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Review Article

The Genetics of Personality Disorder

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Most measurable aspects of normal personality appear to be at least moderately heritable, with direct evidence coming from family, twin and adoption studies and indirect support deriving from psychophysiological research and breeding experiments on animals. Interestingly, genetic studies also shed light on the environmental sources of variation in personality and suggest that shared family environment rarely, if ever, has any positive effect on similarity between relatives. Despite problems of classification, and variations in the use of terms, a survey of the literature provides reasonably consistent evidence of a genetic contribution to several categories of abnormal personality, which we here divide into three groups, antisocial, anxious/avoidant, and schizoid–schizotypal personalities. However, personality disorders are complex traits that do not show simple mendelian patterns of inheritance and so far molecular genetics has been of no help in understanding their aetiology. Fortunately, techniques are now becoming available that enable the detection and potential localisation of genes of small effect and which may help elucidate the molecular basis even of (probably) polygenic traits such as abnormal personality.

Psychopathy, a term usually reserved in the English-speaking world for the most deviant types of personality, is an elusive concept (Lewis, 1974) and it follows that lesser degrees of abnormal personality tend to be even more difficult to define and to measure reliably. This does not present a promising state of affairs for genetic research, since of all the biological sciences, genetics is perhaps the one which depends most heavily on dealing with characters, or phenotypes, which are unequivocally recognisable and which tend to be stable and enduring in a variety of circumstances (Penrose, 1971). Nevertheless, a considerable amount of energy has been expended in attempts to explore the genetic basis of certain personality disorders, particularly those where antisocial behaviour is a prominent feature. Indeed, genetic research has in recent years gone far beyond concern just with antisocial personality and at least one widely accepted category, schizotypal personality disorder, exists almost entirely as a result of genetically orientated research.

Traditionally, psychiatric thinking on personality disorder has been concerned with various (presumed) diagnostic entities and this is still clearly reflected in current classifications such as DSM-III-R (American Psychiatric Association, 1987) and ICD-9 (World Health Organization, 1978). However, much of the dissatisfaction with the concept of psychopathy and other personality deviations stems from the recognition that few patients judged clinically to have abnormal personalities fit neatly into any of the conventional categories but rather have a repertoire of repeated behaviours which differ in some quantitative sense from the clinician's view of the average or 'normal'.

Furthermore, many individuals are encountered who do not warrant a diagnosis of personality disorder but who do have certain exaggerated traits which may or may not be maladaptive. Against this background it is necessary for the genetic researcher to consider a quantitative approach to the assessment of personality and to consider what contribution genes may make to personality variation within the normal range. We will therefore begin by briefly reviewing research into the genetic basis of personality before going on to discuss what is currently known about hereditary influences on personality disorder.

The genetics of personality

The evidence that there is a genetic contribution to individual differences in personality comes from three main sources. The first two are indirect, comprising animal studies of temperamental attributes which might be akin to human personality traits, and studies of individual differences in psychophysiological measures which could possibly reflect the 'biological substrate' of personality. The third approach depends on attempts to measure personality directly with questionnaires usually of the 'paper and pencil' type, and to assess the resemblance in relatives reared together, relatives who have been separated, and in pairs of monozygotic (MZ) and dizygotic (DZ) twins.

Animal studies

Long before anything was known of the science of genetics, animal breeders carried out artificial selection for desirable attributes and although it was

probably never explored in a systematic way, temperamental qualities were among those thought to be inherited. This makes sense to anyone familiar with the obvious variations in aggressiveness or sociability among various breeds of dogs. However, the problem about the systematic study of animal behaviour is that it can only be measured by observer ratings and in most respects the behaviour is simpler and the repertoire more limited than the sorts of measures we usually consider in relation to human personality.

One of the best known models is provided by the Maudsley reactive (MR) and non-reactive (MNR) strains of rats which were selected first to provide a means of studying 'emotionality' (Wimer & Wimer, 1985). Selection was based on the open-field test in which rats were placed in a brightly lit enclosure and where frequency of defaecation was taken as a measure of emotionality. Although there has been debate about the validity of this simple measure and whether it really provides a useful comparison with more complex human manifestations of emotion, it does have the virtue of being simple and easily quantified. The underlying principle of studying inbred strains is that after many generations (at least 20) of brother-sister matings, heterozygosity is eliminated and strains of animals are produced which are virtually genetically identical. Inbreeding experiments are more costly and time-consuming in larger mammals but intriguing observations have been made with certain strains of dog, most notably so-called 'nervous' pointers (Reese, 1979). These show normal activity in the presence of other dogs but become timid and fearful when approached by man, showing immobility and freezing. Nervous pointers are poor at operant conditioning and show low heart rates. Various other physiological and pharmacological response characteristics have been studied and are summarised by Wimer & Wimer (1985). A very useful recent summary of animal models of fearfulness has also been provided by Marks (1986).

