Genetic epidemiology

Pak Sham

Institute of Psychiatry, London, UK

Studies of families, twins, and adoptees have helped to quantify the genetic contributions to and overlaps between depression, anxiety, phobias and alcoholism, and to refine the boundaries of the schizophrenia spectrum. Analyses of covariance structures in twin data have confirmed genetic susceptibility and recent life stresses as the major determinants of depression. Genetic modelling of family data on schizophrenia and bipolar disorder indicates three or more common genes each having a small multiplicative effect on risk, although rare major genes may be present in some families. Linkage studies have localised genes for familial Alzheimer's disease on chromosomes 14 and 21; disease mutations on these chromosomes have since been isolated. Association studies have identified susceptibility (or protective) genes for Alzheimer's disease and alcoholism. Several tentative linkage and association findings in schizophrenia and bipolar disorder require further study.

Genetic variation in human populations is the result of the balance between mutation and selection. Some genetic mutations cause severe, recognisable diseases, almost without regard to the rest of the genome or to the environment. Such Mendelian diseases are usually rare because affected individuals tend to have few children. Other genetic mutations have smaller effects on the organism, and such mutations are usually more frequent because they tend to have less effect on reproductive fitness. The clinical effects of some rare 'major' mutations and certain combinations of common 'minor' mutations and environmental risk factors may be almost indistinguishable. Genetic epidemiology aims to resolve the genetic and environmental aetiological factors for these complex syndromes.

A gene that increases the susceptibility to a disorder can be thought of as a risk factor. However, unlike environmental risk factors, genetic effects can be studied indirectly through the familial aggregation of observed traits. Further disentanglement of genetic and environmental factors can be achieved by the study of twins and adoptees. With recent advances in molecular genetic techniques, genetic factors can now be studied directly by relating the disorder to variations in DNA sequence.

Postal address:
Dr Pak Sham, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

Genetic epidemiology comprises a set of principles and methods for the study of genetic factors. It is built around the 'laws' which govern the transmission of genes from parent to offspring, and their predictable and

testable consequences on the occurrence of the disorder in families and in populations. Morton and Chung[1] define genetic epidemiology as 'a science that deals with the etiology, distribution, and control of disease in groups of relatives, and with inherited causes of disease in populations'. Below is a selective survey of recent applications of genetic epidemiological methods to adult psychiatric disorders.

Family studies

Family studies examine the rates of illnesses in the relatives of probands with different diagnoses or characteristics, with the aims of establishing familial factors in aetiology and clarifying the familial overlap between clinical syndromes and/or associated biopsychosocial traits, and the interaction of familial factors with social and other environmental factors in the development of illness.

Familial aggregation of affective disorders was confirmed by the National Institute of Mental Health (NIMH) Collaborative Study of Depression[2], which included 616 probands and 2,423 first degree relatives. The prevalence of bipolar I disorder was 2.4% in the relatives of schizoaffective probands, 5.8% in the relatives of bipolar I probands, 2.8% in the relatives of bipolar II probands, and 0.6% in the relatives of unipolar probands. The lack of an elevated risk to bipolar illness in the relatives of unipolar probands suggests that the majority of unipolar depression is genetically distinct from bipolar disorder.

Familial and social factors were examined in the Camberwell Collaborative Depression Study[3–5]. The first degree relatives of 83 depressed probands were found not only to have an increased risk of depression, but also an increased frequency of life events. However, the risk of depression in relatives was not significantly related to their own experience of life events during the study period, nor to the presence of life events preceding the index illness in the proband. Based on these findings, the authors suggested that the association between life events and depression in the community were partially due to shared familial factors that predispose to both conditions.

The relationship between depression, anxiety and alcoholism was examined by Merikangas *et al*[6] in a study of 215 probands (133 with major depression and 82 normal controls) and 1331 first degree relatives. They found strong comorbidity between depression and anxiety, and weaker comorbidity between depression and alcoholism and between anxiety and alcoholism, among the probands and relatives. By fitting a trivariate multifactorial model to the data relating the combinations of diagnoses in relatives to the combinations of diagnoses in probands, they

showed that comorbidity was due to correlations between the familial (possibly genetic) components of the liabilities to the three syndromes.

The relationship between familial, biological and social factors in psychosis was examined in the Camberwell Collaborative Psychosis Study[7]. The study included 195 probands with functional psychosis and 891 first degree relatives. In addition to confirming that schizophrenia and affective psychosis are both familial, the study also showed that female and early onset probands with schizophrenia had more relatives with schizophrenia than male and late onset probands[8]. Similar findings have been reported from several recent studies[9–12], but not others[13,14]. Interestingly, there is tentative evidence for an increased frequency of CAG repeat expansions in female and early onset patients with schizophrenia[15].

Two recent large-scale family studies have examined the boundaries of the 'schizophrenia spectrum'. The Roscommon study[16–19] included 384 psychotic and 150 control probands and 1,753 directly interviewed relatives (86% of traceable living relatives). The risk of schizophrenia was increased in the relatives of probands with schizophrenia, schizoaffective disorder, other non-affective psychotic disorders, schizotypal and paranoid personality disorders, and, to a lesser extent, with psychotic affective disorder. The risk of bipolar disorder, on the other hand, was significantly increased only among the relatives of probands with affective psychosis. This suggests two overlapping dimensions of familial predisposition, one for schizophrenia and one for affective psychosis. When an attempt was made to order the diagnostic categories along a continuum of familial loading for schizophrenia by fitting a multi-threshold liability model to the data, schizophrenia and affective psychosis occupied opposite poles of the continuum, but the relative positions of the other diagnostic categories could not be determined[20].

The Mainz study[21] included 525 probands with schizophrenia, schizoaffective disorder, bipolar disorder or major depression, and 64 probands with alcoholism and 109 probands from the general population. A total of 2,070 first degree relatives were directly interviewed (82% of all living relatives). The results were broadly similar to those of the Roscommon study, with significant familial aggregation between schizophrenia and schizoaffective disorder, and between schizoaffective disorder and bipolar disorder, but no significant association between schizophrenia and bipolar disorder. The risk of major depression was increased among the relatives of probands of all diagnostic categories except alcoholism, but the relatives of probands with major depression did not show any increase in risk to any psychotic diagnosis. The increase in risk of major depression in the families of psychotic patients may be due to social as well as genetic factors.

Data from a Swedish family study have been reanalysed to examine a particular prediction generated by the maternal influenza hypothesis of

schizophrenia[22,23]. The prediction was that younger siblings would be at higher risk to schizophrenia because viral infection could be introduced by their older siblings to their mothers during gestation. Consistent with this prediction, relatives who had one sibling three or four years older were found to have a significantly increased risk of schizophrenia (odds ratio 1.66, 95% CI 1.05–2.44), and those with two or more such siblings had an even higher risk of schizophrenia (odds ratio 4.44, 95% CI 2.31–8.56).

Twin studies

Twin studies attempt to untangle genetic from other familial factors in the development of illness by examining the extent to which monozygotic (MZ) twins are more alike than dizygotic (DZ) twins with respect to the illness, and assuming that MZ and DZ twins are equally similar with respect to environmental factors relevant to the illness (the equal environment assumption). Twins can also be used to investigate the genetic overlap between different syndromes, the continuity of genetic factors at different stages of the illness, and the relationship between genetic factors and mediating or environmental variables (e.g. personality and psychosocial stress) in the development of the illness.

Recent analyses of twin data have used structural equation modelling (SEM), which facilitates comparisons between competing causal models[24,25]. Each causal model postulates a number of genetic and environmental variables that cannot be measured directly. However, through their shared effects on the observed variables, these latent variables induce a predictable pattern of correlations between the observed variables. For example, if the only familial influence on a trait is the additive effect of several genes, then the trait should be twice as correlated between MZ twins than between DZ twins. By considering the compatibility between observed and predicted correlations, it is possible to validate a causal model and estimate the relative contributions of the latent variables to the variability of the observed traits. For categorically defined illnesses, correlations in liability can be estimated from the observed twin concordances and the population prevalence by assuming a liability-threshold model for the illness, and a bivariate normal distribution for the underlying liabilities of the twin pairs.

This biometrical approach has been applied to obsessional traits and symptoms, and neuroticism, using a sample of 419 twin pairs from the Institute of Psychiatry Normal Twin Register[26]. The results indicate heritabilities of just under 50% for both obsessional traits and symptoms, and a considerable overlap between the genetic factors for obsessional

traits and those for obsessional symptoms. However, there was a larger genetic overlap between obsessional symptoms and neuroticism, than between obsessional traits and neuroticism. This suggests that genetic factors are involved in obsessional personality traits and in a more general 'neurotic tendency', and that the combination of these factors may be responsible for obsessional neurosis.

The genetic relationship between symptoms of anxiety and symptoms of depression was examined on 3,198 twin pairs from the Australian National Health and Medical Research Council Twin Register[27]. A large genetic factor, called 'genetic-distress', was extracted which loaded on both depression and anxiety items and accounted for about 30% of the total phenotypic variance in both sexes. Two other genetic factors and three environmental factors were also extracted; these were relatively minor and loaded differentially on either depression or anxiety items. The hypothesis of a common set of genetic factors for depression and anxiety was further supported by a study of 1,033 female-female twin pairs from the Virginia Twin Register[28]. The genetic components for major depression and generalised anxiety disorder were perfectly correlated and accounted for about 30% of the variance in liability to both disorders. The environmental components of the two disorders were partially correlated.

