Genome Scan for Determinants of Serum Uric Acid Variability

Subrata D. Nath,* V. Saroja Voruganti,† Nedal H. Arar,* Farook Thameem,* Juan C. Lopez-Alvarenga,† Richard Bauer,* John Blangero,† Jean W. MacCluer,† Anthony G. Comuzzie,† and Hanna E. Abboud*

*Department of Medicine, University of Texas Health Science Center at San Antonio, and †Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, Texas

ABSTRACT
Elevated serum uric acid level is associated with obesity, insulin resistance, diabetes, nephropathy, and hypertension. Epidemiologic studies suggest that serum uric acid levels are heritable. We sought to identify chromosomal regions harboring quantitative trait loci that influence serum uric acid in Mexican Americans using data from 644 participants in the San Antonio Family Heart Study. Serum uric acid was found to exhibit significant heritability (0.42) in this population \( (P = 2 \times 10^{-17}) \) after accounting for covariate effects. In addition, genetic correlations between serum uric acid and other cardiovascular risk factors, such as body mass index, waist circumference, systolic BP, and pulse pressure, were identified, suggesting that the genes associated with uric acid level are also associated with these phenotypes. Multipoint linkage analysis identified quantitative trait loci with measurable effects on serum uric acid variability. The highest multipoint logarithm of odds score of 3.3 was found at 133 cM on chromosome 6q22–23, a region that also contains genes that seem to influence familial IgA nephropathy, obesity, BP, insulin resistance, and type 2 diabetes. Given the relationship between uric acid level and these conditions, future studies should investigate potential candidate susceptibility genes found in this region.


Uric acid is a breakdown product of ingested and endogenously synthesized purines. DNA and RNA are degraded into purine nucleotides and bases, which are then metabolized, via the action of xanthine oxidase, to xanthine and uric acid. Uric acid undergoes no further metabolism in humans and is excreted by the kidneys and intestinal tract. In the kidneys, it is filtered and subsequently reabsorbed or further secreted in the proximal tubule, predominantly under the action of a urate transporter. Several epidemiologic studies have reported that high serum levels of uric acid are strongly associated with prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential hypertension, and renal disease. Population-based studies have shown that hyperuricemia is an independent risk factor for cardiovascular disease (CVD). This association has been found to be particularly robust among individuals at high

Received April 9, 2007. Accepted July 24, 2007.
Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Hanna E. Abboud, Division of Nephrology, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229. Phone: 210-567-4700; Fax: 210-567-4712; E-mail: abboud@uthscsa.edu

Copyright © 2007 by the American Society of Nephrology
risk for CVD, including those with obesity, hypertension, diabetes, and renal disease; however, epidemiologic and meta-analysis studies fail to establish a cause-and-effect relationship between hyperuricemia and CVD.

There is a large interindividual variation in serum uric acid concentration. Although this variation is explained in part by nongenetic progression promoters including impaired renal function, accumulating evidence indicates that serum uric acid values cluster within families, suggesting a role for genetic factors. Studies in twins, path analyses, and segregation analyses estimated that the heritability (h²) of serum uric acid ranges from 0.40 to 0.73. Linkage studies have been conducted to map loci that influence values for serum uric acid in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study pedigrees and the Framingham Heart Study families. The genetic determinants of variation in serum uric acid levels have not been explored in Mexican Americans. In this study, we examined the h² of serum uric acid and conducted linkage analysis using a variance component approach to identify quantitative trait loci (QTL) with measurable effects on quantitative variation in serum uric acid levels in a population-based study of Mexican American families.

RESULTS

The relative pairs used in quantitative genetic and linkage analyses are shown in Table 1. The clinical characteristics of the study participants are presented in Table 2. We analyzed phenotypic data obtained from 644 Mexican Americans (men = 234, women = 410) for whom genotypic data were also available. The mean age of the study participants was 47.65 yr, and the mean serum levels of uric acid was 5.35 ± 1.42 mg/dl. In the total sample, 21 and 24% of the participants had type 2 diabetes and hypertension, respectively (Table 2).

h² estimates of serum uric acid are shown in Table 3. These estimates involved trait-specific screening for significant covariate effects, and the initial covariates included age, gender, and age². After accounting for these initial covariates, serum uric acid levels exhibited significant h² ranging from 0.34 to 0.38 (P = 2 × 10⁻⁷). Subsequently, the estimation of h² of serum uric acid in the final model adjusted for log waist-to-hip ratio, log systolic BP (SBP), BP medication, smoking, alcohol intake, diabetes status, log serum glucose, log serum triglycerides, and log serum HDL cholesterol revealed a higher h² (0.42, P = 2 × 10⁻⁷) than models using only age and gender as covariates (Table 3).