Psychophysiological studies

It has long been suggested that psychophysiological characteristics might reflect the central and autonomic nervous system substrata upon which personality is based. There is much evidence that psychophysiological characteristics are partly genetically determined. One classic study was quite striking in demonstrating the importance of genetic factors in resting encephalographic (EEG) patterns so that blind raters of EEG tracings were able to distinguish zygosity in twin pairs with a high degree of accuracy (Lennox *et al*, 1945). Furthermore, EEG similarities persist in MZ twins who have been reared apart (Juel-Neilsen & Harvald, 1958). By contrast, auditory or visual evoked responses appear to have only a modest heritability (Lewis *et al*, 1972) and correlations in alpha blocking have not been found to be significantly greater in MZ than in DZ pairs (Young *et al*, 1971). Regarding peripheral measures, twin studies suggest that habituation of the galvanic skin response (GSR) and spontaneous fluctuations in GSR and pulse rate are to a large extent genetically determined (Lader & Wing, 1966; Hume, 1973).

More recent studies of psychophysiological trait measures have focused on their possible relevance to abnormal personalities and to psychopathology. In particular, it has been suggested that abnormalities of smooth pursuit eye movements characterise patients with schizophrenia and a proportion of their relatives. It has therefore been proposed that a dysfunction in 'eye tracking' might be a genetically influenced marker of schizotypy or vulnerability to schizophrenia (Iacono & Koenig, 1983). Certainly there is evidence from twin research of a genetic influence on variations in eye tracking (Iacono, 1982), but a recent claim that a single dominant gene can account for both eye-tracking dysfunctions and the inheritance of schizophrenia (Holzman *et al*, 1988) seems to be an oversimplification of a complex problem (McGue & Gottesman, 1990).

Personality questionnaire studies

Virtually all studies which have been based on questionnaire measures of personality agree in finding evidence of a genetic effect (Loehlin *et al*, 1988; Plomin, 1990). However, one area of some dispute is whether there is a modest but significant genetic contribution for all traits (Loehlin & Nichols, 1976), or whether there is a differential heritability of various aspects of personality. Among some of the earlier studies on twins there was fairly good agreement using the Minnesota Multiphasic Personality Inventory (MMPI) that the scales measuring social introversion, depression, psychopathic deviance and schizophrenic-like traits were heritable but there was poor agreement across studies relating to other traits (Gottesman, 1963, 1965; Reznikoff & Honeyman, 1967). Some inconsistencies may have stemmed from sampling errors and sampling bias. There is little doubt that large-scale twin studies depending on volunteers usually attract an excess of pairs who are monozygotic and female. A reanalysis of earlier twin studies using the California Psychological Inventory showed that MZ correlations were consistent across studies despite the fact that DZ correlations and MZ/DZ differences were less easy to replicate (Carey *et al*, 1978).

Recent studies of personality in twins have sought to reduce error by obtaining samples which are large, and as representative as possible of the population. In analysing their data, most researchers now adopt biometric model-fitting approaches. The details of these differ, but the common theme is that there is an attempt to estimate the heritability, or proportion of variance contributed by genes (or more strictly by additive gene effects), the proportion of variance contributed by shared family environment, and the proportion of variance which can be attributed to non-familial environmental effects. The importance of each of these contributors can be tested by fitting reduced models, e.g. a model where there is no heritability or where there is no common environmental effect, and seeing whether these can explain the data just as well (Fulker, 1981). A consistent finding across all domains of personality testing, which has now emerged in such studies, is of heritability of around 35–50% for traits measured by questionnaires, for example, extroversion or neuroticism (Henderson, 1982; Martin & Jardine, 1986). A more curious, but again highly consistent, finding is that shared family environment produces a negligible contribution to the variance and can nearly always be dropped from the model without adversely affecting the fit; i.e. although at least 50% of the variance in most personality traits is environmental it is comprised entirely of non-shared, non-familial factors. The only scales in which family environment does play a detectable part relate to conservatism, and even here the size of the effect appears to be modest at around 20% (Martin & Jardine, 1986).

Interestingly, these recent findings seem to be in keeping with the much earlier results obtained on MZ twins reared apart (MZA). For example, Shields (1962) found that MZA pairs were actually more alike on some personality measures than MZ pairs reared together and suggested that the common environment of reared-together twins had little effect on personality. If anything, Shields suggested, reared-together twins 'react' against one another, presumably in some attempt to assert individual identities. A more recent study of MZA twins confirmed that virtually all of the environmental variance for self-reported measures of personality was of the non-shared type (Pedersen *et al*, 1988). However, there was a hint that common environment might affect some traits so that twins who were reunited shortly after separation were more alike for neuroticism and impulsivity than were twins who never met again after separation. Another important aspect of this study was that it avoided the selection biases present in some earlier MZA studies which recruited twin pairs by advertisement since it was based on a systematic sampling method via the Swedish Twin Registry. This may in part account for the fact that estimates of heritability were slightly lower than those from previous studies. This latter finding is actually in keeping with recent adoption study results (reviewed by Loehlin *et al*, 1988) which showed quite modest biologically based correlations for various personality traits.

