

## Genetics of affective disorders

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### Abstract

Despite substantial evidence for heritability in affective disorders the contributing genes have proven elusive. Here we discuss the genetic epidemiology of depression, as well as methodological issues and results from molecular genetic studies. There has been rapid advances in genetics, genomics and statistical modelling, facilitating the search for molecular mechanisms underlying affective disorders and several strategies reviewed in this paper hold promise to provide progress in the field. Considering the poorly understood biological basis of vulnerability to affective disorders, the identification of genes involved in the pathophysiology will unravel mechanisms and pathways that could permit more personalized therapeutic strategies and result in new targets for pharmacological intervention. © 2001 Published by Elsevier Science B.V.

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### 1. Introduction

Affective disorders constitute a major public health problem, with considerable costs for the society and suffering for the individual. Unfortunately, the aetiologies of these diseases remain largely unknown. The recent tremendous advances in the areas of molecular genetics and biotechnology, as well as more sophisticated statistical methods for analysing complex mode of inheritance, have created new opportunities to detect so-called susceptibility alleles, variants of genes that increase the risk for disease. Identification of these genes and the biological context in which they act, will improve our understanding of depression and is expected to result in more effective and specific therapeutic strategies. Most genetic studies of affective disorders have focused on bipolar disorder, also referred to as manic depressive illness. We will discuss this and other types of depression including unipolar major depression

and seasonal affective disorder (for disease classifications see American Psychiatric Association, 1994).

### 2. Genetic epidemiology of affective disorders

#### 2.1. Familial aggregation

In order to claim that a trait has a genetic component one would first like to observe familiarity, i.e. that it runs in families. One way of expressing the degree of family clustering is by the recurrence risk ratio,  $\lambda_R$ , which is the disease risk of a relative of an affected individual divided by the population prevalence. If there is familial aggregation  $\lambda_R$  will exceed 1 and is expected to be higher for first-degree relatives (parents, siblings or children) than for more distant relationships.

Bipolar affective disorder is reported to have an age-corrected lifetime risk of 0.3–1.5% in the general population, with equal risks for men and women. First-degree relatives have a  $\lambda_R=7$  and monozygotic twins have a  $\lambda_R=60$  (NIMH, 1999). While not exclusive, these findings do not lend support to a single gene model of inheritance

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and several models including a multiplicative model with at least three loci have been suggested (Craddock et al., 1995). Studies of unipolar major depression have yielded varying results for the population prevalence, 2–19%, as well as for the age-adjusted risk for first-degree relatives, 5–25% (NIMH, 1999). These discrepancies could reflect population differences or methodological variations. However, a 2- to 3-fold increased risk for women compared to men seems to be found consistently (NIMH, 1999). In a large population-based study, the  $\lambda_R$  for first-degree relatives (dizygotic twins) was reported to be 1.1–1.6 (Kendler et al., 1992). A recent meta-analysis of five large and carefully selected family studies of major depression gave a summary odds ratio of 2.84 for affected subject versus first-degree relative status (affected or unaffected), clearly demonstrating familiarity in this disease (Sullivan et al., 2000). Notably, it appears that early age of onset and multiple episodes of depression increase the familial aggregation (NIMH, 1999).

In conclusion, both bipolar and unipolar depressions are familial disorders where the disease risk is higher for relatives compared to the general population. Naturally, when evaluating family studies one must bear in mind that family members not only have genetic alleles in common, they also share numerous environmental factors. To separate these components other approaches like twin or adoption studies are applicable.

## 2.2. Genes and environment

Twin studies exploit the unique degree of genetic and environmental sharing between monozygotic (MZ) twins, who share a common set of genes (100%), and dizygotic (DZ) twins, who share on average 50% of segregating genes. In addition both MZ and DZ twins share the same uterus, birth date, age and aspects of their early and later environment. This allows the variation of any trait or disease on a population level to be separated into genetic, shared environmental and unique environmental components, based on the principle that if a trait is not influenced by heredity, MZ twins should not be more similar for the trait in question than DZ twins. On the other hand, if heredity is important, MZ twins will resemble each other to a greater extent than DZ twins. By applying quantitative analytical techniques to twin data, it is possible to estimate the size of the contribution of the individual components of variation. This provides an estimate of heritability ( $h^2$ ), a measure of the extent to which phenotypic variation can be explained by genetic variation (MacGregor et al., 2000). Numerous twin studies indicate that the concordance for MZ twins differs markedly to that of DZ twins with respect to affective disorders. For bipolar disorder, four twin studies have estimated the heritability to be from 30 to 80% (NIMH, 1999). A meta-analysis of seven twin studies on major depression showed an overall heritability of 37% and concluded that there was almost no effect of

shared environment, but a substantial effect of the unique environment of 63% (Sullivan et al., 2000). In a large Swedish twin study higher heritability was found (57% for men and 78% for women), possibly due to an age effect (Kendler et al., 1995).

An alternative to twin studies for delineating genetic and environmental effects are adoption studies. When a child is adopted, genetically related individuals will no longer share the same environment, instead genetically unrelated individuals will. Adoption studies can be performed either by finding adoptees who suffer from a disease and see whether the disease runs in their biological or adoptive family, or by finding affected individuals whose children have been adopted by another family and see whether that has decreased the disease risk for the child. The results from two adoption studies on bipolar disorder and two out of three studies of unipolar major depression are consistent with a significant genetic component in both disorders (NIMH, 1999; Sullivan et al., 2000), thus supporting the conclusions from the twin studies.

## 3. Linkage analysis

### 3.1. Parametric and nonparametric linkage analysis

Since the 1980s linkage analysis in large families has shown enormous success in mapping disease genes for so-called Mendelian monogenic diseases (Collins, 1995). In these studies, known non-pathogenic sequence variations, or polymorphic genetic markers, which are present throughout the human genome constitute the tools for identifying the chromosomal region containing the disease gene. Due to meiotic recombination events, marker alleles that co-segregate with the disease within a family are likely to be located close to the disease-causing gene. To analyse the results from a whole genome screen in kindreds, assumptions have to be made regarding the mode of inheritance, the penetrance of the mutation and the frequency of the disease allele in the population. For many diseases, including affective disorders, these parameters are unknown and, perhaps mistakenly (Hodge, 2001) nonparametric methods have generally been preferred.

In the affected pedigree member method (Weeks and Lange, 1988) hundreds of pairs of affected relatives, in most cases siblings, are studied. Siblings share on average 50% of their alleles, however, pairs of siblings affected by the same illness will have increased allele sharing for markers close to the disease gene. This is independent of whether the disease is dominant, recessive or non-Mendelian making such specifications unnecessary.

### 3.2. Linkage studies of affective disorders

Bipolar disorder is by far the most frequently studied

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