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EDITORIAL

Depression and cardiovascular disease: co-occurrence or shared genetic substrates?

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The World Health Organization Global Burden of Disease Survey estimates that coronary heart disease and depression are the first and second causes of disability in developed countries (and by the year 2020, this estimate will be applicable to all countries). Many individuals suffer from both of those two disorders. Is that the result of the co-occurrence of two common, but independent, conditions or the outcome of shared biological mechanisms?

The fact that psychiatric disorders and heart disease can be different manifestations of the same biological substrates has been well documented. Those substrates include infections and nutritional deficiency, specifically advanced syphilis and thiamine deficiency. Cases of advanced syphilis are rather rare nowadays, but in the pre-antibiotic era about one-third of patients with untreated latent disease developed the tertiary form of syphilis. *Treponeme pallidum* would invade several tissues, and the CNS (neurosyphilis) and cardiovascular (cardiac syphilis) symptoms were quite dramatic and easily recognizable. Thiamine deficiency can be manifested by cardiovascular or central nervous system (CNS) symptoms. The cardiovascular presentation is known as Shoshin beriberi or wet beriberi. The CNS manifestations of thiamine deficiency (dry beriberi) include the Wernicke–Korsakoff syndrome, which is frequently related to chronic alcoholism associated with malnutrition.

What is the relation between depression and heart disease that is seen in clinical practice in the 21st century? It has been well documented that depression increases the risk of cardiovascular disease; on the other hand, patients with cardiovascular disease suffer from depression more frequently than the general population.

Depression is related to coronary heart disease, hypertension and stroke, and it is now recognized as an independent risk factor for cardiovascular disease. Epidemiological data indicate that depression predicts the development of coronary heart disease in otherwise healthy individuals.[1] Several studies reported increased morbidity and mortality in depressed patients with coronary artery disease, particularly after acute myocardial infarction, independent of previous history, thereby implicating depression as a risk factor in the progression of heart disease.[2] Depression is associated with a four-fold increase in the risk of mortality during the first 6 months following acute myocardial infarction, after controlling for covariates. The prognostic significance of depression in patients with heart disease is comparable to that of left ventricular dysfunction and prior myocardial infarction.[3] Additionally, a number of well-designed studies have demonstrated that depressed patients have a higher risk for developing hypertension.[4,5]

A complete understanding of the mechanisms underlying the heart disease–depression relationship is still an unfulfilled goal. Several biological pathways, which may be redundant, are thought to be possible substrates for that relation. Those include hyperactivity of noradrenergic and hypothalamic-pituitary-adrenal (HPA) systems, reduced heart rate variability, myocardial ischemia and ventricular instability in response to psychological stress, and abnormalities in platelet reactivity.[2] Furthermore, depression is associated with several cardiac risk factors, such as diabetes, hypertension and cigarette smoking. Components of the metabolic syndrome, which is a cluster of risk factors for coronary heart disease, have been reported to be present in a significantly higher percentage in patients with depression than in controls.[6] Elevated plasma homocysteine levels and a low intake or reduced levels of omega-3-fatty acids are also suggested to be shared risk factors for depression and cardiovascular disease. The presence of one disease can complicate the management of the other: depressed patients with coronary heart disease show less compliance to cardiac prevention and treatment regimens. Additionally, the choice of antidepressant treatment is limited in patients with heart disease.

An emerging hypothesis raised in the article by Bondy *et al* (pages 1120–1126) in this issue is that depression and cardiovascular disease could be different manifestations of the same genetic substrates. Like other multifactorial and polygenic disorders, these two conditions are the result of the interaction of multiple genetic factors with the environment. The genetics of both disorders is complex, involving multiple genes with small interactive and additive effects. In spite of enormous amounts of work in the field of genetics, studies of depression and cardiovascular risk are often confounded by gene–gene and gene–environment interactions. Such interactions underlie at the molecular level the synergy between the products of various genes or between gene products and environmental factors, resulting in a greater than additive effect on risk. Genetic risk is thus modifiable in an environment-specific manner. Gene effects can amplify the effect of environmental or metabolic factors on the final phenotype rather than directly affect the risk of the disease.

