Association of candidate gene polymorphisms with metabolic syndrome and inflammation

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Background and objectives: Metabolic syndrome is a clustering of phenotypes (central adiposity, glucose intolerance, hypertension, and dyslipidemia) thought to be induced by insulin resistance. These metabolic risk factors are associated with an increased risk of atherosclerotic cardiovascular disease. According to the Third National Health and Nutrition Examination Survey (NHANES III) data and various other studies, the prevalence of metabolic syndrome varies by ethnicity, but ranges between 16-25%. This rate is steadily increasing worldwide. The public health impact of this syndrome is considerable, since associated morbidities include obesity, type 2 diabetes, and diseases of the liver and gallbladder. Inflammation is associated with metabolic syndrome, as indicated by an increase in circulating levels of proinflammatory cytokines. Our objectives were to identify candidate genes polymorphisms associated with both metabolic syndrome and inflammation, and to analyze these polymorphisms in the NHANES III cohort for significant associations with metabolic syndrome.

Methods: The cohort consisted of participants from NHANES III, a cross-sectional, nationally-representative sample of the U.S. population. Twenty-three polymorphisms within the *CCR2*, *CRP, IL1β, IL10, TGFβ1, TLR4, TNF* and *VDR* genes were analyzed based on their biological involvement in metabolic syndrome physiology and the immune system pathways. The Adult Treatment Panel III (ATP III) criteria were used to identify metabolic syndrome cases from approximately 7000 NHANES III individuals collected from 1991-1994. We analyzed data using logistic regression stratified by race/ethnicity, and included three models: crude, adjusted for age and sex, and adjusted for age, sex, serum CRP levels, alcohol consumption, smoking, caloric intake and carbohydrate intake. Analyses were run for both dominant and additive models of inheritance.

Results: The significance of our polymorphisms differed markedly between the three race/ethnic subpopulations. *TNF* (rs361525) was significantly associated with decreased prevalence of metabolic syndrome in all three models for both modes of inheritance, but only for non-Hispanic whites. *CRP* SNP rs1417938 was significantly associated with decreased prevalence only in non-Hispanic blacks, in both adjusted models for both inheritance modes, and in the crude model under the dominant mode of inheritance. *TGFβ1 (*rs1800468) was also significantly associated with decreased prevalence of metabolic syndrome only in non-Hispanic blacks for all models and both inheritance modes. *SERPINE1* (rs1799762) was significant for an increased prevalence only in Mexican-Americans for the crude additive model. For *IL10*, rs180896 was significantly associated with increased prevalence in crude analysis only for non-Hispanic whites (dominant) and with a borderline decreased association in Mexican Americans (additive).

Discussion/conclusion: Our results indicate an association between polymorphisms in *TNF, CRP, TGFβ1, IL10* and *SERPINE1* and metabolic syndrome in at least one race/ethnicity subgroup in a representative sample of the U.S. population. Further research is necessary to identify the functional variants in these genes and the role they play in the development of metabolic syndrome. Understanding how these interactions affect the inflammatory pathway in different subpopulations may enhance development and implementation of public health interventions for those with increased disease susceptibility.