomplishments with proven clinical implications. Nevertheless, it is obvious that these are likely to be forthcoming very soon as findings with respect to schizophrenia (Peltonen, 1995), affective disorder (Detera-Wadleigh et al., 1996) and dyslexia (Grigor-enko et al., 1997) all show.

**Elucidation of causal processes: brain systems**

Without doubt, much the most important purpose of molecular genetic research lies in its potential as a crucial step in the understanding of the processes involved in the causation and course of mental disorders. Even with mental disorders where there is good evidence to suppose that there are abnormalities in basic aspects of brain functioning, as would be the case with both schizophrenia (Mednick & Hollister, 1995) and autism (Bailey et al., 1996), biological research up to now has been surprisingly unhelpful in showing the nature of the specific pathophysiology involved in the causation of these conditions. Where these disorders have been shown to have a strong genetic component (as is the case with schizophrenia and autism), there is every reason to suppose that identification of the susceptibility genes will, in time, lead on to a much greater understanding of the basic causal processes. What needs to be understood, however, is that the identification of susceptibility genes marks the beginning of the research endeavour, and not its end. The discovery that a susceptibility gene is located at some particular site on a certain chromosome is of very limited value in its own right. Indeed, given modern technology, it is not unfair to state that finding the gene location is the easy bit (difficult
though it has proved to be in the past). The real challenge is identifying the gene itself, finding out how it works and determining what it actually does in order to bring about the disorder of concern.

The research required to delineate the causal pathway from gene to mental disorder involves several rather different steps spanning quite disparate scientific domains (Lander, 1996). The first step in linkage studies is showing that a particular psychiatric disorder (or behavioural dimension predisposing to it) is connected with a locus on a particular chromosome (Lander & Schork, 1994). Typically, the specified locus includes many genes and the next step of identifying the actual gene responsible involves cloning and sequencing the genes in that region (Antonarakis & Scott, 1996) and identifying associations between specific mutations and the disorder in question. Human research constitutes the main focus in this step but very important leads may be provided by what is known about genes in other species, particularly the mouse whose genome closely parallels that of humans.

The next step of finding the function of the gene product requires experimental approaches with animals. In essence, gene function must be manipulated experimentally by techniques such as inserting, or ‘knocking out’, genes in order to determine what happens when this is done (Capecchi, 1994; Crabbe et al., 1994; Sibilia & Wagner, 1996). There are problems, however, in that the altered gene in the mouse may not result in a recognisable, or even detectable, behavioural picture. Alternatively, the animal model for the disorder being studied may differ from that in the human in key respects. In addition to genetic manipulation, however, there is a need to study protein structure and function directly – a field of science that requires the expertise of biochemists and biophysicists. The need to integrate information across different fields has led to the new field of bioinformatics (the use of computing techniques in the collection, storage and interpretation of biological information). At present we know much more about how to go from gene to protein structure than we do about how to proceed from structure to function, but this last step is a crucial one in the causal pathway.

This research road is a long and difficult one with many problems to be overcome. Nevertheless, what is needed with respect to single gene disorders is relatively straightforward compared with what is required for multifactorial disorders. At present, molecular biology tends to be extremely reductionist, so that the focus is on the elucidation of mechanisms at the molecular level, although it is appreciated that there is a need to understand the structure and function of supermolecular complexes and of protein–protein interactions. With multifactorial disorders, it will also be essential to move on to the role of these proteins in complex systems with multiple interacting components. That is already happening in immunology and metabolic regulation and it will have to happen, too, with behavioural systems.

The research challenge is considerable but it can be met. To begin with, connections with other bodies of knowledge are likely to be very helpful. For example, the apolipoprotein E, which is a gene for cholesterol transport, was discovered to be associated with Alzheimer's disease, so far the only common confirmed genetic risk factor. It was found to be a functional polymorphism and although its mechanism at first seemed to be puzzling, its possible role in the amyloid cascade theory coalesced (Hardy & Higgins, 1992; Hardy & Hutton, 1995).

Moreover, finding this susceptibility gene for Alzheimer's disease has revolutionised research in this field and may well have effects on clinical practice in the future. Nevertheless, it is necessary to be realistic in recognising that sometimes it may take a considerable time to find out just how particular susceptibility genes do work. Progress will be enhanced, by ensuring that genetics is well integrated with other branches of science.

**Elucidation of causal processes: nature—nurture interplay**

Across the range of psychiatric disorders, there will be immense variation in the sorts of causal mechanisms that will have to be considered. With respect to a few conditions, such as schizophrenia and autism, the main focus may well need to be on the persistent abnormal functioning of brain systems. In other cases, by contrast, the focus may need to be much more on the interplay between genes and environment. For example, although it will clearly be useful to know more about the brain mechanisms involved in susceptibility traits such as novelty seeking or emotionality, it is very probable that the risks lie less in what goes on in the brain all the time than in what a particular form of brain functioning does when the person is having to deal with environmental risks of various kinds.