Personality disorder

Despite the difficulties in definition and measurement, the results of animal studies, psychophysiological investigations and studies using questionnaires, suggest that personality probably has a partly genetic basis. We would therefore seem to be on reasonably safe ground to go and explore the genetic basis of personalities which deviate from normality. In doing so we will somewhat arbitrarily divide personality disorders into three main groups which have some similarities to the main clusterings contained in DSM–III (American Psychiatric Association, 1980) and we will call these antisocial personality, anxious or 'avoidant' personalities and schizoid-schizotypal personalities. In doing so, we are not attempting any new method of classification nor are we suggesting that these groupings have any inherent biological validity but we are simply using them as a means of facilitating description and of reviewing a literature where a lot of empirical data have been generated by many different investigators using different terminologies and theoretical frameworks.

Antisocial personality

Although few researchers will accept a simplistic argument that criminality and antisocial personality are one and the same, a history of convictions for criminal offences, particularly repeated convictions, is at least a reliable marker. An early and influential study was by Lange (1931) who, in a provocatively entitled book *Crime as Destiny*, reported concordance for criminality in 10 of 13 MZ pairs compared with only two of 17 DZ pairs. Like many early twin studies, this one suffered from methodological problems. In particular there was non-blind diagnosis and non-systematic ascertainment of twins, which usually results in an overinclusion of the most conspicuous sort of pairs (i.e. MZ twins who are concordant). Ascertainment biases are best overcome using twin registers, and the study of Christiansen (1974), based on a survey of several thousand pairs, showed concordance for criminality of 35% in MZ twins compared with 13% in DZ twins. Another Scandinavian study based upon a smaller but again

systematically ascertained sample, produced even more modest MZ/DZ differences with a concordance of 26% in 31 MZ pairs compared with 15% concordance in 54 DZ pairs (Dalgaard & Kringlen, 1976).

The results of combining data in twin studies of criminality need to be viewed with caution because of differing methods, definitions and base rates across different centres. Nevertheless, McGuffin & Gottesman (1984) considered that there was enough comparability to pool the results of seven studies of adult criminality and five studies of juvenile delinquency where twin concordance was reported as actual numbers and where ascertainment could be presumed to be systematic. The weighted-mean concordance for adult criminality in MZ twins was 51% and in DZ twins was 22% suggesting a definite genetic contribution. By contrast, for juvenile delinquency there was little difference in the MZ and DZ concordance rates at 87% and 72% respectively, suggesting that juvenile delinquency is almost certainly familial but probably does not have a genetic component.

Criminality in most cultures is much less common in women than in men and this was evident in the Danish study of Christiansen (1974). These data were reanalysed by Cloninger *et al* (1978) who applied a two-threshold model. Here it is assumed that liability to become criminal is contributed by an additive combination of genetic and environmental factors, and those whose liability at some stage exceeds a certain threshold, manifest criminal behaviour. Under this model, the threshold for women is more extreme than that for men and, hence, female criminals will have more of a genetic loading than male criminals. This hypothesis appears to fit very well with the Danish twin data.

Adoption studies have been more consistent than twin studies in suggesting a genetic contribution to antisocial personality. In a study of adoptees with 'psychopathy', Schulzinger (1972) found that a significantly greater proportion of biological relatives compared with adoptive relatives and controls could be given the same diagnosis. Similarly, Cadoret (1978), Cadoret & Cain (1980) and Cadoret *et al* (1985), in a series of adoptee family studies, reported a genetic influence on antisocial behaviour and the diagnosis of antisocial personality. In studies of the offspring of female offenders, adopted offspring had significantly more convictions, repeated arrests and incarceration for an offence than controls and also had higher rates of antisocial personality (Crowe, 1972, 1974). The study of Bohman (1978) at first appeared to go against this general trend in failing to show a genetic influence on criminality. However, the findings may have been partly confounded by problems of alcohol abuse and subsequently this author reported that non-alcoholic criminal adoptees had an excess of petty crime without alcohol abuse in their biological compared with their adopting parents (Bohman *et al*, 1982). Whereas petty property offences appeared to be genetically influenced, violent and highly repetitive crime appeared to be more closely related to alcoholism. Similarly, Mednick *et al* (1984) found a significant relationship between biological relatedness for criminality concerning property offences but not violent crimes.