This multivariate approach to genetic analysis has been extended by the Virginia group to include six psychiatric disorders: major depression, generalised anxiety disorder, phobia, panic disorder, bulimia and alcoholism[29]. The results suggest two sets of shared genetic factors, one predisposing mainly to major depression and generalised anxiety disorder, and the other to phobia, panic disorder and bulimia. The genetic component to alcoholism was substantial but largely disorder-specific.

A similar analytic approach has been applied by the Virginia group to address the question of whether the same set of genes operated at different times to cause depression. Female-female twins were assessed on two occasions one year apart, and it was found that the same genetic factors accounted for just under 50% of the liability to major depression on the two occasions, but the environmental factors were occasion-specific[30]. Neuroticism was found to be strongly predictive of an onset of major depression over the one year period, and it was estimated that 70% of the correlation between neuroticism and major depression was due to common genetic factors[31].

The Virginia group have also started to utilise their twin sample to examine the interaction between genetic factors and social adversity in causing depression in women. Adverse life events over a 1 year period were found to be familial, with genetic and shared environment each accounting for 20% of the variance in liability[32]. Genetic factors were

more important for 'personal events' whereas shared environment was more important for 'network events'. Over the period, genetic factors were found to intensify the effects of stressful life events in causing depression[33]. An attempt was made to create an integrated model incorporating many childhood and adult variables in the aetiology of depressive episodes in women[34]. Variables were placed in three layers of a causal network, a distal layer consisting of genetic factors, parental warmth and childhood parental loss, an intermediate layer consisting of neuroticism, lifetime trauma and past depression, and a proximal layer consisting of social support, recent difficulties and recent stressful life events. The model accounted for 50% of the variance in the liability to major depression, with recent life events, genetic factors, and past history of depression being most important.

Because of the smaller number of subjects, twin studies on psychotic disorders tend to have the more modest aim of estimating heritability. Kendler[35] summarised data from 9 twin studies on schizophrenia, which gave MZ and DZ concordances of 53% (211/401) and 15% (74/478), and an overall heritability estimate of 68% for the underlying liability to schizophrenia. Similar figures were obtained in a subsequent study based on the National Psychiatric and Twin Registries of Norway[36] which gave MZ and DZ concordances of 48.4% (15/31) and 3.6% (1/28), respectively. For bipolar disorder, Bertelson *et al*[37] found MZ and DZ concordances of 21/34 and 3/37, giving a heritability estimate of 59%.

The relative magnitudes of the genetic contribution to several different diagnostic definitions of the schizophrenia spectrum have been examined in the Maudsley Twin Sample of 21 MZ and 21 DZ twin pairs[38]. The most 'genetic' definition, which consisted of DSM-III schizophrenia, schizotypal personality disorder, affective disorder with psychosis, and atypical psychosis, gave an MZ/DZ concordance ratio of almost 8:1.

MZ discordance for schizophrenia may be caused by the 'reduced penetrance' of a schizophrenic genotype, or by the presence of sporadic (i.e. non-genetic) cases. The first but not the second explanation would predict an increased risk of schizophrenia among the children of discordant twin pairs. The risk of schizophrenia among the children of ill and well members of discordant MZ twin pairs was estimated at 16.8% (6/47) and 17.4% (4/24) in one study[39] and 17.9% (5/28) and 4.4% (1/45) in another[40]. The similarity of these risk estimates to those obtained on the children of schizophrenics in the general population indicates that most discordant MZ twins are genetically predisposed to schizophrenia. This suggests that environmental factors alone are seldom sufficient to cause schizophrenia, although they may play a decisive role in some individuals genetically predisposed to schizophrenia. An intensive study of 23 discordant MZ twin-pairs showed that 7 pairs had diverged in behaviour by the age of 5 years, indicating early

environmental factors[41]. The second trimester of fetal development has been suggested as a critical window for environmental insults. The development of dermatoglyphic patterns in hands and feet is completed by the end of the second trimester, and discordant MZ twins have been shown to be less alike in dermatoglyphic patterns than normal MZ twins[42]. If prenatal environment is important in schizophrenia, then concordance is expected to be higher in monochorionic than in dichorionic MZ twins. Consistent with this, one study has found 60% (9/15) concordance for MZ twins with opposite-hand preference (an indicator of monochorionicity), and only 32% (18/56) for MZ twins with same-hand preference[43].

Adoption studies

The aim of adoption studies is to distinguish genetic from nongenetic aetiological factors, by comparing the risk of illness in the biological and adoptive relatives of ill adoptees, or by comparing the risk of illness in the biological relatives of ill and control adoptees. Although adoption studies do not rely on the equal environment assumption of twin studies, both the biological and the adoptive families of adoptees are unlikely to be representative of the general population. Moreover, the extent that adoption studies achieve separation between genetic and environmental factors depends critically on the age at adoption.

The Copenhagen adoption study[44], historically important in demonstrating a genetic component in schizophrenia, has been extended to the rest of Denmark[45]. The results from the new 'provincial sample' were consistent with those from the original sample; the biological relatives of schizophrenic adoptees showed an increased risk of chronic schizophrenia (8/171) and latent schizophrenia (14/171), but not affective disorders, compared to the adoptive relatives of the same adoptees, or the biological and adoptive relatives of control adoptees. The combined sample was re-diagnosed using DSM-III criteria[46], which showed that schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder mainly schizophrenia, schizotypal personality disorder, and paranoid personality disorder) were significantly more frequent in the first and second degree biological relatives of schizophrenic adoptees (16/68 and 14/141) than in the first and second degree relatives of control adoptees (5/107 and 4/192).

Adoption studies have also demonstrated genetic components in affective disorders and in alcoholism. Mendlewicz and Rainer[47] found that the risk of bipolar or schizoaffective disorder was 6/57 among the biological parents but only 1/57 among the adoptive parents of bipolar

adoptees. Wender *et al*[48] found that the risk of bipolar or unipolar disorder was 20/387 in the biological relatives and only 5/180 in the adoptive relatives of adoptees with an affective disorder. Goodwin *et al*[49] demonstrated a significantly increased risk of alcoholism in the adopted away sons of alcoholic fathers (12/67), compared to the adopted away sons of non-alcoholic fathers (5/97). In a later study on female adoptees[50], there was no increased risk of alcoholism among the daughters of alcoholic biological parents. However, more recent studies[51,52] have found an increased risk of alcoholism in both male and female adoptees with an alcoholic biological parent, compared to adoptees with normal parents. These findings are consistent with recent twin studies[53] in suggesting a modest genetic component in the liability to alcoholism.

Cloninger *et al*[54] classified 862 adopted men in the Stockholm Adoption Study into 4 groups: non-abusers, and mild, moderate, and severe abusers of alcohol, and applied discriminant function analysis to variables concerning alcohol abuse and other characteristics of the biological parents ('congenital' factors), and variables that might affect upbringing before and after placement in the adoptive family ('post-natal environment'), in order to find combinations of variables that best distinguish the four groups. The most significant discriminant function associated the moderate abusers with biological fathers who had recurrent alcohol abuse and criminal convictions since adolescence. The other two discriminant functions were similar, with recurrent alcohol abuse not requiring treatment in the biological parents and low occupational status in the adoptive parents. Two types of alcoholism were suggested: a common 'milieu-limited' type (Type I) that occurs in both sexes as a result of gene-environment interaction, and a rarer 'male-limited' type (Type II) that is more genetic, affects men from adolescence, and is associated with sociopathy. Hill[55] found very high rates of alcoholism (60%) but not sociopathy in the parents of 29 pairs of alcoholic siblings, and suggested a third type of highly familial alcoholism not associated with sociopathy (Type III).

Genetic models

Having demonstrated that a disorder has a genetic component, the next logical step is to uncover its 'mode of inheritance', i.e. the number of loci involved and the manner in which the genes at these loci determine the phenotype. Since the true 'mode' is likely to be complex, it is customary to consider simplified models with the modest aim of demonstrating the existence of a single locus (or at most two or three loci) whose alleles

have a major effect on the liability to illness, and partition the remainder of the variance in liability to familial and non-familial factors[56,57]. The analysis usually involves assessing the probability of the observed family data under alternative models, to see what kind of genetic and environmental factors are most compatible with the data. Technically, the probability of the observed family data under a model is defined as the likelihood of the model, and is used as a measure of the support for the model provided by the data.

Efforts to isolate major genes by model-fitting have focused mainly on the psychoses, probably because these disorders are relatively rare and distinct compared to neurotic conditions such as depression and anxiety. However, the numerous studies that attempted to discriminate monogenic from polygenic inheritance for schizophrenia have produced conflicting results[58]. Results for bipolar disorder are similarly inconclusive[59].

There was some tentative evidence of a major locus for bipolar disorder in the family data from the NIMH Collaborative Depression Study[60]. A mixed model incorporating a major locus and a polygenic background gave a better fit to the data than a model with only polygenic background. However, this evidence relied on using age-at-onset as an indicator of liability, and was tempered by the rejection of Mendelian transmission probabilities. No evidence of a major locus was found in a reanalysis of the same dataset that used a different approach to model age-at-onset[61]. Similarly, a mixed model analysis on the Lindelius family data of 270 schizophrenics and their relatives found no evidence for a major gene[62].

