Segregation analysis was performed on the serum uric acid measurements from 523 randomly ascertained Caucasian families from the NHLBI Family Heart Study. Gender-specific standardized residuals were used as the phenotypic variable in both familial correlation and segregation analysis. Uric acid residuals were adjusted for age, age², age³, body mass index (kg/m²), creatinine level, aspirin use (yes/no), total drinks (per week), HOMA insulin resistance index [(glucose * insulin)/22.5], diuretic use (yes/no), and triglyceride level. Sibling correlations (r=0.193) and parent-offspring correlations (r=0.217) were significantly different from zero, but these two familial correlations were not significantly different from one another. After adjustment for covariates, the heritability estimate for serum uric acid was 0.399. Segregation analysis rejected the “no major gene” model but was unable to discriminate between an “environmental” and a “Mendelian major gene” model. These results support the hypothesis that uric acid is a multifactorial trait possibly influenced by more than one major gene, modifying genes, and environmental factors.

Introduction

Uric acid levels in the blood have been found to be associated with both coronary heart disease (CHD) and many of the established risk factors for CHD. Studies have produced inconsistent results as to whether high levels of uric acid are an independent risk factor for CHD or part of a clustering of risk factors. Increased uric acid concentrations in the blood can be the result of an overproduction of uric acid in the body and/or diminished renal excretion. Reports from the Framingham Study and the British Regional Heart Study have shown uric acid to be a significant predictor of CHD in univariate analysis, but the association is attenuated after adjustment for other known CHD risk factors (Brand et al. 1985; Wannamethee et al. 1997). An updated report from the Framingham Heart Study has identified diuretic use as the covariate responsible for attenuating the observed association between uric acid and cardiovascular disease outcomes (Culleton et al. 1999). However, recent results from a male cohort in the Augsburg MONICA Study have demonstrated an increased risk of all cause mortality, CHD mortality, and myocardial infarction associated with the highest quartile of serum uric acid levels after adjustment for confounding by CHD risk factors (Liese et al. 1999).

The association between uric acid and conventional CHD risk factors has been observed in several cardiovascular epidemiology studies. The Bogalusa Heart Study and the Coronary Artery Risk Development in Young Adults (CARDIA) study have examined uric acid levels in children and young adults. Both studies report that uric acid levels are inversely related to high density lipoprotein cholesterol levels and positively associated with...
blood pressure, body mass index (BMI), triglyceride, serum creatinine, and fasting insulin levels (Rathmann et al. 1998; Agamah et al. 1991). The Honolulu Heart Program has explored uric acid levels in a population of Japanese-American men, and BMI, alcohol intake, diastolic blood pressure, triglyceride levels, and the ratio of animal to vegetable protein in the diet were found to be positively correlated with serum uric acid levels (Iribarren et al. 1996). The Normative Aging Study has identified uric acid levels as being positively influenced by alcohol consumption and BMI, and negatively associated with physical activity (Lee et al. 1995). The association between hyperuricemia and glucose intolerance, high insulin and triglyceride levels, and dyslipidemia has led researchers to hypothesize that uric acid levels play a role in the obesity-insulin-resistance syndrome (Leyva et al. 1998).

Past analyses of the familiality of uric acid levels are inconsistent. Heritability estimates range from 25% in family studies to 70% in twin studies. Early studies with families ascertained through a proband with hyperuricemia or gouty arthritis suggest that a major gene for uric acid levels exists (Smyth et al. 1948; Stecher et al. 1949). Later studies exploring the transmission of uric acid through segregation and path analysis have not found evidence for a major gene (Gulbrandsen et al. 1979; Morton 1979; Rao et al. 1982). A more recent study of Jerusalem families attributes familial resemblance in uric acid levels to both a genetic and a common environmental component (Friedlander et al. 1988). In a segregation analysis from the Lipid Research Clinics (LRC) Family Study, a multifactorial component for uric acid levels was found to be consistent with the data (Rice et al. 1992). In the five centers involved in the LRC, heterogeneity in the aggregation of uric acid levels was observed, and differences in genetic heritabilities were observed between generations (Rice et al. 1990). In this paper, we describe the evidence for a genetic contribution to serum uric acid levels in randomly ascertained Caucasian families from the NHLBI Family Heart Study.