For this reason, it also follows that one of the main gains that will come from identification of susceptibility genes is the much greater power to study both environmental risk mechanisms and the interplay between nature and nurture (Plomin & Rutter, 1997). Thus, for example, quantitative genetic research has been helpful in showing that, even when full account has been taken of genetic risk, there are valid and important associations between environmental risk factors and various types of mental disorder. But research has been much less helpful in the elucidation of how environmental risk mechanisms operate and in determining what the experience of environmental risks does to the organism. In other words, we know little about how the results of environmental risk exposure are carried forward in time through their effects on a person's functioning (whether in terms of neuroendocrine functioning, styles of thinking, or habits of behaviour).

There is the further difficulty that it has proved extremely difficult in practice to separate the effects of deviant behaviour of the child on environmental functioning, from the effects of environmental risks predisposing to the child's disorder. For example, clearly there is likely to be a two-way interplay between family discord and disruptive behaviour in the child but it proved difficult to go beyond that truism to a precise elucidation of how this two-way process actually works in practice. The research into environmental risk mechanisms will be greatly aided by the discovery of the susceptibility genes so that it will be possible to identify the individual risk in advance of the development of the disorder. In this way, the operation over time of environmental risk factors can be studied in a much more satisfactory fashion (Plomin & Rutter, 1997).

In the same sort of way, the study of nature—nurture interplay will be greatly facilitated by identification of susceptibility genes. It is all very well to be able to say that there is a strong genetic component to some form of psychopathology (for example, schizophrenia) but it is quite another thing to be able to assess the particular genetic risk in a given individual. That is what quantitative genetics cannot do, but molecular genetics can. It is obvious, therefore, that the study of gene—environment correlations and interactions will be able to be undertaken directly and meaningfully on a person by
person basis once susceptibility genes have been discovered (Plomin & Rutter, 1997).

**Diagnosis**

Quantitative genetic findings have demonstrated the extent to which the genetic liability for many psychiatric disorders is far from coterminous with the traditional diagnostic boundaries. Thus, for example, it has been shown that some schizotypal personality disorders are associated with the genetic liability for schizophrenia (e.g. Kendler et al., 1993, 1995b; Erlenmeyer-Kimling et al., 1995) and that some social and communicative deficits are associated with the genetic liability for autism (Bailey et al., 1996). But the same research has also indicated that these broader patterns of disorder also include many instances in which the disorder seems completely separate from schizophrenia or autism or whatever psychiatric condition is being considered (Bailey et al., 1996). Molecular genetic findings should be very helpful in sorting out, within this broader pattern of disorder, which individuals do and which do not have the liability to the traditional diagnosis. There is no doubt that that will help immensely in sorting out diagnostic boundaries and patterns in a much more satisfactory way than is possible now. Exactly the same applies with respect to the elucidation of the mechanisms involved in the co-occurrence of two supposedly separate psychiatric conditions – a very common circumstance indeed (Caron & Rutter, 1991). Some psychiatrists undertaking research in the biology of disorders have gone further in their hope that molecular genetic research will lead to diagnostic tests for mental disorders. Nowadays, in somatic medicine, it is usual for there to be laboratory tests to confirm or disconfirm clinical diagnoses. There is no longer a need to rely entirely on patterns of signs and symptoms. Thus, for example, conditions such as diabetes or thyrotoxicosis can be diagnosed precisely as a result of laboratory findings, in a way that is not possible at all at the moment in relation to virtually all forms of psychiatric disorder. Clearly, it would indeed be most useful to have such tests in the field of psychiatry. Nevertheless, a careful consideration of the issues makes it apparent that our expectations in that connection must be quite modest. To begin with, most diagnoses in medicine are based on particular patterns of abnormal physiology or chemistry and not on the identification of a single basic cause. That is because most medical diseases are multifactorial and, therefore, do not have a single basic cause, any more than psychiatric disorders do. Accordingly, the identification of a susceptibility gene will not, in itself, usually lead to a diagnostic test. On the other hand, if such identification leads on to an understanding of the basic abnormal processes within the body that lead to the disorder in question, that could proceed to the development of a useful diagnostic test. Whether or not that takes, place, however, will be dependent, not so much on the identification of the gene, but rather on whether the identification of the gene leads to the hoped-for understanding of the causal processes.

The identification of a gene is much more likely to lead to a diagnostic test in the case of monogenic disorders where the genetic mutation constitutes a necessary and sufficient cause of the underlying disease process (although as discussed above, not necessarily of the disorder itself, as it is shown in the form of behaviour). Even with Mendelian disorders, however, there is the quite important added complication that in many, probably most, cases the same disorder may be due to several different genes or a large number of mutations of the same gene. Such genes are not interchangeable but they provide alternative single gene routes to the disease in question. Thus, for example, it is known that tuberous sclerosis may be due to one or other of two genes and several different genes are involved with fragile X anomaly (Simonoff et al., 1996). In these circumstances, the identification of a known single gene that operates in Mendelian fashion does provide certainty on the diagnosis. The problem comes with what you do with a negative finding. That is, if a person is shown not to have a particular gene, that may simply mean that there is another gene involved in that Mendelian disorder, the nature of which has still be discovered.