There have been some attempts to include in genetic modelling a biological trait ('endophenotype') correlated with the liability to illness, in the hope that the trait would provide additional information about the liability and improve the power to resolve a major locus effect. Holzman *et al*[63] fitted a 'Mendelian latent structure' model to data on 210 children and grandchildren of MZ and DZ twins discordant for schizophrenia or bipolar disorder, and found suggestive evidence for a dominant gene having an effect on both liability and eye-tracking. However, the estimated penetrance of about 10% would predict MZ and DZ concordances of about 10% and 5%, values inconsistent with estimates obtained from twin studies. Sham *et al*[64] fitted a two locus model to 18 Scottish families with schizophrenia in which auditory P300 latency had been measured, and found tentative evidence for a major locus that affects both liability and P300 latency. However, the alternative that the correlation between liability and P300 latency is caused by multiple small genetic effects was not considered.

McGue and Gottesman[65] have argued against a monogenic model for schizophrenia on several grounds. The prevalence is too high and the MZ

concordance is too low, in comparison to typical Mendelian disorders. Large pedigrees with multiple affected members in several generations are rarely encountered, but recessive inheritance is also unlikely because the risk of illness is as high in the children as in the siblings of schizophrenics. Moreover, a polygenic model is better able to account for the apparent steep drop in recurrence risk from MZ twins (about 50%) to first degree relatives (about 10%), and from first degree relatives to second degree relatives (about 3%), than a monogenic model. This is because the probability of sharing a combination of several alleles falls off much more rapidly than the probability of sharing a single allele as relationship becomes more distant. The high risk among the children of two schizophrenic parents (about 50%) also supports a polygenic rather than a monogenic model.

Risch[66] has also considered the compatibility of multilocus models with the observed recurrence risks in schizophrenia and concluded that at least three loci acting multiplicatively on risk of illness would be necessary. Similarly, Craddock *et al*[67] have concluded that the observed recurrence risks for bipolar disorder are within the limits compatible with models containing three or more loci acting multiplicatively on risk of illness, but incompatible with a multiplicative model with fewer loci, or with a heterogeneity model where each locus constitutes a separate and sufficient cause for the illness. Since additive effects on the liability scale translate approximately to multiplicative effects on risk to illness[68], the models favoured by McGue and Gottesman, Risch, and Craddock *et al* are not substantially different.

The validity of these conclusions depends on the accuracy of the recurrence risk estimates and on the appropriateness of the model assumptions. Adequate diagnostic information might be more difficult to obtain from distant relatives than from close relatives, and environmental risk factors might be shared to a greater extent by close relatives than by distant relatives. However, twin studies have found little evidence for a shared environmental component in schizophrenia or in bipolar disorder. On balance, it appears unlikely that schizophrenia or bipolar disorder is caused entirely by a single major gene, or by several major genes each responsible for a proportion of cases in the population. There are probably several common genes each with a small effect on risk, but rare major genes may also be present in some highly familial cases.

Linkage studies

Linkage studies attempt to infer the relative positions of two or more loci by examining how combinations of alleles at the loci are transmitted from

generation to generation. The formation of gametes involves the 'segregation' of the parental alleles into two equal subsets, so that each gamete contains half the parental alleles. The set of alleles contained in a gamete is known as a haplotype. An individual's genotype consists of a paternal haplotype and a maternal haplotype. Linkage refers to the tendency for a combination of alleles co-transmitted as a haplotype in one gametic generation to be co-transmitted again in the next gametic generation. In other words, the alleles at these loci in any gamete tend to be derived from either the paternal or the maternal haplotype, but not both.

The biological basis of linkage is that groups of alleles are connected to each other on chromosomes, and that for such a group to be separated in meiosis requires crossing over and exchange of genetic material between the two chromosomes of different parental origins. When two loci are considered, a gamete that contains one allele from the paternal haplotype and the other from the maternal haplotype is called a recombinant, and the fraction of gametes that are recombinant is called the recombination fraction between the two loci. A recombination fraction of 0 means that crossing over never occurs between the two loci, so that the loci must be extremely close to each other. A recombination fraction of 0.5 means that alleles at the two loci are combined at random during meiosis, so that the loci are either on different chromosomes or are very far apart on the same chromosome. The smaller the recombination fraction, the closer are the two loci.

If we were able to examine alleles directly in two successive generations of gametes, linkage analysis would involve simply counting the number of recombinants and non-recombinants. However, we are usually only able to make inferences about the recombination fraction indirectly through phenotypic data that provide partial information on genotypes (rather than haplotypes). The standard lod score method of linkage analysis is based on the likelihoods of the observed familial patterns of the phenotypes over a range of recombination fractions (θ) from 0 to 0.5 under assumed genetic models for the phenotypes[69,70]. The lod score at a particular value of θ is defined as the logarithm (base 10) of the ratio of likelihoods evaluated at that value of θ and evaluated at $\theta = 0.5$. The maximum lod score over the entire range of possible values of θ is taken as a measure of the evidence in favour of linkage. When several families are studied, the lod score can be maximised jointly over θ and the proportion of families linked, to obtain a test of linkage assuming heterogeneity. A maximum lod score of 3 or more is traditionally taken as sufficient evidence to declare linkage, because theoretical consideration and empirical evidence indicate that, for Mendelian traits, less than 5% of linkages declared at this level are chance findings. Similarly, a lod score of below –2 at a certain value of θ is traditionally taken as sufficient evidence to exclude linkage at that value of θ.

The lod score method of linkage analysis requires a model for the disease locus, i.e. gene frequencies and penetrances, to be specified. Misspecification reduces the power of detecting linkage but does not increase the probability of falsely declaring linkage. Since genetic parameters are unknown for common psychiatric disorders, researchers have tended to use either a single 'best-guess' model or a range of different models. 'Non-parametric' methods which do not require a disease model to be specified are becoming increasingly used. Some of these methods are based on the excessive sharing of marker alleles by affected sibling pairs[71], while others are based on adaptations of the lod score method[72]. Most linkage studies select large multi-generational pedigrees with multiple affected members on the basis that such pedigrees are most likely to segregate a major gene for the disorder, and are more powerful for detecting linkage, than smaller families with fewer affected individuals. The appropriateness of this approach for complex disorders caused by the interaction of a number of common genes has recently been questioned, and it has been suggested that affected sibling pairs with unaffected parents may be more informative because the parents in such families are less likely to be homozygous (and hence uninformative for linkage) when the susceptibility genes are common[73].

Linkage studies in psychiatry have focused mainly on the dementias and the psychoses. The localisation of major genes for early-onset familial Alzheimer's disease on chromosomes 21 and 14[74,75] and the subsequent identification of several disease mutations on these chromosomes[76,77] is a major triumph for the application of the linkage strategy to complex disorders. However, families in which the disorder is transmitted, without skipping, through several successive generations, are far more common for early onset Alzheimer's disease than for schizophrenia and bipolar disorder. Such families indicate the presence of dominant genes with high penetrance, and provide promising material in which to search for linkage. The relative sparsity of such families for schizophrenia and bipolar disorder is probably responsible for the failure so far of linkage analysis to unequivocally demonstrate and localise genes for these disorders.

The earliest linkage studies on the functional psychoses relied on classical markers such as colour blindness and HLA antigens, severely limiting the regions that can be studied. With the availability of DNA markers, the first regions to be studied were those in which cytogenetic abnormalities have been reported to be associated with psychosis. With subsequent technological developments, many centres have started to conduct systematic genome scans using hundreds of markers. Some of the more prominent findings are summarised in Tables 1 and 2. Currently, the strongest candidate regions are probably Xq26–28 and the pericentromeric region of chromosome 18 for bipolar disorder and the

Table 1 Some linkage findings in bipolar affective disorder

Region/locus	Findings
Xq26-28	Possible reduced father-son transmission[78,79]
	Possible association with fragile X[80]
	14 of 16 linkage studies reviewed in 1990[59] were positive
	Subsequent positive linkage studies[81–83,86,87]
	Subsequent negative linkage studies[85]
	Largest lod=9.2[81], but subsequently retracted[84]
	Current status: strong candidate
6p (HLA)	4 of 11 studies showed positive results[59]
	Largest lod = 8.0, but questionable diagnostic definition[88]
	Combined analysis of several studies negative[89]
	Current status: weak candidate
11p	Amish study: lod=4.3[90], but later retracted[91]
	Subsequent negative studies[92,93]
	One weakly positive study (lod > 1)[94]
	Current status: weak candidate
21q22	Genome scan: lod=2.3, (one family had lod 3.4)[95]
	Subsequent weakly positive study: lod=1.3[96]
	Combined analysis with TH: lod=3.6[96]
	Current status: moderately strong candidate
18 pericentromeric	Genome scan: excessive allele sharing over 50 cM ($p < 0.001$)[97]
	Subsequent weakly positive studies[98–101]
	Subsequent negative studies[102–104]
	Current status: moderately strong candidate

short arm of chromosome 6 for schizophrenia, but the evidence remains inconclusive even in these regions.

The lack of entirely consistent linkage results for the psychoses may reflect locus heterogeneity with several rare major genes each operating in a small proportion of families. Different samples will then have a different 'mix' of these forms, making replication difficult. Confirmation of tentative linkage results may then depend on the identification of disease mutations in a small number of large pedigrees. An alternative view is that major genes are extremely rare, so that the combined action of several common susceptibility genes are responsible for illness in the majority of large pedigrees selected for linkage analysis. A sensible strategy would then be to collect large numbers of nuclear families with affected sib-pairs, in addition to large multiplex pedigrees, for linkage analysis, and to look for associations between disease and marker alleles near linkage 'hot-spots' or candidate genes.

