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Genetic epidemiology of major depression

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The aim of genetic epidemiology is to study how much of the variation in a characteristica is due to genetic variation, and how much is due to variation in environment. The genetic variation can be additive, or non-additive implying the configuration of genes. The environment can be the effect of growing up in a particular family (shared family environment) or the effect of factors only influencing one family member (non-shared in the family environment). Unfortunately, less than ideal reliability is included in the non-shared environmental effect. Since the sum is 100%, a bloated non-shared environment effect wrongly reduces the effect of genes as well as shared environment.

The methods used are family studies, twin studies, adoptive studies and microgenetic studies. The last kind of studies is not the topic of this article. Unfortunately, family studies cannot distinguish between genes and shared environment and not so easily detect non-additive genetic effects. Adoptive studies are informative, but they can also not detect non-additive genetic effects. However, the combined information from all three kinds of studies gives us a good picture of the relative importance of genes and environment for some specific characteristica.

Earlier family studies were most common, in the latest decades twin studies are mostly applied. The ideal is a combination of twin and family studies, studies of twins reared apart. However, such twin pairs are very rare.

To have or have not a major depression is an important variation that genetic epidemiological studies investigate. Ideally one should study the life time risk. However, in practice this is difficult because of the age of the twins, and the fact that one forgets episodes of depression.

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Some early twin studies of major depression were conducted in Norway (Torgersen, 1986), McGuffin et al. (1996) have contributed importantly in England. However, the most informative studies were conducted by Ken Kendler and his research group in Virginia.

Common for all these studies is that to find any effect of shared family environment appears very difficult. That means that you are not more likely to get a major depression if you grow up in one particular family than if you grow up in another family. However, what kind of genes you receive from your parents mean a lot. Some will say that the family environment means a lot through the effect of gene-environment interaction. The effect of genes depends on the environment. Caspi et al. (2003) and Kendler et al. (2005) have published studies suggesting this. However, what is taken for gene-environment interaction can in reality be gene-gene interaction. If you grow up in an unfavourable environment, the source of the obnoxious environment may be un-known genes you inherit as well in addition to the target gene, increasing the risk of depression.

The Virginia studies have found a heritability of 39% (Kendler and Prescott, 1999). This is close to what Sullivan et al. (2000) found was the average of a number of studies (37%). Studies of clinical populations have given a higher estimate, more than 50% heritability. A reason can be methodological short-comings. However, there may also be another explanation. Clinical cases are more severe than those never treated in psychiatry. And more severe major depression appears to be more strongly influenced by genes (Torgersen, 1986). Some cases in population studies may be false positives, reducing the numbers for the genetic effects in the population studies. The highly valuated techniques of letting different interviewers interview the twin partners, usually used in population studies, may reduce bias connecting to falsely rating monozygotic twins as too similar. However an interviewer bias is introduced. The two interviewers may be different as to how good they are in making the twins talk about their problems, and they may have different thresholds for rating a verbal answer as a symptom. Hence the concordance of the twins are falsely reduced (fig. 1).

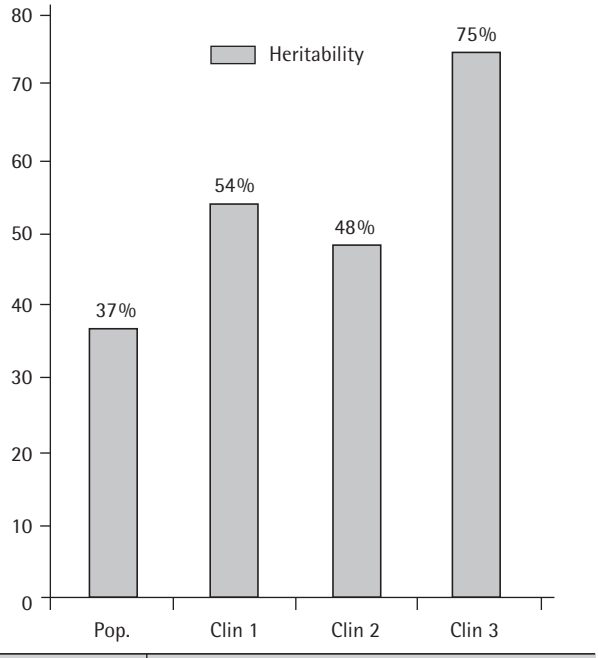

Figura 1 *Heritability of major depression. Pop.: Sullivan et al., 2000, population studies; Clin 1: Torgersen, 1986, patients; Clin 2: McGuffin et al., 1996, patients, minimum calculation; Clin 3: MaGuffin et al., 1996, maximum calculation.*

