

***A serotonergic model of CVD risk - genes, behavior and physiology***  
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The cause of covariation and aggregation of biological, psychological and lifestyle related risk factors of CVD is as yet unclear. Evidence, that low central serotonergic responsivity is associated with disturbances of mood and affect, aggressive disposition, physical inactivity, central adiposity, blood pressure, insulin resistance and metabolic syndrome suggests that a common neurobiologic mechanism involving altered central nervous system serotonergic (5-HT) function may be responsible. The high heritability of these risk factors suggests the influence of genetics, prompting investigation of serotonin-related genes in association with several risk factors. However, these investigations have largely remained within specific biological, psychological or health risk behavior domains. If several related risk phenotypes share a common genetic origin, this can only be concluded by examining biological, psychological and lifestyle related factors in a single investigation. This project aims to test for the association between psychological, biological and lifestyle-related CVD risk factors and variations in the serotonin transporter (5-HTT) and serotonin receptor 2A (HTR2A) genes, which have previously been associated with several CVD risk factors. Using DNA samples and phenotype data collected on 2000 unrelated subjects as part of the University of Pittsburgh's HeartSCORE project, this study proposes to 1) test for multivariate genetic association with each domain of risk, and when significant association is observed, conduct univariate tests of association for component risk factors. 2) examine the genetic influence on covariation of risk factors. 3) confirm genetic associations by implementation of Genomic Control approaches in European Americans and Individual Admixture based approaches in African Americans, to mitigate confounding by population stratification. 4) determine whether serotonin-regulating genetic variation predicts progression of biological risk factors and development and persistence of the metabolic syndrome in prospective analyses. Obtaining a more parsimonious understanding of the shared genetic pathway underlying covarying CVD risk factors is likely to lead to more effective study designs for preventative interventions and treatments and pharmacogenetic applications, where instead of treating each risk domain separately, efforts could be made to devise common susceptibility detection and treatment protocols.