Association studies

Association studies attempt to establish the physical proximity of two loci by demonstrating associations between alleles of the loci, i.e. the

Table 2 Some linkage findings in schizophrenia

Region/locus	Findings
5q11-13	Balanced translocation associated with psychosis[105] English & Icelandic pedigrees: lod = 6.5[106] (but see[107]) Combined analysis of several datasets: negative[108] Review of subsequent studies[109]: 12 negative, 1 weakly positive[110] Current status: weak candidate
Pseudoautosomal	Excess sex-concordance among affected sib-pairs[111,112] (but see[113]) Subsequent positive studies[114,118] Subsequent negative studies[115–117,119,120] Current status: weak candidate
Dopamine receptors	
DRD1	Negative studies[121–123]
DRD2	Negative studies[122–128] (but translocation at 11q associated with psychosis[136–138])
DRD3	Negative studies[122,129,130]
DRD4	Negative studies[122,123,131–134]
DRD5	Negative studies[122,135] Current status: very weak candidates
22q	Genome scan: lod=1.5[139] (candidate genes IL2Rς[140], COMT[141]) First multi-centre replication study negative[142] (despite 2 weakly positive studies[143,144]) Second multi-centre replication study weakly positive (p=0.001)[145] Current status: moderately strong candidate
6p	Genome scan: lod=3.2[146] (in enlarged sample lod=3.5[147]) Subsequent positive studies[148–150] Subsequent negative studies[151,152] Current status: strong candidate

occurrence of certain combinations of alleles in the same gamete more frequently than expected given the allele frequencies in the population. In a large randomly mating population, allelic associations are diminished rapidly in successive generations by random recombination events in meiosis, unless the two loci are tightly linked. However, allelic associations can exist in the absence of linkage if there is population stratification or recent in-migration.

Association and linkage are two complementary approaches for gene mapping. Both methods are based on the increased frequencies of certain combinations of alleles (haplotypes) in gametes. A haplotype persists from generation to generation until a recombination event takes place between the loci, when a new haplotype is generated. In a population, haplotypes of loci that are unlinked or loosely linked tend to the product of recent recombination events, whereas haplotypes of loci that are tightly linked have probably been 'in coupling' for many generations. Linkage analysis attempts to detect 'local' increases in haplotype frequencies that apply only to closely related individuals, whereas association analysis attempts to detect 'global' increases for the entire population. In other words, under loose linkage, each pedigree will have a marker allele associated with the disease gene, but there will be no

tendency for the associated marker alleles to be the same for any two pedigrees. Linkage analysis will be more powerful than association analysis in this situation. Under tight linkage, however, most pedigrees that have inherited the same disease gene from a distant common ancestor will show an association between the disease and the same marker allele. Association analysis is potentially more powerful than linkage analysis in this situation. Association analysis is most powerful when the marker locus is the susceptibility locus itself, and is therefore the method of choice for testing candidate genes.

Two designs are commonly used to detect associations between disease and marker alleles. The first design is based on comparing the marker genotypes in patients and unrelated controls from the same population. The second design is based on comparing marker genotypes in patients and their parents. One variation of the second approach, the transmission disequilibrium test (TDT), is robust to hidden population stratification[153,154]. The TDT considers heterozygous parents to see if some marker alleles are more likely than others to be transmitted to affected children.

An association between Alzheimer's disease and the apolipoprotein E (ApoE) ε_4 allele on chromosome 19 has been established by numerous studies which compared ApoE genotype frequencies in cases and controls[155]. ApoE ε_4 has a frequency of about 13% in Caucasian populations, and increases the risk of Alzheimer's disease multiplicatively by a factor of about 3 per copy (so that the risk is increased about 9-fold among homozygous $\varepsilon_4\varepsilon_4$ individuals) by the age of 75 years[156,157]. In some families segregating an Alzheimer's mutation at the APP (amyloid precursor) locus, ApoE ε_4 reduces the age-at-onset of dementia in individuals with the Alzheimer's mutation[158,159].

A negative association between alcoholism and the low activity form of ALDH2 (aldehyde dehydrogenase-class 2) on chromosome 12 has been found in oriental populations. The low activity allele (ALDH2-2) has a frequency of 15–25% in these populations[160] and causes a 'flush reaction' to alcohol due to the accumulation of acetaldehyde. In Japan, Shibuya and Yoshida[161] compared 23 patients with alcoholic liver disease to 49 controls and found gene frequencies for ALDH2-2 of 0.07 and 0.35, respectively. In Taiwan, Thomasson *et al*[162] compared 50 subjects with DSM-III alcohol dependence to 50 controls, and found gene frequencies for ALDH2-2 of 0.06 and 0.30, respectively. None of the alcoholics was homozygous for ALDH2-2. These data indicate that ALDH2-2 is strongly protective against alcoholism, although the allele is rare in Caucasian populations.

Another candidate locus for alcoholism is DRD2 (dopamine D2 receptor) on chromosome 11, because of the role of limbic dopamine pathways in the positive reinforcement of behaviours. Blum *et al*[163] found that the A1 allele at the TaqI restriction fragment length polymorphism

(RFLP) was present in 69% of 35 deceased alcoholics and only 20% of 28 non-alcoholic controls. A meta-analysis of the original and 10 subsequent studies found no evidence for an association when data from the original group were excluded, although one of the studies had no alcoholics and another had no controls[164]. In another meta-analysis of 9 studies containing 491 alcoholics and 495 controls, Noble[165] found that TaqI–A1 was present in 25.7% of controls, 43.0% of all alcoholics and 56.3% of severe alcoholics, suggesting a dose-response relationship. Smith *et al*[166] found that among substance abusers, 84% of 89 individuals with the TaqI–A1 allele were moderate or heavy abusers, compared to 74% of 159 of individuals without the allele. Similarly, in a study of 200 white male substance users, Comings *et al*[167] found that 45% of the 73 subjects with the TaqI–A1 allele habitually spent more than $25 on two or more drugs, compared to only 20% of the 127 subjects without the TaqI–A1 allele. Among the 39 subjects who had been expelled from school for fighting, 59% had the TaqI–A1 allele, compared to 31% of the other 154 subjects. The TaqI–A1 allele was significantly associated with early onset of substance abuse in these subjects. A role for DRD2 in substance abuse is also supported by genetic studies on animals selectively bred for propensity to drug dependence[168]. On balance, there is highly suggestive evidence that DRD2 is involved in substance abuse.

Table 3 summarises some of the more prominent findings from association studies on the functional psychoses. No definite association has been found but the suggestion of an association of schizophrenia with alleles at D22S278 is interesting in relation to the positive linkage results obtained in this region. Also of interest are the tentative associations of schizophrenia with HLA antigens, as immunological factors have been hypothesised to be involved in schizophrenia.

Association analysis has therefore contributed to the finding of susceptibility (or protective) genes for Alzheimer's disease and alcoholism. However, definite allelic associations have not yet been established for bipolar disorder or schizophrenia.

Conclusions

Genetic epidemiology draws on the mechanisms of heredity and the reproductive characteristics of populations to formulate methods of investigating genetic factors in human diseases. These methods can only be applied in conjunction with techniques from other fields, including clinical, psychological and social sciences, neurobiology and molecular genetics. The relative importance of these areas of knowledge in terms of

Table 3 Some association findings in psychosis

Region/locus	Findings
Bipolar disorder	
TH	Allelic association reported[169]
	Subsequent negative studies[170–173]
	Subsequent weakly positive study[174]
	Current status: weak candidate
MAOA	Allelic association reported[175,176]
	Subsequent negative study[177]
	Current status: weak candidate
Schizophrenia	
HLA-A9	Allelic associations reported in 7 of 9 studies[178]
	Subsequent negative studies[179,180]
	Subsequent positive studies[181]
	Current status: moderately strong candidate
HLA-DR4	Negative association reported[182]
	Current status: awaiting replication
PBGD	Allelic association reported[183]
	Subsequent negative studies[184,185]
	Current status: very weak candidate
DRD2	Allelic association reported[186]
	Subsequent negative studies[187–192]
	Current status: very weak candidate
DRD3	*Increased homozygosity reported*[193]
	Subsequent negative studies[194–201]
	Current status: weak candidate
DRD4	Negative studies[202,203]
	Current status: very weak candidate
D22S278	Weakly positive TDT results (p=0.1[204], p=0.001[205])
	Current status: moderately strong candidate

TH, tyrosine hydroxylase; MAOA, monoamine oxidase A; PBGD, porphobilinogen deaminase.

aetiological research depends somewhat on the nature of the syndrome. The combination of genetic epidemiological principles and molecular genetic techniques has isolated high risk mutations for 'organic' syndromes such as Alzheimer's disease. The mechanisms whereby these mutations increase the risk to disease now require further clinical and neurobiological studies. The same combination of genetic epidemiology and molecular genetics may well succeed for the functional psychoses, but it is possible that additional input from other sciences, to help resolve aetiological heterogeneity and create quantitative measures of underlying vulnerability, is also necessary for the isolation of susceptibility genes for these more complex disorders. Aetiological research on depression, anxiety and other common conditions that merge with normality have so far tended to adopt a more 'holistic' approach to genetic factors, as genes of major effect are usually considered less likely for these conditions. However, as more candidates loci in the neurochemical pathways regulating mood and behaviour are discovered, it is likely that the effects

of particular alleles at these loci will be examined in conjunction with psychological and social factors.

