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Cardiovascular Disease, Psychosocial Factors, and Genetics: The Case of Depression

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ABSTRACT

Psychosocial factors are associated with cardiovascular disease, but little is known about the role of genetics in this relationship. Focusing on the well-studied phenotype of depression, current data show that there are *shared* genetic factors that may give rise to both depression and CVD, and these genetic risks appear to be modified by gender. This pleiotropic effect suggests that a single pathway, when perturbed, gives rise to the dual phenotypes of CVD and depression. The data also suggest that women contribute disproportionately to the depression–CVD comorbidity, and this unbalanced contribution is attributable, in part, to genetic factors. While the underlying biology behind this relationship is unclear, recent data support contributions from inflammatory or serotonergic pathways toward the comorbidity between CVD and depression. Even without knowledge of a specific mechanism, epidemiological observations offer new directions to explain the relationship between depression and CVD that have both research and clinical applications.

It is well established that psychosocial factors are associated with cardiovascular disease (CVD). Low socioeconomic status, lack of social support, stress at work and in family life, anxiety disorders and depression have all been shown to increase risk of developing CVD.[1,2] These factors are also associated with poor outcomes among patients with established CVD — for example, a higher mortality after myocardial infarction. It is also known that there is a substantial genetic component to the risk for CVD.[3] What is less known, however, is whether there is a genetic component influencing psychosocial factors, and whether this genetic component has an impact on CVD risk. At first blush, it might appear that psychosocial factors belong firmly in the domain of "environmental risk factors," and are mostly independent of genetic influences. Increasingly, however, evidence suggests that at least some psychosocial factors are influenced by genes, and that some of these genes may have implications for CVD risk. These data point to new ways of thinking about CVD disease mechanisms, which may provide critical novel information relevant to the pathophysiology and management of CVD.

Cardiovascular disease is a complex and multifactorial phenotype, but even with the crudest measures familial influences are apparent. For the extreme phenotype of death from coronary heart disease, heritability is estimated at 57% for males and 38% for females.[4] The younger a person dies from a cardiac event, the stronger the genetic influence is

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Abbreviations and Acronyms

CFR = coronary flow reserve

CVD = cardiovascular disease

DZ = dizygotic

GWAS = genome-wide association studies

HRV = heart rate variability

IL-6 = interleukin-6

MI = myocardial infarction

MZ = monozygotic

likely to be.[5] There are also substantial genetic influences on traditional cardiovascular risk factors, such as plasma lipid levels (50% heritable),[6] where genome wide association studies (GWAS) have identified over 95 genetic loci that contribute to the quantitative distribution of LDL cholesterol, HDL cholesterol, and/or triglyceride level.[6] Similarly, blood pressure is estimated to be between 31% and 68% heritable,[7,8] and GWAS have identified >20 loci that appear to influence either blood pressure or susceptibility to hypertension.[9] Despite these successes, results from GWAS have only identified risk variants with very small odds ratios, and their clinical relevance is unclear.[10] Given that psychosocial factors are associated with CVD risk, it is possible that the genetic risk for CVD is modified or shared by these psychosocial risk factors. As GWAS of CVD or CVD risk factors typically have not examined psychosocial factors, this hypothesis has not been tested.[11]

Depression

Depression is one of the most well-studies psychosocial risk factors for CVD, and it too has a strong genetic component. For example, individuals with a first degree relative suffering from depression have a 2.8-fold higher risk for depression themselves, compared to someone in the general population.[12] Heritability, or the proportion of the variance due to genetic factors, is estimated to be 37%.[12] This has inspired GWAS to identify common genetic variants (with frequency >5%) that contribute to the risk for depression. A mega-analysis was recently conducted, where in the primary analysis data were contributed from nine different datasets, ultimately comprising 9240 cases with major depression and 9519 controls.[13] Genetic polymorphisms were analyzed for 1.2 million genome-wide sites, and of these 544 were selected for replication in an independent sample of 6783 cases and 50,695 controls. In addition to the primary case–control analysis, secondary analyses included sex, age at onset, illness recurrence, and a specific subclass of depression where patients exhibit weight loss and insomnia. Despite this comprehensive effort, no polymorphism was significant after multiple-test correction in the discovery phase, in the replication phase or in any of the pre-planned secondary analyses.[13] These surprising results may be due to etiologic heterogeneity of the depression phenotype. If subtypes of depression could be identified to reduce heterogeneity, this might increase the power to detect genetic risk variants. Individuals with comorbid depression and CVD might represent one of these separate homogeneous subclasses. At the present time, however, GWAS approaches in this subset of individuals remain unexplored.

Depression itself is associated with CVD risk factors.[14] For example, depression is associated with becoming a smoker, an increased rate of daily smoking, and a lower probability of quitting smoking.[15–18] Depression is also associated with type 2 diabetes; three prospective studies have shown that individuals with depressive symptoms have an estimated 40% increase in risk for type 2 diabetes, even after adjusting for other risk factors.[19–21] Additionally, depression is associated with increased body mass index and obesity.[22,23] These data suggest an obvious hypothesis to explain the association between CVD and depression: that it is entirely accounted for by an increase in CVD risk factors. However, in statistical models that adjust for these risk factors, depression usually remains an independent risk factor for CVD,[24,25] suggesting a biological relationship between these two disease states that remains in part unexplained by an increase in traditional CVD risk factors.

Several models could explain the comorbidity between CVD and depression. Depression may precede CVD and accelerate CVD risk and progression, perhaps due, in part, to the association described above between depression and other CVD risk factors. Alternatively, CVD may come first, and its presence may cause biological or behavioral changes that ultimately promote depression. A third possibility is that there is a core biological pathway that, when disrupted, manifests with both CVD and depression phenotypes. If this third hypothesis were true, a genetic model, where inherited variation contributes to disruption of this core pathway resulting into the two phenotypes of CVD and depression, is highly plausible.

Twin studies

One way to unravel the genetic contribution to a trait is with the use of a twin study. This is a standard study design comparing concordance rates for a given trait or phenotype between monozygotic (MZ) and dizygotic (DZ) twins. Conceptually, in a twin study it is assumed that whether a twin pair is MZ or DZ, their environmental exposures are approximately equivalent. This includes *in utero* exposures and beyond, continuing throughout life. Therefore, differences in concordance rates are assigned to genetic influences, since DZ twins share, on average, approximately 50% of their genetic material (the same proportion as non-twin siblings), but MZ twins are genetically identical. With a large sample size of twin pairs and sophisticated statistical procedures, it is possible to estimate the genetic and environmental components of single disorders or comorbid disorders.

A genetic pleiotropic effect (i.e., the finding that a single gene or set of genetic factors can influence the variance in multiple and diverse phenotypic traits) can be studied in twin studies using multivariate structural equation modeling, a technique that partitions variance due to genetic and environmental factors considering two or more phenotypes simultaneously. It can also be inferred using a co-twin design of MZ and DZ twins discordant for the risk factor of interest.[26] If a larger difference in the outcome is found within DZ pairs discordant for the risk factor than within MZ pairs (i.e., a significant interaction is present), this suggests that genetic