If the co-morbidity of depression and cardiovascular

disease is etiologically determined, genetic approaches might increase our understanding of the mechanisms that are common to these two conditions. Bondy *et al* (pages 1120–1126) report on two genes that seem to be associated with depression. Those same genes have been shown to increase the risk for myocardial infarction. The authors studied the angiotensin I converting enzyme (ACE) insertion/deletion (ID) and the G-protein β3-subunit (Gβ3) C825T polymorphism in 201 patients with unipolar major depression and 161 ethnic- and age-matched controls. They found a significant increase in the Gβ3 T allele, and a marginal altered genotype distribution of the ACE ID polymorphism with decrease in the II genotypes in the patient group. This shows an effect of combined ACE and Gβ3 genotypes in the carriers of the ACE D allele (ID and DD) and Gβ3 TT homozygotes, with ID/DD-TT carriers showing a more than five-fold increase in the risk for major depression.

There is increasing evidence that implicates involvement of the renin-angiotensin system in the regulation of affect. G proteins and second messenger systems have also been implicated in the pathophysiology of mood disorders.

Several studies have examined genetic variations of the genes encoding the elements of these systems, and the interaction of those susceptibility genes with other risk factors for coronary heart disease. Over the past decade, the ID polymorphism of a 287-bp Alu element in intron 16 of the ACE gene has attracted significant attention and has been extensively investigated in a spectrum of cardiovascular phenotypes. A majority of previous studies has shown a positive association between the DD genotype and an increased risk of myocardial infarction, whereas results in hypertension, left ventricular hypertrophy and cardiomyopathy are controversial.[7] Naber *et al*[8] demonstrated a significant interaction between the ACE D allele and the Gβ3 T825 allele in a group of 585 patients with coronary heart disease with (n = 270) and without (n = 315) previous myocardial infarction. The risk for myocardial infarction associated with the T825 allele was not increased in carriers of the ACE II genotype, but was significantly elevated in carriers of the ACE ID genotype, and further increased in individuals with the ACE DD genotype. The highest odds ratio was found in those who were homozygous for both Gβ3 T825 allele and ACE D alleles. As ACE ID is an intronic marker, the actual mechanism for its possible impact on ACE enzyme activity remains to be identified, and could be due to this marker being in linkage disequilibrium with another (causative) locus.

Both Gβ3 C825T polymorphism and ACE ID polymorphism have been studied in affective disorders. Bondy and colleagues previously documented higher frequency of the T allele for the Gβ3 C825T polymorphism in patients with depression. In a study assessing ACE ID polymorphism, the frequency of allele D and the DD genotype was increased in Japanese patients with affective disorders,[9] whereas a study of 169 German patients and matched controls found no significant association with depression and polymorphism of the ACE gene.[10] Association studies can yield conflicting results among research centers for a variety of reasons, such as local bias in ascertaining phenotypes, different allele frequencies in various communities, and variations in the relative contribution of specific alleles to complex, polygenic phenotypes across populations. Moreover, consideration of potential gene–gene and gene–environment interactions is crucial to a better understanding of the contribution of genetic factors. The present study is highly relevant because it examines gene–gene interactions that contribute to our understanding of the role of genetic factors in depression and possibly associated cardiovascular risk. In the context of gene–environment interactions, patients and controls in Bondy's study were comparable for common risk factors for cardiovascular disease, including cigarette smoking, total cholesterol, triglyceride, fasting glucose, blood pressure and body mass index. However, these data do not preclude the possibility that the patients with ID/DD-TT genotype might have subclinical differences in cardiovascular status that could have only been assessed by imaging methods and functional tests. The lack of such assessments is a limiting factor of this study, because subclinical cerebrovascular disease may potentially affect the phenotype of depression. This type of methodological limitation is however hard to circumvent in patient-oriented investigation.

The article by Bondy *et al* contributes to the elucidation of gene–gene interactions of relevance to depression (and also thought to have a role in heart disease). Replication of their interesting findings in an independent population with large sample size and detailed cardiovascular evaluation is therefore justified. Elucidation of the genetics of depression awaits dissection of sequence variations affecting pathways involved in mood regulation and associated somatic sequelae of this disorder, such as heart disease. Moreover, gene–environment interactions need to be better understood. Further studies in this area ought to include genome-wide scans, large sample sizes, well-characterized cohorts and the availability of high-density, genome-wide markers.

J Licinio, B Yildiz and M-L Wong
UCLA Laboratory for Pharmacogenomics
E-mail: licinio@ucla.edu

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