Acknowledgements

I am grateful to Professor Robin Murray and Dr David Curtis for critical reading of the manuscript, and to the Wellcome Trust for financial support.

References

1 Morton NE, Chung CS. *Genetic Epidemiology*. New York: Academic Press, 1978
2 Andreasen NC, Rice JP, Endicott J *et al.* Familial rates of affective disorders. *Arch Gen Psychiatry* 1987; 4:, 461–9
3 Bebbington P, Brugha T, MacCarthy B *et al.* The Camberwell Collaborative Depression Study. I. Depressed probands: adversity and form of depression. *Br J Psychiatry* 1988; **152**: 754–65
4 McGuffin P, Katz R, Bebbington P *et al.* The Camberwell Collaborative Depression Study. 2. Investigation of family members. *Br J Psychiatry* 1988; **152**: 766–75
5 McGuffin P, Katz R, Bebbington P. The Camberwell Collaborative Depression Study. 3. Depression and adversity in the relatives of depressed probands. *Br J Psychiatry* 1988; **152**: 775–82
6 Merikangas KR, Risch NJ, Weissman MM. Comorbidity and cotransmission of alcoholism, anxiety and depression. *Psychol Med* 1994; **24**: 69–80
7 Jones PB, Bebbington P, Foerster A *et al.* Premorbid social underachievement in schizophrenia: Results from the Camberwell collaborative psychosis study. *Br J Psychiatry* 1993; **162**: 65–71
8 Sham PC, Jones P, Russell A *et al.* Age at onset, sex, and familial psychiatric morbidity: Report from the Camberwell Collaborative Psychosis Study. *Br J Psychiatry* 1994; **165**: 466–73
9 Shimizu A, Kurachi M, Noda M *et al.* Morbidity risk of schizophrenia to parents and siblings of schizophrenic patients. *Jpn J Psychiatry Neurol* 1987; **41**: 65–70
10 Goldstein JM, Faraone SV, Chen WJ *et al.* Sex differences in the familial transmission of schizophrenia. *Br J Psychiatry* 1990; **156**: 819–26
11 Pulver AE, Brown CH, Wolyniec PS *et al.* Schizophrenia, age at onset, gender and familial risk. *Acta Psychiatr Scand* 1990; 81: 344–51
12 Kendler KS, MacLean CJ. Estimating familial effects on age at onset and liability to schizophrenia. I. Results of a large sample family study. *Genet Epidemiol* 1990; 7: 409–17
13 Kendler KS, Tsuang MT, Hays P. Age at onset in schizophrenia: a familial perspective. *Arch Gen Psychiatry* 1987; **44**: 881–90
14 Sham PC, Gottesman II, MacLean CJ *et al.* Schizophrenia: sex and familial morbidity. *Psychiatry Res* 1994; 52: 125–34
15 Morris AG, Gaitonde E, McKenna P *et al.* CAG repeat expansions and schizophrenia: association with disease in females and with early age-at-onset. *Hum Mol Genet* 1995; **4**: 1957–61
16 Kendler KS, McGuire M, Gruenberg AM *et al.* The Roscommon family study. I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch Gen Psychiatry* 1993; 50: 527–40
17 Kendler KS, McGuire M, Gruenberg AM *et al.* The Roscommon family study. II. The risk of non-schizophrenic non-affective psychoses in relatives. *Arch Gen Psychiatry* 1993; 50: 645–52
18 Kendler KS, McGuire M, Gruenberg AM *et al.* The Roscommon family study. III. Schizophrenia-related personality disorders in relatives. *Arch Gen Psychiatry* 1993; 50: 781–8

19 Kendler KS, McGuire M, Gruenberg AM *et al.* The Roscommon family study. IV. Affective illness, anxiety disorders and alcoholism in relatives. *Arch Gen Psychiatry* 1993; 50: 781–8
20 Kendler KS, Neale MC, Walsh. Evaluating the spectrum concept of schizophrenia in the Roscommon Study. *Am J Psychiatry 1995; 152: 749–54*
21 Maier W, Lichtermann D, Minges J *et al.* Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. *Arch Gen Psychiatry* 1993; 50: 871–83
22 Sham PC, O'Callaghan E, Takei N *et al.* Schizophrenia following prenatal exposure to influenza epidemics between 1939 and 1960. *Br J Psychiatry* 1992; 160: 461–6
23 Sham PC, MacLean CJ, Kendler KS. Risk of schizophrenia and age difference with older siblings: evidence for a maternal viral infection hypothesis. *Br J Psychiatry* 1993; 163: 627–33
24 Kendler KS. Twin studies of psychiatric illness. *Arch Gen Psychiatry* 1993; 50: 905–15
25 Neale MC, Cardon LR. *Methodology for Genetic Studies in Twins and Families.* New York: Kluwer Academic, 1992
26 Clifford CA, Murray RM, Fulker DW. Genetic and environmental influences on obsessional traits and symptoms. *Psychol Med* 1984; 14: 791–800
27 Kendler KS, Heath AC, Martin NG *et al.* Symptoms of anxiety and symptoms of depression. Same genes, different environments? *Arch Gen Psychiatry* 1987; 44: 451–7
28 Kendler KS, Neale MC, Kessler RC *et al.* Major depression and generalised anxiety disorder. Same genes, (partly) different environments. *Arch Gen Psychiatry* 1992; 49: 716–22
29 Kendler KS, Walters EE, Neale MC *et al.* The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression and alcoholism. *Arch Gen Psychiatry* 1995; 52: 374–83
30 Kendler KS, Neale MC, Kessler RC *et al.* A longitudinal study of 1-year prevalence of major depression in women. *Arch Gen Psychiatry* 1993; 50: 843–52
31 Kendler KS, Neale MC, Kessler RC *et al.* A longitudinal twin study of personality and major depression in women. *Arch Gen Psychiatry* 1993; 50: 853–62
32 Kendler KS, Neale MC, Kessler RC *et al.* A twin study of recent life events and difficulties. *Arch Gen Psychiatry* 1993; 50: 789–96
33 Kendler KS, Kessler RC, Walters EE *et al.* Stressful life events, genetic liability and onset of an episode of major depression in women. *Am J Psychiatry* 1995; 152: 833–42
34 Kendler KS, Kessler RC, Neale MC *et al.* The prediction of major depression in women: toward an integrated etiologic model. *Am J Psychiatry* 1993; 150 1139–48
35 Kendler KS. Twin studies of schizophrenia: a current perspective. *Am J Psychiatry* 1983; 140: 1413–25
36 Onstad S, Skre I, Torgrerson S *et al.* Twin concordance for DSM-IIIR schizophrenia. *Acta Psychiatr Scand 1991; 83: 395–402*
37 Bertelsen A, Harvald B, Gauge M. A Danish twin study of manic-depressive disorders. *Br J Psychiatry* 1977; 130: 330–51
38 Farmer AE, McGuffin P, Gottesman II. Twin concordance for DSM-III schizophrenia: scrutinising the validity of the definition. *Arch Gen Psychiatry* 1987; 44: 634–41
39 Gottesman II, Bertelsen A. Confirming unexpressed genotypes for schizophrenia. *Arch Gen Psychiatry* 1989; 46: 867–72
40 Kringlen E, Cramer G. Offspring of monozygotic twins discordant for schizophrenia. *Arch Gen Psychiatry* 1989; 46: 873–7
41 Torrey EF, Taylor EH, Bracha HS *et al.* Prenatal origin of schizophrenia in a subgroup of discordant monozygotic twins. *Schizophr Bull* 1994; 20: 423–32
42 Bracha HS, Torrey EF, Gottesman II *et al.* Second trimester markers of fetal size in schizophrenia: a study of monozygotic twins. *Am J Psychiatry* 1992; 149: 1355–61
43 Davis JO, Phelps JA. Twins with schizophrenia: genes or germs? *Schizophr Bull* 1995; 21: 13–8
44 Kety SS. Mental illness in the biological and adoptive relatives of schizophrenic adoptees, findings relevant to genetic and environmental factors in etiology. *Am J Psychiatry* 1983; 140: 720–7
45 Kety SS, Wender PH, Jacobson B *et al.* Mental illness in the biological and adoptive relatives of schizophrenic adoptees. Replication of the Copenhagen Study in the rest of Denmark. *Arch Gen Psychiatry* 1994; 51: 442–55

46 Kendler KS, Gruenberg AM, Kinney DK. Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. *Arch Gen Psychiatry* 1994; 51: 456–68

47 Mendlewicz J, Rainer JD. Adoption study supporting genetic transmission in manic-depressive illness. *Nature* 1977; 268: 326–9

48 Wender PH, Kety SS, Rosenthal D *et al.* Psychological factors in the biological and adoptive relatives of individuals with affective disorders. *Arch Gen Psychiatry* 1986; 43: 923–9

49 Goodwin DW, Schulsinger F, Hermansen L *et al.* Alcohol problems in adopted raised apart from alcoholic biological parents. *Arch Gen Psychiatry* 1973; 28 238–43

50 Goodwin DW, Schulinger F, Knop J *et al.* Drinking problems in adopted and nonadopted daughters of alcoholics. *Arch Gen Psychiatry* 1977; 34: 1005–9

51 Bohman M. Some genetic aspects of alcoholism and criminality: a population of adoptees. *Arch Gen Psychiatry* 1978; 35: 269–76