In a cross-fostering study using the Danish register, Hutchings & Mednick (1975) found that when neither biological nor adoptive parents had a criminal record, 11% of adoptees were 'known to the police'. This did not differ significantly from the rate of 12% of having a police record in those adoptees where the adoptive father also had a police record. However, where only the biological father was known to the police, 21% of adoptees had a criminal record, and this rose to 36% where both biological and adoptive fathers were known to the police. The advantage of a cross-fostering design of this type is that genetic factors and factors to do with the environment of rearing can be examined at the same time. Thus there is a suggestion here that family background does play a part, but only when there is already a genetic predisposition towards criminality. More recent studies extending the Swedish adoption investigations of Bohman have also suggested that most of the explained variability concerning criminality is due to differences in genetic predisposition (Cloninger *et al*, 1982; Sigvardsson *et al*, 1982). However, environmental contributions were also identified. In particular, the risk of criminality was increased in those with prolonged institutional care; it was also higher in men who had had multiple temporary placements and where the socioeconomic status of the adoptive home was low.

A controversial area is whether criminal behaviour and antisocial personality has a familial or genetic association with other types of abnormal personality. In particular, it has been suggested that somatisation disorder or Briquet syndrome is a sort of female equivalent to antisocial personality, and that there is a high prevalence of antisocial personality disorder among the relatives of women diagnosed as having Briquet syndrome (Guze *et al*, 1967; Cloninger & Guze, 1973; Cloninger *et al*, 1975). Again, a multiple-threshold model has been evoked whereby Briquet syndrome and antisocial personality in women occupy differing positions on a continuum of liability. Those women whose liability exceeds the less extreme threshold present as Briquet syndrome, and those beyond a more extreme threshold present with criminal or antisocial behaviour. At least one

set of family data has been held to fit with this hypothesis (Cloninger *et al*, 1975). Similarly, the results of at least one adoption study support an association between antisocial personality and 'hysteria' of the Briquet type (Cadoret, 1978). We return to the topic of Briquet syndrome in discussing the genetics of hysterical personality.

Even more controversial is the suggestion of a genetic association between antisocial personality and schizophrenia. One recent study (Silverton, 1988) found a familial association between criminal or antisocial behaviour and schizophrenia. Similarly, Heston's (1966) classic adoption study found that eight of 42 offspring of schizophrenic mothers had criminal records, compared with only one out of 50 control adoptees. High rates of criminality have not been a consistent feature of other adoption studies of schizophrenia, however, and we cannot exclude the possibility that there was a high rate of criminality among the fathers of the adoptees in Heston's study (Gottesman & Shields, 1982).

In summary, most twin and adoption studies suggest that antisocial personality, albeit often crudely defined in terms of criminal convictions or repeated convictions, has a partly genetic aetiology. There is a strong suggestion that the heritable form of criminality has to do with petty recidivism and property offences rather than violent crimes against the person. It remains to be seen whether the results so far obtained are relevant when modern operational definitions of antisocial personality are applied.

Anxious or avoidant personalities

In genetic studies, as in clinical real life, one of the major problems is in differentiating between neurotic *traits* and anxious *states*. There certainly appears to be evidence from twin studies that anxiety disorder is partly genetic, showing consistently higher concordances in MZ than in DZ twins (Slater & Shields, 1969; Torgersen, 1983). There is also good evidence that the more extreme forms of anxiety, manifesting as panic disorder, are highly familial (Crowe *et al*, 1981). Similarly, we have already discussed how neuroticism, e.g. as measured by the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975), has shown a consistent modest level of heritability in twin studies. What is less clear is whether there are certain individuals who have lifelong high levels of anxiety and whether this too is heritable.

One approach to this problem has been to focus on 'normal' phobias in non-patient samples of twins. Torgersen (1979) interviewed 99 twin pairs ascertained via the Norwegian National Register. All subjects responded to a phobia questionnaire and the results were submitted to an analysis which yielded five factors. MZ twins were found to be more alike with respect to fears of animals, social fears, mutilation fears (medical procedures, blood etc.), 'nature fears' (heights, enclosed spaces, etc.) and separation fears which include agoraphobic-like items. Only separation fears showed a non-significant MZ/DZ difference. Similarly, Rose *et al* (1981) administered a fear questionnaire to 91 MZ and 60 DZ college-age twin pairs and a proportion of their parents. There was a substantial heritability for many common fears and, for example, animal phobia appeared to be 72% heritable. As with the questionnaire measures of normal personality described earlier there was little evidence of a common environmental effect. Rose *et al* (1981) remarked that the question of a genetic basis for trait anxiety had been considered more than a century earlier by Charles Darwin, who pointed to the selective advantage of fearfulness in certain circumstances. It is of particular interest in this context that the range of common phobic cues in modern man is quite limited (Marks, 1986). Snakes and spiders often produce phobic results whereas guns and knives rarely do so, suggesting that as Darwin put it, the phobic cues represent "the inherited effects of real dangers . . . during ancient savage times".