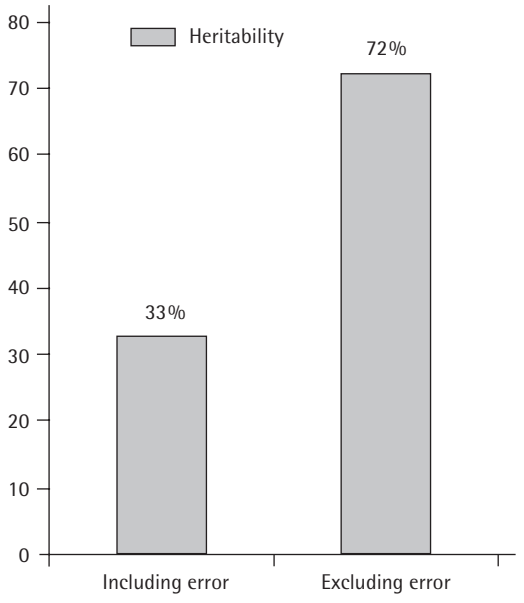

Figura 2 *Heritability of major depression. Kendler et al., 1993. Heritability calculated based on the twins direct information and based on correction for measurement error (taking into account the difference between information from mail and from interview).*

Studies based on repetitive measurements have given higher heritability estimates, with an increase from 33% to 72% (Kendler et al., 1993). This is a dramatic demonstration of how measurement errors can reduce the heritability. It may also imply that more chronic depression is more highly influenced by genes. In any case, the usual reported heritability estimates for depression is probably far too low (fig. 2).

Generally, we can state that the more severe the depression is, the higher heritability. Psychotic and melancholic major depression is more heritable than milder depression. The heritability is also higher in recurrent depression, but probably not in so called endogenous depression. Major depression is genetically linked to dysthymic depression and depressive adjustment disorder, and to bipolar I, bipolar II and cyclothymic disorder (Torgersen, 1986; Rapaport et al., 2002; Edvardsen et al., 2007). Furthermore, it is genetically linked to anxiety disorders, to alcohol and drug disorders, bulimia (Kendler et al., 1995; Kendler et al., 2003) and probably to somatoform disorders (masked depression) (figs. 3 and 4).

The way genes influence the manifestation of major depression may be directly influencing affects and thoughts. However, the effects also seem to be indirect (Kendler et al., 2002). Genes influence the childhood conditions. The parents share genes with the offspring, genes that in some influence the way the parents behave. Also the gene-influenced behaviour of the child may make people around to behave toward the child in specific ways. Genes and childhood conditions influence the development of personality disorders as well as personality generally. Personality disorders, together with childhood conditions influence the likelihood of experiencing negative life-events. Negative life-events as well as personality disorders, and childhood conditions influence the risk of major depression. The risk of major depression can also be directly influenced of genes. Major depression is not seldom, elicited by negative life-events. But these are not so seldom, caused by the person. Furthermore,

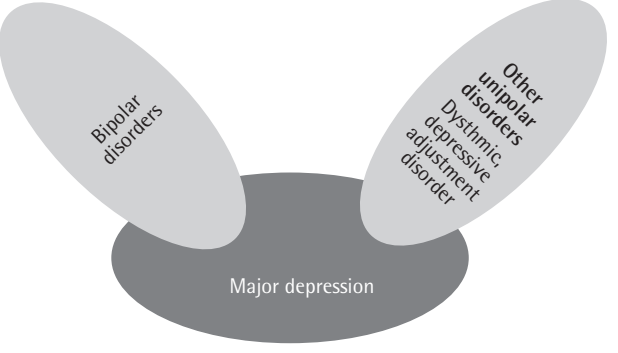

Figura 3 *Major depression shares genes with both bipolar disorders and milder unipolar disorders.*

