Brain-heart (cardiovascular) interactions in stress and anxiety related disorders

Implications for increased cardiovascular disease risk

**GENETICS**

The brain-heart interactions in psychological disorders have not been extensively studied, with a majority of genome-wide association studies (GWAS) limited to identifying genes and expression. In the literature, there have not been systematic reviews of genes that examine the relationship of genetic components to brain-heart interactions in psychological disorders. We used the National Center for Biotechnology Information (NCBI) Phenotype-Genotype integration system, which merges genome-wide association study (GWAS) catalog data from several databases, including the NHGRI (National Heart Genome Research Institute), Gene, dbGaP (database of Genotypes and Phenotypes), OMIM (Online Mendelian Inheritance in Man), eQTL (expression Quantitative Trait Loci), and dbSNP (database of Single Nucleotide Polymorphisms). We conducted a phenotype-based search using MeSH terms for cardiac arrhythmias, coronary artery disease, depression, anxiety, psychological stress, and post-traumatic stress disorders, with a significance set to p-value < 1 x 10-5. We reviewed genes that had overlapping findings between cardiac and psychiatric phenotypes, identifying the genes of highest interest.

BIN1 (chromosome 2, rs10207628), a bridging integrator for synaptic vesicle endocytosis, iss associated with SCD and depression and is expressed in the brain. It functions include regulation of calcium ion transportation, cardiac muscle cell action potential, and neuronal differentiation. It is thought to localize to cardiac T-tubules and help with cardiomyocyte release of microparticles,1,2 but also associated with Tau protein in dementia.3

PHARCTR1 (chromosome 6, rs4615376), a phosphatase and actin regulator of endothelial cell survival, is associated with CAD and depression and expressed in the brain and heart. It functions include actin cytoskeleton reorganization. It is thought to play a part in migraine pathogenesis,4 and susceptibility for CAD in type 2 diabetes mellitus.5

CNNM2 (chromosome 10, rs12413409), a divalent metal cation transport mediator, is associated with CAD and depression and expressed in the kidneys. It functions include magnesium ion homeostasis and transmembrane transport. It is thought to be common among major psychiatric disorders,6 a susceptibility locus in CAD,7 and increases the risk of hypertension.8

PRTFDC1 (chromosome 10, rs11014306), a phosphoribosyl transferase domain protein, is associated with SCD and anxiety/stress disorders and is expressed in the brain and adrenal glands. It functions as part of purine salvage pathways. It is thought to be part of the cardiometabolic profile in heart failure,9 and also implicated as a predictor of combat stress vulnerability in the development of PTSD.10

CDH13 (chromosome 16, rs8055236), a cadherin protein, is associated with CAD and depression and is expressed in the brain and heart. It functions in protein signal transduction, endothelial cell migration, and is protective against apoptosis, provides resistance to atherosclerosis, and is part of neural differentiation. It is thought to play a role in the cardioprotective effects of sleep and in incident coronary artery disease,11 and is identified in hyperactivity, impulsivity, violent behavior, and extraverted personality traits.6,12-15

BMP2 (chromosome 20, rs6117734), a bone morphogenetic transforming growth factor-beta protein, is associated with CAD and depression and is expressed broadly. It functions as part of cardiac epithelial transition and cardiomyocyte differentiation. It is thought to be associated with depressive traits and stressful life events,16 cardiac progenitor cell differentiation,17 and atherosclerosis in type 2 diabetes mellitus.18

Other important overlapping genes included RORA (chromosome 15, rs12912233), GRIN2A (chromosome 16, rs8058295), FAM155A (chromosome 13, rs1509091), ENOX1 (chromosome 13, rs17538444), QKI (chromosome 6, rs7756185), EGFLAM (chromosome 5, rs2561805), and SNX7 (chromosome 1, rs11581859). The remaining coding genes included ACVR1 (chromosome 2, rs35806662), MYL10 (chromosome 7, rs1722229), KSR2 (chromosome 12, rs7973260), PARVA (chromosome 11, rs7120489), SNCA (chromosome 4, rs356228), SORCS3 (chromosome 10, rs7074335), MAML3 (chromosome 4, rs1877075), DCLK2 (chromosome 4, rs150175932), LPPR5 (chromosome 1, rs1329461). Several pseudogenes were identified in addition that shared overlapping findings in CAD, SCD, depression, and stress disorders. They include RNA5SP87, RPL26P5, RNA5SP404, HSPE1P20, MTCO3P1, RPL6P18, and MTCL1P1.

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