Obsessional personality

Obsessive–compulsive disorder and obsessional-personality disorder are often difficult to disentangle, both in research studies and in clinical practice. Slater (1943) noted, in his classic study of 'neurotic constitution' in soldiers, that obsessional neurosis seemed to be more closely associated with pre-existent personality traits than are most other neurotic disorders. Most studies which have focused on obsessional disorders have shown an increased risk of obsessional traits among family members but the estimated rates vary widely from 5% (Carey *et al*, 1978) to 37% (Lewis, 1935) which must surely reflect varying breadths of diagnostic inclusiveness. There have been various case reports of concordance for obsessive–compulsive disorder and obsessional traits in MZ twins (McGuffin & Mawson, 1980; Marks, 1986). However, to date only one systematic twin study of overt obsessive–compulsive disorder has been published (Carey & Gottesman, 1981) which showed a proband-wise concordance rate of 13 out of 15 in MZ twins compared with seven out of 15 DZ twins when concordance was defined broadly according to obsessional features in the co-twin. A study of obsessional traits and 'normal symptoms' in a large sample of volunteer twins used the Leyton Obsessional Inventory Test (Clifford *et al*, 1984). MZ

twins were more highly correlated than DZ twins and the estimated heritabilities were 0.4 for obsessional traits and 0.47 for obsessional symptoms. These authors also found a highly significant correlation between obsessional symptom scores and N scores measured by the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975). It was therefore suggested that genetic factors contribute to obsessional neurosis by influencing both obsessional personality traits and a more general neurotic tendency such that these two in combination may manifest as obsessional symptoms.

Somewhat surprising in view of this, Torgersen (1980) found that an obsessional dimension derived from factor analysis was not heritable and Young *et al* (1971) found that obsessional symptoms in the Middlesex Hospital Questionnaire (MHQ) were not influenced genetically. Again differences of definition must be playing a part in these disparate findings. However, it has to be said that the study of Clifford *et al* (1984) which did find evidence of a modest but significant genetic component in obsessionality used better established measures and a more sophisticated approach to genetic analysis than the earlier negative investigations.

Hysterical personality

Hysterical personality disorder provides particular difficulties for reviewers of genetic studies because researchers have used the term 'hysteria' in so many different ways. When considered as a personality trait measured by the MMPI, Gottesman's (1963) twin study showed negligible genetic influences. By contrast, Torgersen (1980) found that a hysterical dimension derived by factor analysis showed higher correlations in MZ than in DZ twins, especially in women. Yet another twin study, this time using the MHQ, suggested that there was a modest genetic influence on hysterical personality traits (Young *et al*, 1971). Here, however, the authors expressed doubts as to whether it was extraversion rather than hysterical personality traits as such which were being measured by the questionnaire. In a small twin study of classical conversion or dissociative symptoms, Slater (1961) found zero concordance in both 12 MZ and 12 DZ pairs. However, a rather different clinical concept of hysteria is prevalent in some parts of the United States influenced in particular by the Washington University, St Louis School. Arkonac & Guze (1963) proposed that hysteria could be defined as a syndrome occurring in early adult life, mainly affecting women and presenting as recurrent and often dramatic symptoms affecting many organ systems. The syndrome is said to be similar to that originally described by the 19th-century French clinician, Briquet, and hence the eponymous term 'Briquet syndrome'. A somewhat modified concept has been incorporated in DSM–III (American Psychiatric Association, 1980), and is called somatisation disorder. Although it is strictly a DSM–III axis-I diagnosis and hence is not classified as a personality disorder, the early onset of the condition, its enduring nature and its supposed familial relationship to antisocial personality (mentioned earlier) make somatisation disorder a concept which is more closely allied to a personality defect than an illness.

Schizoid–schizotypal disorders

Here again the definition of terms and the derivation of concepts need to be carefully considered. Family and genetic studies have played a particularly influential role and there has long been a view among researchers that the relatives of schizophrenics show an excess of individuals with abnormal personalities and schizophrenic-like features in the absence of overt schizophrenia. Meehl (1962) coined the terms 'schizotaxia' to cover the psychological abnormalities inherent in the predisposition to schizophrenia and 'schizotypy' to describe characteristic symptoms in those predisposed but still non-schizophrenic individuals. A much broader concept of 'schizoid disease' was put forward by Heston (1970) in his formulation of a monogenic hypothesis of transmission of schizophrenia. Schizoid disease included not just classical schizoid and paranoid features but also creative and intellectual abilities. Subsequently, the publication of Danish adoption studies demonstrated that there appeared to be a broad range of abnormalities, so-called 'schizophrenia spectrum disorders', which were commoner in the biological relatives of schizophrenics than in adoptive relatives or controls (Kety *et al*, 1971). While the veracity of the adoption study findings was widely accepted, the concept of spectrum disorders seemed unacceptably broad for some researchers. Therefore, based on the Danish adoption study records, Spitzer *et al* (1979) devised stricter, more explicit operational criteria for schizotypal personality disorder. This was later incorporated in a somewhat modified form in DSM–III (American Psychiatric Association, 1980).