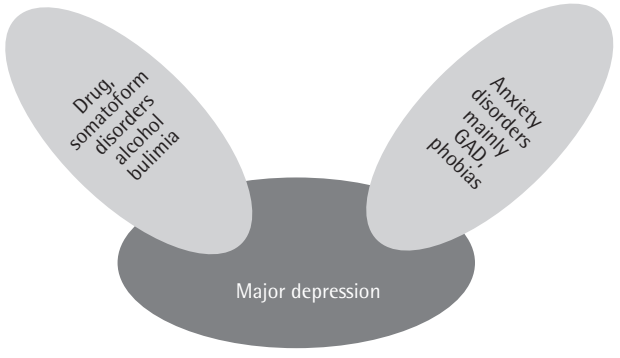

Figura 4 *Major depression shares genes with alcohol, drug disorders, bulimia, somtoform and anxiety disorders.*

eliciting life-events may more determine when the depression shall occur, not whether a person shall experience a depression in his lifetime. The depression may influence personality, create new negative life-events and make the basis for a new depressive episode, and so on (fig. 5).

CONCLUSION

At least half the causes of the fact that some experience a clinical depression, others not, are due to genes. More severe subtypes of major depression are probably more strongly genetically influenced. The specific family in which you grow up is probably not so important. The other half of the causality is non-shared family or unique environment. This is far from only psycho-social environment. It is also influence from things taking place before the birth, during the delivery, physical, somatic events later, illness, virus, may be even nourishment and the physical environment, physical work conditions, everything that may influence the likelihood of developing depression. Major depression is genetically linked to a number of other mental disorders, and the whole spectrum of mood disorders.

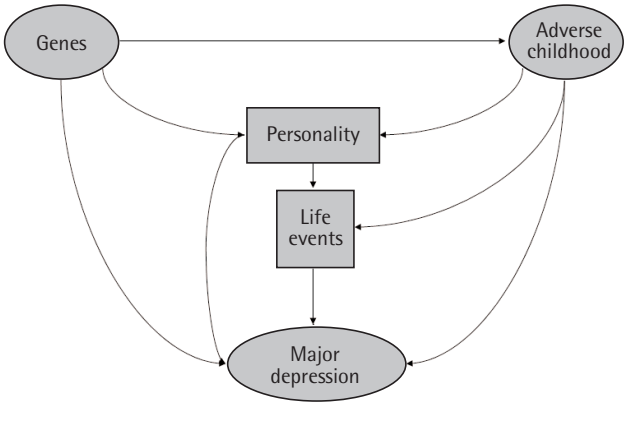

Figura 5 *The relationship within risk factors and between risk factors and major depression.*

The way genes influence the various aspects of the elements in the road to the clinical depression, childhood conditions, personality, life-events, supportive and obnoxious environment, the working-together of genes and environment, is still largely unknown. The same is true for the pathway from genes, via brain functions to experience. Also the interaction of genes and the possible subdivisions of major depression based on the genetic under-pinning await the future discoveries.

REFERENCES

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.

Edvardsen J, Torgersen S, Røysamb E, Lygren S, Skre I, Onstad S, et al. Heritability of bipolar spectrumdisorders. Unity or heterogenity? J Affect Disord 2007. (In press).

Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in women. Am J Psychiatry 2002;159:115-24.

Kendler KS, Kuhn JW, Wittchen J, Prescott CA, Riley B. The interaction of stressful life events and serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch Gen Psychiatry 2005;62:529-35.

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women: reliability of diagnosis and heritability. Arch Gen Psychiatry 1993;50:863-70.

Kendler KS, Prescott CA. A population-based twin study of lifetime major depression in men and women. Arch Gen Psychiatry 1999; 56:39-44.

Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorder in men and women. Arch Gen Psychiatry 2003; 60:929-37.

Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. 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.

McGuffin P, Katz R, Watkins S, Rutherford J. A hospital-based twin register of the heritability of DSM-IV unipolar depression. Arch Gen Psychiatry 53:129-36.

Rapaport MH, Judd LL, Schettler PJ, Yokers KA, Thase ME, Kupfer DJ, et al. A descriptive analysis of minor depression Am J Psychiatry 2002;159:637-43.

Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157: 1552-62.

Torgersen S. Genetic factors in moderately severe and mild affective disorders. Arch Gen Psychiatry 1986;43:222-6.