52 Cardoret R, O'Gorman TW, Troughton E *et al.* Alcoholism and antisocial personality: interrelationships, genetic and environmental factors. *Arch Gen Psychiatry* 1978; 42: 161–7

53 Ball DM, Murray RM. Genetics of alcohol misuse. *Br Med Bull* 1994; 50: 18–35

54 Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse. *Arch Gen Psychiatry* 1981; 38: 861–8

55 Hill SV. Absence of paternal sociopathy in the etiology of severe alcoholism: is there a type III alcoholism? *J Stud Alcohol* 1992; 53: 161–9

56 Elston RC. Segregation analysis. *Adv Hum Genet* 1981; 11: 63–120

57 Lalouel JM, Rao DC, Morton NE *et al.* A unified model for complex segregation analysis. *Am J Hum Genet* 1983; 35: 816–26

58 Baron M. Genetics of schizophrenia: I. Familial patterns and mode of inheritance. *Biol Psychiatry* 1986; 21: 1051–66

59 Tsuang MT, Faraone SV. *The Genetics of Mood Disorders.* Baltimore: Johns Hopkins University Press, 1990

60 Rice J, Reich T, Andreasen NC *et al.* The familial transmission of bipolar illness. *Arch Gen Psychiatry* 1987; 44: 441–7

61 Sham PC, Morton NE, Rice JP. Segregation analysis of the NIMH collaborative study family data on bipolar disorder. *Psychiatr Genet* 1991; 2: 175–85

62 Vogler GP, Gottesman II, McGue MK *et al.* Mixed model analysis of schizophrenia in the Lindelius Swedish pedigrees. *Behav Genet* 1990; 20: 461–72

63 Holzman PS, Kringlen E, Matthysse S *et al.* A single dominant gene can account for eye tracking dysfunctions and schizophrenia in offspring of discordant twins. *Arch Gen Psychiatry* 1988; 45: 641–7

64 Sham PC, Morton NE, Muir WJ *et al.* Segregation analysis of complex phenotypes: An application to schizophrenia and auditory P300 latency. *Psychiatr Genet* 1994; 4: 29–38

65 McGue MK, Gottesman II. Genetic linkage in schizophrenia, perspectives from genetic epidemiology. *Schizophr Bull* 1989; 15: 453–64

66 Risch NJ. Linkage strategies for genetically complex traits. I. Multilocus models. *Am J Hum Genet* 1990; 46: 222–8

67 Craddock N, Khodel V, van Eerdewegh P *et al.* Mathematical limits of multilocus models: the genetic transmission of bipolar disorder. *Am J Hum Genet* 1995; 57: 690–702

68 Sham PC, Walters EE, Neale MC *et al.* Logistic regression analysis of twin data: estimation of parameters of multifactorial liability-threshold model. *Behav Genet* 1994; 24: 229–38

69 Morton NE. Sequential tests for the detection of linkage. *Am J Hum Genet* 1955; 7: 277–318

70 Ott J. *Analysis of Human Genetic Linkage*, 2nd edn. Baltimore: Johns Hopkins University Press, 1991

71 Holmans P. Asymptotic properties of affected sib pair linkage analysis. *Am J Hum Genet* 1993; 52: 362–74

72 Curtis D, Sham PC. Model-free linkage analysis using likelihoods. *Am J Hum Genet* 1995; 57 703–16

73 Risch NJ. Mapping genes for psychiatric disorders. In: Gershon ES, Cloninger CR. (Eds) *Genetic Approaches to Mental Disorders.* Washington: American Psychiatric Press, 1994; 47–61

74 St George-Hyslop PH, Tanzi RE, Polinsky RJ *et al.* The genetic defect causing familial Alzheimer's disease maps to chromosome 21. *Science* 1987; 235: 885–90
75 Schellenberg GD, Bird TD, Wijsman EM *et al.* Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14. *Science* 1992; 258: 668–71
76 Goate AM, Chartier-Harlin MC, Mullan M *et al.* Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991; 349: 704–6
77 Sherrington R, Rogaev EI, Liang Y *et al.* Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995; 375: 754–60
78 Winokur G. Genetic findings and methodological considerations in manic-depressive disease. *Br J Psychiatry* 1970; 117: 267–74
79 Risch NJ, Baron M, Mendlewicz J. Assessing the role of X-linked inheritance in bipolar-related major affective disorder. *J Psychiatr Res* 1986; 20: 275–88
80 Reiss AL, Feinstein C, Toomey KE *et al.* Psychiatric disability associated with the fragile X-chromosome. *Am J Med Genet* 1986; 23: 394–401
81 Baron M, Risch N, Hamburger R *et al.* Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature* 1987; 326: 289–92
82 Mendlewicz J, Simon P, Sevy S *et al.* Polymorphic DNA marker on X-chromosome and manic-depression. *Lancet* 1987; i: 1230–2
83 Gill M, Castle D, Duggan C. Cosegregation of Christmas disease and major affective disorder in a pedigree. *Br J Psychiatry* 1992; 160: 112–4
84 Baron M, Freimer NF, Risch N *et al.* Diminished support for linkage between manic-depressive illness and X-chromosome markers in three Israeli pedigrees. *Nature Genet* 1993; 3: 49–55
85 Berretini WH, Goldin LR, Gelernter J *et al.* X-chromosome markers and manic-depressive illness. Rejection of linkage to Xq28 in nine bipolar pedigrees. *Arch Gen Psychiatry* 1990; 47 366–73
86 Lucotte G, Landoulsi A, Berriche S *et al.* Manic-depressive illness is linked to factor IX in a French pedigree. *Ann Genet* 1992; 35: 93–5
87 Pekkarinen P, Brebacka PE, Terwilliger J *et al.* Evidence for a susceptibility locus for manic-depressive disorder in Xq26. *Am J Hum Genet* 1994; A27
88 Turner WJ, King S. BPD2: an autosomal dominant form of bipolar affective disorder. *Biol Psychiatry* 1983; 18: 63–87
89 Price RA. Affective disorder not linked to HLA. *Genet Epidemiol* 1989; 6: 299–304
90 Egeland JA, Gerhard DS, Pauls DL *et al.* Bipolar affective disorders linked to DNA markers on chromosome 11. *Nature* 1987; 325: 783–7
91 Kelsoe JR, Ginns EE, Egeland JA *et al.* Re-evaluation of linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. *Nature* 1989; 342: 238–43
92 Detera-Wadleigh SD, Berretini H, Goldin LR *et al.* Close linkage of c-Harvey-ras-1 and the Insulin gene to affective disorders is ruled out in three North American Pedigrees. *Nature* 1987; 325: 806–8
93 Hodgkinson S, Sherrington R, Gurling H *et al.* Molecular genetic evidence for heterogeneity in manic depression. *Nature* 1978; 325: 805–6
94 Lim LC, Gurling H, Curtis D *et al.* Linkage between tyrosine hydroxylase gene and affective disorder cannot be excluded in two of six pedigrees. *Am J Med Genet* 1993; 48: 223–8
95 Straub RE, Lehner T, Luo Y *et al.* A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nature Genet* 1994; 8: 291–6
96 Gurling H, Smyth C, Kalsi G *et al.* Linkage findings in bipolar disorder. *Nature Genet* 1995; 10: 8–9
97 Berretini WH, Ferraro TN, Goldin LR *et al* Chromosome 18 markers and manic-depressive illness: evidence for a susceptibility gene. *Proc Natl Acad Sci USA* 1994; 91: 5918–21
98 De Bruyn A, Souery D, Mendelbaum K *et al.* Positive linkage results with 18q21.33-q23 markers in a bipolar II family. *Psychiatr Genet* 1995; 5: S16
99 Craddock N, Nothen M, Parfitt E *et al.* Linkage studies of bipolar disorder with chromosome 18 markers. *Psychiatr Genet* 1995; 5: S16–S17.
100 Foroud T, Lahiri D, Guscar T *et al.* Chromosome 18 and bipolar affective disorder. *Psychiatr Genet* 1995; 5: S17

101 McMahon FJ, Stine OC, Xu J *et al.* Evidence for linkage of bipolar disorder to chromosome 18. *Psychiatr Genet* 1995; 5: S18

102 Kelsoe JR, Sadovnick AD, Kristbjarnarson H *et al.* Genetic linkage studies of bipolar disorder and chromosome 18 markers in North American, Icelandic and Amish pedigrees. *Psychiatr Genet* 1995; 5: S17–S18

103 Merette C, Rouillard E, Cliche D *et al.* No conclusive evidence of susceptibility loci for bipolar disorder on 18p11 and 21q22 in extended pedigrees of Eastern Quebec. *Psychiatr Genet* 1995; 5: S18

104 Smyth C, Kalsi G, Brynjolfsson J *et al.* Linkage analysis of manic depression (bipolar affective disorder), in Icelandic and British Kindreds, on the short arm of chromosome 18. *Psychiatr Genet* 1995; 5: S19

105 Bassett AS, McGillivary BC, Jones BD *et al.* Partial trisomy chromosome 5 cosegregating with schizophrenia. *Lancet* 1988; i: 799–801

106 Sherrington R, Brynjolfsson J, Petersson H *et al.* Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature* 1988; **336**: 164–7

107 Watt DC, Edwards JH. Doubt about evidence for a schizophrenia gene on chromosome 5. *Psychol Med* 1991; **21**: 279–85