Deriving from a quite different conceptual background of psychoanalytic clinical practice is the notion of borderline states. The term is particularly confusing since schizophrenia spectrum disorders have sometimes been referred to as 'borderline schizophrenia' (Kety *et al*, 1971). However, borderline states, as described by Gunderson & Singer (1975) show more depressive-like features (Stone, 1981),

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and provided the basis for Spitzer *et al*'s (1979) description of 'unstable personality' which was later modified and incorporated in DSM–III as borderline personality disorder. Most recent authors concur that borderline personality disorder does not show a genetic relationship to schizophrenia or schizotypy but rather have emphasised the higher rate of affective disorder in individuals with borderline personalities, and in their first-degree relatives (Loranger *et al*, 1982; Baron *et al*, 1985). Family studies have also suggested that the rate of borderline personality is increased among the relatives of borderline probands but that the category of borderline personality disorder is very mixed so that there is an increased risk also of histrionic and antisocial personality disorder among relatives (Pope *et al*, 1983). The one available twin study was based on a very small sample and suggested that although borderline personality disorder may be familial, there is no evidence to support genetic transmission (Torgersen, 1984).

Genetic studies of schizotypal personality disorder suffer from two shortcomings. First, most studies have been based upon schizophrenic probands and have attempted to identify schizophrenia and schizotypal personality disorder among relatives. Few studies have taken schizotypal probands as their starting point. Second, several of the key published papers have consisted of 'recycling' exercises where new criteria have been applied to old data. Moreover, the most frequently used dataset in diagnostic reanalysis has been the Danish adoption study from which the forerunners of DSM–III criteria for schizotypal personality disorder were derived. Despite the inherent circularity of the exercise, the reanalysis of the Danish adoption data has been informative. For example, the original non-operational clinical diagnosis applied in the adoptees family study of Kety *et al* (1971) produced rates of schizophrenia and related disorders of 20% in the biological relatives of schizophrenics compared with 6% in the adoptive relatives and controls. However, when the diagnostic criteria were restricted to DSM–III schizophrenia and schizotypal personality disorder, the rates became 22% in the biological relatives of schizophrenics versus 2% of adoptive relatives and controls (Kendler *et al*, 1981). The increase in magnitude of the difference between those genetically related and those not genetically related to a schizophrenic suggests that the DSM–III concept of schizotypal personality disorder is not only a more restricted concept but, from a genetic point of view, has a greater validity than the less explicit concept of spectrum disorder. Some support for the genetic relationship between schizophrenia and schizotypal personality disorder comes also from a reanalysis of a classic twin study of schizophrenia (Gottesman & Shields, 1972). On applying DSM–III criteria, a definition of illness in co-twins, which included schizotypal personality disorder as well as schizophrenia, produced a higher MZ to DZ concordance ratio than when the diagnosis was restricted to schizophrenia alone (Farmer *et al*, 1987). Although MZ:DZ ratio provides a fairly crude measure of how genetic is a condition, the findings support the idea that adding schizotypy to schizophrenia enhances the definition of the phenotype and is not simply adding 'noise'. Almost all studies of the families of schizophrenic probands have found an excess of both schizophrenia and schizotypal personality disorder among relatives (Kendler *et al*, 1984; Baron *et al*, 1983). Only one study so far has failed to find a relationship between schizotypal personality disorder and either schizophrenia or other psychoses (Coryell & Zimmerman, 1989).

As we have pointed out, there have been few studies of families ascertained via schizotypal probands. There has been one report that schizotypal personality disorder aggregates in families, particularly in the families of probands with pure schizotypal disorder rather than a mixed schizotypal/borderline personality type (Baron *et al*, 1985). However, this and the only other published studies did not show an increased risk of schizophrenia among the relatives of probands with schizotypal personality disorder (Soloff & Millward, 1983; Schulz *et al*, 1986). How then do we reconcile these two groups of findings, evidence of a genetic relationship between schizotypy and schizophrenia in studies based on schizophrenic probands but not in studies based on schizotypal probands? One explanation is to invoke a severity-liability model as we have done elsewhere in this article. Here schizophrenia and schizotypy could be regarded as lying on the same continuum of liability with schizotypy being a milder, commoner disorder where only a moderately high liability is required to cross the threshold of being affected, whereas schizophrenia is considered as a more severe and less common disorder occupying a more extreme position on the liability continuum. We would then predict that the relatives of schizophrenics would have higher rates of both schizotypy and schizophrenia than the relatives of schizotypal personality disorder probands. In general, this would then mean that larger sample sizes would be required to detect an excess of schizophrenia among the relatives of schizotypal probands than among the relatives of schizophrenics, and hence any failure to detect such an excess in a family study might reflect a lack of power rather than a true absence of familial relationship between schizophrenia and schizophrenia personality disorder.