With respect to multifactorial disorders, it could still be the case that a genetic factor is a necessary predisposing feature, although not a sufficient one. For example, that could prove to be the case with schizophrenia. Although the genetic component in schizophrenia does not account for all the variance in liability, it has not so far proved possible to identify any environmental risk that leads to schizophrenia in the absence of a genetic liability. It is not that that possibility has been ruled out (see, for example, the findings with respect to risks during pregnancy – McGrath et al., 1995; Wyatt, 1996) but so far, it does appear that in most instances a genetic predisposition is required. In such cases, although the discovery of susceptibility genes will not indicate that the person is certain to develop schizophrenia it could mean that if they do not have any of the susceptibility genes, then the likelihood of their developing schizophrenia is either very low or perhaps even absent. Much more commonly, probably, a multifactorial pattern of causation will involve genetic factors that play a substantial role in susceptibility but that are neither necessary nor sufficient. In that case, there will be an inevitably high proportion of both false negatives and false positives. The information deriving from the identification of susceptibility genes will be of huge help in understanding risk processes and in estimating risks but they will be of quite limited use for the purpose of individual diagnosis.

**Genetic counselling**

At the moment, genetic counselling in the field of psychiatric disorders is quite severely constrained both by the uncertainties over diagnostic boundaries and uncertainties over how genetic factors operate. As already indicated, molecular genetic findings are likely to help in both connections. One specific way in which molecular genetic findings have already been informative is in their identification of novel, hitherto unappreciated, genetic mechanisms. One of the puzzles in the family findings with respect to the fragile X anomaly was that the pattern did not seem to follow any of the known modes of genetic transmission (Simonoff et al., 1996). There was also appreciation that carriers of the gene sometimes themselves had milder disabilities of one kind or another and it was not clear quite what that meant. The discovery that the basis of the fragile X anomaly lay in a much expanded set of trinucleotide repeat sequences, that a lesser degree of expansion occurred in the preceding generation, and that the transmission of the genetic anomaly across generations led to the expansion solved the riddle. Since then, several other neuropsychiatric disorders, including Huntington's disease, have been found to have somewhat similar expanding sequences (Petronis & Kennedy, 1995). The ways in which this works differ somewhat in detail among the various disorders but the findings are already of considerable help in genetic counselling. The discovery of so-called
that manipulation of trait levels through drugs would be the treatment of choice. Instead, the focus may be on the interactions with environmental risks. Also, drugs that affect key processes may carry with them serious undesirable side-effects. For example, there are many drugs that have been shown to be effective in the reduction of anxiety but the risks of dependence on those drugs has meant that their utility is substantially constrained and long-term treatment involves quite major risks (Petursson & Lader, 1984).

There are also quite tricky issues involved when a pharmacological approach is the treatment of choice. For example, the stimulant drug methylphenidate has been shown to be effective in improving attention in normal individuals, and in those with other psychiatric disorders as well as in children who show the specific seriously disabling syndrome of hyperkinetic disorder (Taylor, 1994). But that does not necessarily mean that it would be sensible and appropriate to put everyone on this drug because it improves their attention to some small degree. Similarly, although it appears that selective serotonin reuptake inhibitors have beneficial effects across a wide span of affective disorders, it does not mean that everyone should take such drugs on the grounds that everyone feels depressed sometimes (although that has been suggested – Kramer, 1994). In summary, an understanding of causal processes brought about by molecular genetic advances will be helpful in the development of new pharmacological treatments but this will be so in only some cases.

**Conclusions**

It is evident that advances in genetics will make a major impact on clinical psychiatry and that there are several ways in which the practical benefits should be very considerable. Most especially, these apply to the implications for improved prevention and treatment that should stem from a better understanding of the causal processes involved. The relevant causal mechanisms need to be considered in relation to both the functioning of brain systems and the interplay between nature and nurture as played out in people’s social lives. In addition, there should be real gains with respect to diagnosis, genetic counselling and the development of improved pharmacological treatments. However, what molecular genetics should not bring about is either biological determinism or the ‘medicalisation’ of either normal variations in behaviour or maladaptive responses to psychosocial stress or adversity. Any appreciation of the real benefits and opportunities that will derive from genetic advances requires a recognition of the numerous misconceptions and false hopes associated with genetic findings.

**REFERENCES**


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(First received 9 January 1997, final revision 14 April 1997, accepted 16 April 1997)
Opportunities for psychiatry from genetic findings.
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Access the most recent version at DOI: 10.1192/bjp.171.3.209

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