Materials and methods

Sample

The study subjects were ascertained as part of the NHLBI Family Heart Study (FHS), a multi-center population-based family study designed to identify and evaluate genetic and non-genetic determinants of CHD, preclinical atherosclerosis, and cardiovascular risk factors. The design of the FHS has been described previously (Higgins et al. 1996). The FHS subjects in the present study are members of families from previously established population-based cohort studies: The Framingham Heart Study in Framingham, Massachusetts; the Atherosclerosis Risk in Communities cohorts in Forsyth County, North Carolina, and the northwest suburbs of Minneapolis, Minnesota; and the Utah Health Family Tree Study in Salt Lake City, Utah. Individuals were randomly selected from the four study centers and invited to provide an updated family health history. From these data, 588 families were chosen at random, and 657 families were chosen because of a higher than expected CHD rate among the family members (high family risk score).

For this report, only individuals from the randomly ascertained group were analyzed. The small African-American family component and participants with medical examinations that did not include uric acid measurements were excluded from the analysis. Only one member of each identical twin pair was retained for analysis. Families in which only one member had uric acid measurements were also not included in the analysis. After exclusions, the randomly ascertained Caucasian family data under study consisted of 523 families and 2255 individuals.

Data collection

Study participants were asked to fast for 12 h prior to their clinical examination. Blood samples were collected to assess serum uric acid, triglycerides, creatinine, fasting glucose, and fasting insulin levels. Blood was collected, processed at the FHS field centers as previously described (Higgins et al. 1996), and analyzed at the FHS Central Laboratory at the Fairview-University Medical Center in Minneapolis, Minnesota. Serum uric acid was measured by using the Ortho Clinical Diagnostics (Rochester, N.Y.) Vitros thin-film clinical analyzer method (Trivedi et al. 1978). Information concerning the use of alcohol and medication was obtained by interview at the clinical examination. The use of aspirin and diuretics was assessed from a medication history and review of current medication, which the study subject brought to the clinic. Height and weight were measured at the clinical examination.

Standardized residuals

The uric acid measurements were adjusted by regression methods for the effects of factors traditionally recognized as influencing uric acid levels. The covariates used to generate residuals were those retained in stepwise regression with a significance level of 0.2 for both inclusion and retention in the model. The uric acid measurements were adjusted for the effects of age, age2, age3, BMI (kg/m2), creatinine level, aspirin use (yes/no), total drinks (per week), HOMA insulin resistance index [(glucose + insulin)/22.5], diuretic use (yes/no), and triglyceride level. Standardized residuals (mean=0, SD=1) for uric acid were calculated separately for males and females, because males traditionally have higher serum uric acid levels than women. The amount of explained variance, the r-square value, for the set of covariates in each gender was 20.4% for males and 37.2% for females. Each study center was evaluated as a potential source of heterogeneity in the data but was not found to be a significant predictor of uric acid levels and thus was not adjusted for in the present analysis.

Statistical analysis

Descriptive statistics for the covariates age, BMI, creatinine level, aspirin use, total drinks, HOMA index, diuretic use, triglyceride level, and for the uric acid measurements were calculated for men and women separately. Familial correlations were calculated by using the FCOR program in S.A.G.E. (Statistical Analysis for Genetic Epidemiology 1997). Correlation coefficients for spouse pairs (rsp), parent-offspring pairs (rpo), sibling pairs (rsib), and sex-specific parent-offspring and sibling pairs were computed, adjusting for repeated observations in pedigrees, and 95% confidence intervals were constructed by using Fisher’s z transformation (DeStefano et al. 1996). Heritability estimates, adjusted for degree of spouse resemblance, were computed from the correlation coefficients by using the equation

\[
h^2 = \frac{(r_{sb} + r_{po})}{1 + r_{po} + (2r_{sb} + r_{po})} \]

(Rice et al. 1997).

Segregation analysis was performed using the Class D regressive model of Bonney (1984), the program REGC for quantitative traits in S.A.G.E. (1997), assuming equal sibling correlations. We first assessed whether the spouse-pair correlation was significantly