A different approach to the problem is, as with other types of personality disorder, to regard schizotypy as something measurable on a continuous scale rather than a disorder which is qualitatively distinct from normality. Various scales attempting to measure schizotypy have been devised (Claridge, 1988; Venables *et al*, 1990) and there is some evidence from a twin study of a heritable component in schizotypy scores (Claridge & Hewitt, 1987). However, measurements of schizotypy in general tend to be correlated with neuroticism scores and so it is hard to decide whether they are measuring true schizotypy or some more general propensity to psychopathology. Schizotypy scores derived from MMPI items have been shown to have positive correlations within families and moreover to have a pattern of distribution which would be compatible with major factor inheritance (Moldin, 1990). The search for continuous measures of schizotypy is important. If reliable and valid continuous measures of schizotypy can be devised they have considerable potential in genetic studies of schizophrenia as an indicator of which unaffected relatives of a schizophrenic have a schizophrenia-prone genotype. This applies both in statistical studies which attempt to resolve mode of transmission and in studies using DNA polymorphisms as genetic linkage markers.

Molecular genetics and the biological basis of personality disorder

Although the data are fragmentary and the definitions of the phenotypes untidy, the traditional methods of psychiatric genetics, family, twin and adoption studies, suggest a genetic contribution to personality disorders. However, it becomes apparent that in studying personality disorders we are not dealing with 'all-or-none' traits, but rather with phenotypes which are best regarded as continuous or semi-continuous. That is, we can either regard personality disorders as one extreme of a continuum which blends imperceptibly with normality or we can impose a dichotomy where the population is divided into those with or without personality disorders. If we take this second course, the personality disorder group itself varies from those who have a set of comparatively mild abnormal behaviours to those who are severely disordered. It follows that the patterns of inheritance must be complex and we are not dealing with traits where simple monogenic explanations of transmission will suffice. In fact, personality disorders do not show simple mendelian patterns of transmission, and concordances in MZ twins of well below 100%, or correlations well below unity, mean that there must be a substantial environmental component. For personality measures within the normal range, we have seen that this environmental component is nearly always non-familial but this is not necessarily true of deviant personalities and it seems likely that at least part of the reasons for the familial aggregation of criminality lie in shared family environment.

Given this complicated series of affairs, can we go any further with the genetics of personality disorder and progress from stating that *something* is transmitted to specify more precisely *what* is transmitted? Cytogenetic studies initially appeared to offer an improved insight into the physical basis of personality disorder. In particular, the finding that men with an extra Y chromosome having the so-called 47XYY karyotype accounted for about 3% of the inmates of Carstairs, a hospital for mentally abnormal offenders in Scotland, provoked considerable interest (Jacobs *et al*, 1968). Subsequent studies have found a consistent slight excess of men with the 47XYY constitution in similar institutions. Such men have a mean IQ below that of the rest of the population but are thought to have no characteristic physical abnormalities other than greater than average height. The incidence of the abnormality among new-born boys is in the region of 1 to 2 per 2000 (0.05 to 0.1%) and the syndrome has not been shown to shorten life. It therefore seems that the majority of infants reach adulthood and hence only a very small minority of XYY males are so conspicuously abnormal as to be placed in special institutions. A survey of over 4000 ostensibly normal men of greater than 1.84 metres in height uncovered 12 individuals (0.3%) with the 47 XYY karyotype (Witkin *et al*, 1976). Five of these (42%) turned out to have had criminal records compared with only 9% of normal XY males. The offences committed by the XYY subjects were not predominantly acts of aggression and included relatively minor crimes. This study therefore suggests that there is an increased risk of social deviance among non-institutionalised XYY men but seriously sociopathic or criminal individuals account for only a tiny proportion of those with this syndrome. It may be, therefore, that the initial impression of an association between the XYY constitution and serious crime requiring treatment in a special hospital reflects socio-legal factors, rather than purely genetic influences. A court faced with sentencing a convicted offender who is tall and dull may be more inclined to recommend disposal in a special hospital than if the offender is of average height and intelligence.

Biochemical genetics have so far shed little light on the causes of personality disorder and we have very few clues about biochemical markers which

might possibly indicate personality deviations. The suggestion that lowered activity of platelet monoamine oxidase characterises subjects with schizophrenia and some of their relatives or co-twins has proved controversial (Reveley *et al*, 1986). However, the finding has led to researchers studying other aspects of personality than those which may obviously be related to schizophrenia. In particular, a relationship has been reported between scores on sensation-seeking scales and platelet monoamine oxidase levels (Buchsbaum *et al*, 1976). Unfortunately, it is still not clear how firm a finding this is or indeed what is the mechanism by which monoamine oxidase activity and sensation seeking are associated.