108 McGuffin P, Sargeant M, Hetti G *et al.* Exclusion of a schizophrenia susceptibility gene from the chromosome 5q11-q13 region: New data and a reanalysis. *Am J Hum Genet* 1990; **47**: 524–35

109 Kendler KS, Diehl SR. The genetics of schizophrenia: a current genetic epidemiologic perspective. *Schizophr Bull* 1993; **19**: 261–85

110 Mankoo B, Sherrington R, Brynjolfsson J *et al.* New microsatellite polymorphisms provide a highly polymorphic map of chromosome 5 bands q11.2–q13.3 for linkage analysis of Icelandic and English families affected by schizophrenia. *Psychiatr Genet* 1991; **2**: 17

111 Crow TJ. Sex chromosomes and psychosis: The case for a pseudoautosomal locus. *Br J Psychiatry* 1988; **153**: 675–83

112 Crow TJ, Delisi LE, Johnstone EC. Concordance by sex in sibling pairs with schizophrenia is paternally inherited: evidence for a pseudoautosomal locus. *Br J Psychiatry* 1989; **155**: 92–7

113 Curtis D, Gurling H. Unsound methodology in investigating a pseudoautosomal locus in schizophrenia. *Br J Psychiatry* 1990; **156**: 415–6

114 Collinge L, De Lisi LE, Boceio E *et al.* Evidence for a pseudoautosomal locus for schizophrenia using the method of affected sibling pairs. *Br J Psychiatry* 1991; **158**: 624–9

115 Asherson P, Parfitt E, Sargeant M *et al.* No evidence for a pseudoautosomal locus for schizophrenia. Linkage analysis of multiply affected families. *Br J Psychiatry* 1992; **161**: 63–8

116 Wang ZW, Black D, Andreasen N *et al.* Pseudoautosomal locus for schizophrenia excluded in 12 pedigrees. *Arch Gen Psychiatry* 1993; 50: 199–204

117 Barr CL, Kennedy JL, Pakstis AJ *et al.* Linkage study of a susceptibility locus for schizophrenia in the pseudoautosomal region. *Schizophr Bull* 1994; **20**: 277–86

118 d'Amato T, Waksman G, Martinez M *et al.* Pseudoautosomal region in schizophrenia: linkage analysis of seven loci by sib-pair and lod-score methods. *Psychiatry Res* 1994; **52**: 135–47

119 Crow TJ, Delisi LE, Lofthouse R *et al.* An examination of linkage of schizophrenia and schizoaffective disorder to the pseudoautosomal region (Xp22.3). *Br J Psychiatry* 1994; **164**: 159–64

120 Kalsi G, Brynjolfsson J, Mankoo BS *et al.* Investigation by linkage analysis of the XY pseudoautosomal region in the genetic susceptibility to schizophrenia. *Br J Psychiatry* 1995; **167**: 390–3

121 Jensen S, Plaetke R, Holik J *et al.* Linkage analysis of schizophrenia: the D1 dopamine receptor gene and several flanking DNA markers. *Hum Hered* 1993; **43**: 58–62

122 Coon H, Byerley W, Holik J *et al.* Linkage analysis of schizophrenia with five dopamine receptor genes in nine pedigrees. *Am J Hum Genet* 1993; **52**: 327–34

123 Campion D, d'Amato T, Bastard C *et al.* Genetic study of dopamine D1, D2 and D4 receptors in schizophrenia. *Psychiatry Res* 1994; **51**: 215–30

124 Moises HW, Galenter J, Giuffra L *et al.* No linkage between D2 dopamine receptor gene region and schizophrenia. *Arch Gen Psychiatry* 1991; **48**: 643–7

125 Gill M, McGuffin P, Parfitt E *et al.* A linkage study of schizophrenia with DNA markers from the long arm of chromosome 11. *Psychol Med* 1993; **23**: 27–44

126 Su Y, Burke J, O'Neill A *et al.* Exclusion of linkage between schizophrenia and the D2 dopamine receptor gene of chromosome 11q in 112 Irish Multiplex families. *Arch Gen Psychiatry* 1993; **50**: 205–11

127 Hallmayer J, Maier W, Schwab S *et al.* No evidence of linkage between the dopamine D2 receptor gene and schizophrenia. *Psychiatry Res* 1994; **53**: 203–15

128 Kalsi G, Mankoo B S, Curtis D *et al.* Exclusion of linkage of schizophrenia to the gene for dopamine D2 receptor (DRD2) and chromosome 11q translocation sites. *Psychol Med* 1995; **25**: 531–7

129 Wiese C, Lannfelt L, Kristbjarnarson H *et al.* No evidence of linkage between schizophrenia and D3 dopamine receptor gene locus in Icelandic Pedigrees. *Psychiatry Res* 1993; **46**: 69–78

130 Sabate O, Campion D, d'Amato T *et al.* Failure to find evidence for linkage or association between the dopamine D3 receptor gene and schizophrenia. *Am J Psychiatry* 1994; **151**: 107–11

131 Barr CL, Kennedy JL, Lichter JB *et al.* Alleles at the dopamine D4 receptor locus do not contribute to the genetic susceptibility to schizophrenia in a large Swedish kindred. *Am J Med Genet* 1993; **48**: 218–22

132 Maier W, Schwab S, Hallmayer J *et al.* Absence of linkage between schizophrenia and the dopamine D4 receptor gene. *Psychiatry Res* 1994; **53**: 77–86

133 Macciardi F, Petronis A, Van Tol HHM *et al.* Analysis of the dopamine D4 receptor gene variant in an Italian Schizophrenia Kindred. *Arch Gen Psychiatry* 1994; **51**: 288–93

134 Shaikh S, Gill M, Owen M *et al.* Failure to find linkage between a functional polymorphism in the dopamine D4 receptor gene and schizophrenia. *Am J Med Genet* 1994; **54**: 8–11

135 Ravindranathan A, Coon H, DeLisi L *et al.* Linkage analysis between schizophrenia and a microsatellite polymorphism for the D5 dopamine receptor gene. *Psychiatr Genet* 1994; **4**: 77–80

136 Smith M, Wasmuth J, McPherson JD *et al.* Cosegregation of an 11q22–9p22 translocation with affective disorder: proximity of the dopamine receptor gene relative to the translocation breakpoint. *Am J Hum Genet* 1989; **45**: A220

137 Holland A, Gosden C. A balanced translocation partially cosegregating with psychotic illness in a family. *Psychiatry Res* 1990; **32** 1–8

138 St Clair D, Blackwood D, Muir W *et al.* Association within a family of a balanced autosomal translocation with major mental illness. *Lancet* 1990; **336**: 13–6

139 Pulver AE, Karayiorgou M, Wolyniec PS *et al.* Sequential strategy to identify a susceptibility gene for schizophrenia: Report of potential linkage on chromosome 22q12–q13.1: Part 1. *Am J Med Genet* 1994; **54**: 36–43

140 Ganguli R, Rabin BS. Increased serum interleukin 2 receptor concentration in schizophrenic and brain damaged subjects. *Arch Gen Psychiatry* 1989; **46**: 292

141 Shprintzen RJ, Goldberg R, Golding-Kushner KJ *et al.* Late onset psychosis in the velo-cardio-facial syndrome. *Am J Med Genet* 1992; **42**: 141–2

142 Pulver AE, Karayiorgou M, Lasseter VK *et al.* Follow-up of a report of a potential linkage for schizophrenia on chromosome 22q12-q13.1: Part 2. *Am J Med Genet* 1994; **54**: 44–50

143 Vallada HP, Collier D, Sham PC *et al.* Linkage studies on chromosome 22 in familial schizophrenia. *Am J Med Genet* 1995; **60** 139–46

144 Coon H, Holik J, Hoff M *et al.* Analysis of chromosome 22 markers in nine schizophrenic pedigrees. *Am J Med Genet* 1994; **54**: 72–9

145 Gill M, Vallada H, Collier D *et al.* A combined analysis of D22S278 marker alleles in affected sib-pairs: Support for a susceptibility locus for schizophrenia at chromosome 22q12. *Am J Med Genet* 1995; In press

146 Wang W, Sun C, Walczak CA *et al.* Evidence for a susceptibility locus for schizophrenia on chromosome 6pter-p22. *Nature Genet* 1995; **10** 41–6

147 Straub RE, MacLean CJ, O'Neill A *et al.* A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. *Nature Genet* 1995; **11**: 287–93

148 Moises HW, Yang L, Kristbjarnarson H *et al.* An international two-stage genome-wide search for schizophrenia susceptibility genes. *Nature Genet* 1995; **11**: 321–4

149 Schwab SC, Albus M, Hallmayer J *et al.* Evaluation of a susceptibility gene for schizophrenia on chromosome 6p by multipoint affected sib-pair linkage analysis. *Nature Genet* 1995; **11**: 325–7

150 Antonarakis AE, Blouin JL, Pulver AE *et al.* Schizophrenia susceptibility and chromosome 6p24-22. *Nature Genet* 1995; **11**: 235–6

151 Mowry BJ, Nancarrow DJ, Lennon DP *et al.* Schizophrenia susceptibility and chromosome 6p24-22. *Nature Genet* 1995; **11**: 233–4

152 Gurling H, Kalsi G, Chen AHS *et al.* Schizophrenia susceptibility and chromosome 6p24-22. *Nature Genet*: 1995; **11**: 234–5