In summary then, the explanatory power of cytogenetic techniques is limited, and biochemical markers or the sorts of psychophysiological measures which we discussed earlier can at best provide us with 'endophenotypes' which lie a step closer to the abnormal genotypes than do clinical descriptions, but still represent vague and indistinct signposts on the complicated pathway between abnormal genes and abnormal behaviour. A more attractive proposition might be to utilise the techniques of recombinant DNA research and go straight for the genotypes themselves. Recent rapid advances in the discovery of DNA polymorphisms has allowed the construction of a nearly complete human genetic linkage map covering the 22 pairs of autosomes and the sex chromosomes (Donis-Keller *et al*, 1989). This means that it is feasible to undertake linkage studies with any inherited trait where there is a real prospect of major gene effects. For example, there have now been several studies focusing on manic–depressive illness (McGuffin & Katz, 1989), and schizophrenia (Owen & Mullan, 1989; Owen & McGuffin, 1991). The aim here is to study the co-segregation within families of the disease and DNA polymorphisms with the aim of detecting co-inheritance of a marker and the disease. This assumes that the inheritance of the disorder is, at least in some families, explicable in terms of a gene of major effect and not just multiple genes of small effect at many loci. Therefore, the important question is whether the approach can be extended further to cover even more loosely defined entities than the major psychoses, including personality disorders. We think that this probably would not be wise. The main reasons are those outlined earlier which persuade us that personality traits within the normal range and personality deviations are most likely to have polygenic modes of transmission. That is, there are likely to be many genes of small effect at different loci acting in a predominantly additive fashion and each on its own accounting for only a small proportion of the variance. This unfortunately means that linkage strategies are unlikely to prove successful.

If this is so, can genes of minor effect be detected or usefully studied at all using molecular genetic techniques? Surprisingly, the best evidence that they can be studied comes not from work on humans or even on laboratory animals, but from breeding experiments with tomatoes. By studying crosses and then back-crosses between domestic tomato and wild South American tomato, Paterson *et al* (1988) made use of a complete genetic linkage map consisting of DNA restriction fragment length polymorphisms (RFLP) distributed throughout the tomato genome. The aim was to define so-called quantitative trait loci (QTL), that is, loci responsible for certain forms of continuous variation. These workers were able to map six QTL controlling fruit mass, five influencing fruit pH and four influencing liquid soluble concentrations in tomato fruit. They have thus provided a convincing demonstration that comparatively simple continuous traits in plants are polygenically inherited and that the polygenes can be localised. As Plomin (1990) has put it, it seems unlikely that human behaviour will turn out to be "less complicated than salad"! Indeed, experiments described by Plomin using recombinant inbred strains of rat strongly suggest that behaviour which can be quantified in the laboratory is most unlikely to be monogenically transmitted. Hence animal behaviour which might be viewed as a prototype for human personality is more likely to be elucidated by a search for QTL than by classical linkage strategies.

Searching for QTL which may influence human personality is much more problematic. Just as Mendel's insights into patterns of transmission came from breeding experiments with plants, so also has the discovery of QTLs, discrete mendelian factors encoding for quantitative traits, come from plant genetics. The application of mendelian genetics in studies of human disease took some time because breeding experiments are not possible, and the investigator has to rely on 'natural experiments' such as observing recurrence risks of 'inborn errors' in siblings (Garrod, 1908).

In searching for markers of small genetic effects it may be necessary to focus not on the segregation of disorders in families but on their distribution in populations. It has long been known that consistent population associations between genetic markers and diseases can be demonstrated even when association accounts for only a tiny proportion of variance. For example, the association between blood group O and duodenal ulcer explains just over 1% of the variance in liability to the disorder (Edwards, 1965). Associations with particular marker alleles occur for a

variety of reasons but the most important are either that the marker allele has some pleiotropic influence on the trait of interest or there is very tight linkage between the trait locus and the marker resulting in *linkage disequilibrium*. This means that the two loci are so physically close that a particular marker allele continues to be co-inherited with the trait over many generations. Probably the maximum physical distances between loci which would still be compatible with linkage disequilibrium is about 10^6 base pairs. Since the human genome is about 3×10^9 base pairs long, a minimum of 1500 evenly spaced DNA markers would be required therefore in order to be fairly confident of detecting QTL in association studies. This would obviously be an enormous undertaking in studies of human personality but one way of reducing the work entailed in the initial search might be to focus on loci of bio-behavioural interest, for example, genes encoding for neuroreceptors or other proteins involved in neurotransmission (Plomin, 1990).

This 'candidate gene' approach depends for its success upon variability detected by molecular biological methods actually having some effect on function. This is not guaranteed since most variability in DNA resulting in RLFP is probably due to random base changes in introns (or non-coding intervening sequences of DNA). Nevertheless, mapping of the human genome is progressing so rapidly that it seems inevitable that all functional human genes including QTL will eventually be detected and localised. How long we mean by 'eventually' is impossible to say. The vast majority of genes discovered so far are not of relevance to complex traits which are polygenic and partially environmental; however, the total number is about 2000 and already accounts for 2–4% of all human genes. This represents a more than ten-fold increase over the past decade suggesting that the end, if not in sight, is definitely foreseeable.

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