153 Spielman RS, McGinnis RE, Ewens WJ. Transmission test for linkage disequilibrium: the insulin gene region and insulin dependent diabetes mellitus (IDDM). *Am J Hum Genet* 1993; **52**: 506–16

154 Sham PC, Curtis D. An extended transmission/disequilibrium test (TDT) for multi-allele marker loci. *Ann Hum Genet* 1995; **59**: 323–36

155 Hardy J. Apolipoprotein E in the genetics and epidemiology of Alzheimer's disease. *Am J Med Genet* 1995; **60**: 456–60

156 Corder EH, Saunders AM, Strittmatter WJ *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; **261**: 921–3

157 Yu CE, Payami H, Olson JM *et al.* The apolipoprotein E/CI/CII gene cluster and late onset Alzheimer disease. *Am J Hum Genet* 1994; **54**: 631–42

158 Houlden H, Collinge J, Kennedy A *et al.* ApoE genotype and Alzheimer's disease. *Lancet* 1993; **342**: 737–8

159 St George-Hyslop PH, Crapper McClachlan D, Tsuda T *et al.* Alzheimer's disease and possible gene interaction. *Science* 1994; **263**: 537

160 Goedde HW, Agarwal DP, Fritze G. Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet* 1992; **88**: 344–6

161 Shibuya A, Yoshida A. Genotypes of alcohol metabolising enzymes in Japanese with alcohol diseases: a strong association of the usual Caucasian-type aldehyde dehydrogenase gene (ALDH2/1) with the disease. *Am J Hum Genet* 1988; **43**: 744–8

162 Thomasson HR, Edenberg HJ, Crabb DW *et al.* Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. *Am J Hum Genet* 1991; **48**: 677–81

163 Blum K, Noble EP, Sheridan PJ *et al.* Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA* 1990; **263**: 2055–60

164 Gelernter J, Goldman D, Risch N. The A1 allele at the D2 dopamine receptor gene and alcoholism: a reappraisal. *JAMA* 1993; **269**: 1673–7

165 Noble EP. The D2 dopamine receptor gene: a review of association studies in alcoholism. *Behav Genet* 1993; **23**: 119–29

166 Smith SS, O'Hara BF, Persico AM *et al.* Genetic vulnerability to drug abuse: the D2 receptor TaqI B1 restriction fragment length polymorphism appears more frequently in polysubstance abuse. *Arch Gen Psychiatry* 1992; **49**: 723–7

167 Comings DE, Mullemen D, Ahn C *et al.* The dopamine D2 receptor gene: a genetic risk factor in substance abuse. *Drug Alcohol Depend* 1994; **34**: 175–80

168 Crabbe JC, Belknap JK, Buck KJ. Genetic animal models of alcohol and drug abuse. *Science* 1994; **264**: 1715–23

169 Leboyer M, Malafosse A, Boularand S *et al.* Tyrosine hydroxylase polymorphism associated with manic-depressive illness. *Lancet* 1990; **335**: 1219

170 Korner J, Fritze J, Propping P. RFLP alleles at the tyrosine hydroxylase locus: no association found to affective disorders. *Psychiatry Res* 1990; **32**: 375–80

171 Gill M, Castle D, Hunt N *et al.* Tyrosine hydroxylase polymorphisms and bipolar disorders. *J Psychiatr Res* 1991; **25** 179–84

172 Inayama Y, Yoneda H, Sakai T *et al.* Lack of association between bipolar affective disorder and tyrosine hydroxylase DNA marker. *Am J Med Genet* 1993; **48**: 87–9

173 Korner J, Rietshel M, Hunt N *et al.* Association and haplotype analysis at the tyrosine hydroxylase locus in a combined German-British sample of manic depressive patients and controls. *Psychiatr Genet* 1994; **4**: 167–75

174 Meloni R, Leboyer M, Bellivier F *et al.* Association of manic-depressive illness with tyrosine hydroxylase microsatellite marker. *Lancet* 1995; 345: 932

175 Lim LC, Powell JF, Murray RM *et al.* Monoamine oxidase A gene and bipolar affective disorder. *Am J Hum Genet* 1994; 54: 1122–4

176 Kawada Y, Hattori M, Dai XY *et al.* Possible association between monoamine oxidase A gene and bipolar affective disorder. *Am J Hum Genet* 1995; 56: 335–6

177 Nothen MM, Eagermann K, Albus M *et al.* Association analysis of the monoamine oxidase A gene in bipolar affective disorder by using family-based internal controls. *Am J Hum Genet* 1995; 57: 975–7

178 McGuffin P, Sturt E. Genetic markers in schizophrenia. *Hum Hered* 1986; 36: 65–88

179 Alexander RC, Coggiano M, Daniel DG *et al.* HLA antigens in schizophrenia. *Psychiatry Res* 1990; 31: 221–3

180 Campion D, Leboyer M, Hillaire D *et al.* Relationship of HLA to schizophrenia not supported in multiplex families. *Psychiatry Res* 1992; 41: 99–105

181 Wright P, Donaldson PT, Curtis VA *et al.* Immunogenetic markers in schizophrenia: HLA A9 revisited. *Schizophr Res* 1995; 15: 50

182 Wright P, Donaldson P, Underhill J *et al.* Schizophrenia is negatively associated with HLA DR4 in probands and their mothers. *Schizophr Res* 1995; 15: 203

183 Sanders A, Hamilton J, Chakraborty R *et al.* Association of genetic variation at the porphobilinogen deaminase gene with schizophrenia. *Schizophr Res* 1993; 8: 211–21

184 Owen MJ, Mant R, Parfitt E *et al.* No association between RFLP's at the porphobilinogen deaminase gene and schizophrenia. *Hum Genet* 1992; 90: 131–2

185 Nimgaonkar VL, Ganguli R, Washington SS *et al.* Schizophrenia and porphobilinogen: an association study. *Schizophr Res* 1992; 8: 51–8

186 Arinami T, Itokawa M, Anhuchi H *et al.* Association of dopamine D2 receptor molecular variant with schizophrenia. *Lancet* 1994; 343: 703–4

187 Asherson P, Williams N, Roberts E *et al.* DRD2 ser311/cys311 polymorphism and schizophrenia. *Lancet* 1994; 343: 1045

188 Gejman P, Ram A, Gelernter J *et al.* No structural mutation in the dopamine D2 receptor gene in alcoholism and schizophrenia. *JAMA* 1994; 19 204–8

189 Laurent C, Bodeau-Pean S, Campion D *et al.* No major role for the dopamine D2 receptor Ser-Cys311 mutation in schizophrenia *Psychiatr Genet* 1994; 4: 299–30

190 Nanko S, Hattori M, Fukuda R *et al.* DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* 1994; 343 *1044*

191 Nothen MM, Wildenauer D, Cichon S *et al.* Dopamine molecular variants and schizophrenia. *Lancet* 1994; 343: 1301–2

192 Shaikh S, Collier D, Arranz M *et al.* DRD2 ser311/cys311 polymorphism in schizophrenia. *Lancet* 1994; 343 1045–6

193 Crocq MA, Mant R, Asherson P *et al.* Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. *J Med Genet* 1992; 29: 858–60

194 Nothen MM, Cichon S, Propping P *et al.* Excess of homozygosity at the dopamine D3 receptor gene in schizophrenia not confirmed. *J Med Genet* 1993; 30: 708–9

195 Nimgaonkar VL, Zhang XR, Caldwell JG *et al.* Association study of schizophrenia with dopamine D3 receptor polymorphism: probable effect of family history of schizophrenia. *Am J Med Genet* 1993; 48: 214–7

196 Jonsson E, Lannfelt L, Sokoloff P *et al.* Lack of association between schizophrenia and alleles at the D3 receptor gene. *Acta Psychiatr Scand* 1993; 87: 345–9

197 Mant R, Williams J, Asherson P *et al.* Relationship between homozygosity at the dopamine D3 receptor gene and schizophrenia. *Am J Med Genet* 1994; 54: 21–6

198 Di Bella D, Catalano M, Strukel M *et al.* Distribution of the MscI polymorphism of the dopamine D3 receptor in an Italian psychotic population *Psychiatr Genet* 1994; 4:, 39–42

199 Nanko S, Sasaki T, Fukuda R *et al.* A study of the association between schizophrenia and the dopamine D3 receptor gene. *Hum Genet*: 1993; 92, 336–8

200 Yang L, Weise C, Lannfelt L *et al.* No association between schizophrenia and homozygosity at the D dopamine receptor gene. *Am J Med Genet* 1993; 48: 83–6

201 Saha N, Tsoi WF, Low PS *et al.* Lack of association of the dopamine D3 receptor gene polymorphism (BalI) in Chinese schizophrenics. *Psychiatr Genet* 1994; **4**: 201–4
202 Daniels J, Williams J, Mant R *et al.* Repeat length variation in the dopamine D4 receptor gene shows no evidence of association with schizophrenia. *Am J Med Genet* 1994; **54**: 256–8
203 Petronis A, Macciardi F, Athanassiades A *et al.* Association study between the dopamine D4 receptor gene and schizophrenia. *Am J Med Genet* 1995; 60: 452–5
204 Moises HW, Yang L, Li T *et al.* Potential linkage disequilibrium between schizophrenia and locus D22S278 on the long arm of chromosome 22. *Am J Med Genet* 1995; 60: 465–7
205 Vallada HP, Curtis D, Sham PC *et al.* Chromosome 22 markers demonstrate transmission disequilibrium with schizophrenia. *Psychiatr Genet* 1995; In press