We investigated the genetic correlation between uric acid and potential covariates that could determine its level. These included body mass index (BMI), waist circumference, triglycerides, HDL cholesterol, SBP, and pulse pressure. As can be seen from Table 4, bivariate quantitative genetic analysis demonstrated significant genetic correlations between serum uric acid and BMI (ρₕ = 0.37; P = 0.04), waist circumference (ρₕ = 0.46; P = 0.01), SBP (ρₕ = 0.68; P = 0.002), and pulse pressure (ρₕ = 0.47; P = 0.04). Our analysis did not find any significant genetic correlation between serum uric acid and triglycerides or HDL cholesterol.

After the estimation of h², we performed multipoint linkage analysis across 22 autosomes to identify chromosomal regions that influence variation in serum uric acid levels. After accounting for the final-adjusted covariate effects, evidence for
linkage of serum uric acid was found to occur on three chromosomes (Figure 1). The strongest evidence for linkage of serum uric acid (logarithm of odds [LOD] score 3.3) occurred between the genetic markers D6S474 and D6S1040 on chromosome 6q22–23 (Figures 1 and 2). In addition, regions on chromosomes 3 (at 31 cM) and 4 (at 211 cM) exhibited suggestive evidence for linkage (LOD score ≥2.0) of serum uric acid (Figure 1).

DISCUSSION

Population-based studies document that high serum levels of uric acid are strongly associated with insulin resistance, metabolic syndrome, type 2 diabetes, hypertension, and kidney disease. The association between uric acid and CVD is robust among people with obesity, hypertension, diabetes, and renal disease. Variation in serum uric acid level is multifactorial and is influenced by both environmental and genetic factors, which are mostly unknown.

In this study, we used data from the San Antonio Family Heart Study (SAFHS), a Mexican American cohort at high risk for CVD and its complications, to examine the genetic determinants of variation in serum uric acid levels. Our results demonstrate that serum uric acid levels are significantly heritable (h² = 0.42, P = 2 × 10⁻⁷) in this population after accounting for several factors that could potentially influence serum uric acid levels. Given that the h² estimates are population specific, several studies found that serum uric acid values are under strong genetic influences. For example, in a cohort of 1258 offspring from the Framingham Heart Study the h² estimates for serum uric acid were found to be 0.37, 0.59, and 0.63 for unadjusted, age- and gender-adjusted, and fully adjusted models, respectively. In addition, our analysis demonstrates that the covariates accounted for more than half of the variance in serum uric acid levels, indicating environmental influence for this phenotype as reported in other studies. Thus, our h² findings are consistent with other h² reports on serum uric acid in non-Hispanic populations, suggesting that this trait is influenced both by environment and by genetics.

This study also provides evidence of significant genetic influence on variation in serum uric acid and its relationship with other cardiovascular risk traits. BMI, waist circumference, serum triglycerides, SBP, and pulse pressure demonstrated high heritabilities, indicating a substantial genetic influence on their variations and suggesting that a common set of genes may influence these phenotypes. The positive correlations found in this study between serum uric acid and other cardiovascular risk factors such as BMI, waist circumference, SBP, and pulse pressure suggest that the genes associated with serum uric acid

Table 4. Genetic correlations of serum uric acid with other cardiovascular risk factors

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>ρg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.37</td>
<td>0.035</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.46</td>
<td>0.011</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.08</td>
<td>NS</td>
</tr>
<tr>
<td>SBP</td>
<td>0.68</td>
<td>0.002</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.47</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Figure 1. Summary of the linkage analysis of serum uric acid by each chromosomal location is represented on the y axis and LOD score on the x axis.
levels are also associated with these phenotypes. We further tested the genetic correlations between serum uric acid and SBP and pulse pressure after adjusting for either BMI or waist circumference. The correlations remained significant, indicating that these correlations are independent of obesity. To our knowledge, no other study in the literature has performed similar analysis with regard to serum uric acid and BP or cardiovascular risk traits; hence, our results are unique.

Our genome-wide linkage scan provides evidence for the presence of a susceptibility locus between the markers D6S474 and D6S1009 (LOD score 3.3) on chromosome 6q22–23, influencing variation in serum uric acid after accounting for significant covariates. To our knowledge, only three studies have conducted genome-wide linkage analysis in search for chromosomal regions influencing serum uric acid level. Yang et al.14 carried out a linkage analysis in 1258 white individuals from 330 pedigrees from the Framingham Heart Study and reported significant evidence for linkage of serum uric acid at 50 cM on chromosome 15q (age- and gender-adjusted LOD score 3.3); however, their LOD score was attenuated to 1.5 after adjustment for covariates such as age, gender, BMI, serum creatinine, alcohol consumption, diabetes, diuretic treatment, and triglycerides. Tang et al.13 performed linkage mapping for serum uric acid in the families who participated in the NHLBI Family Heart Study and found suggestive linkage (LOD score 1.88) on chromosome 2q at 228 cM. Another study consisting of 21 multiplex pedigrees from aboriginal Taiwan tribes ascertained with gout identified a linkage (LOD score 1.1) for serum uric acid at 114 cM on chromosome 4q25.15 In addition, the study observed a significant linkage with an LOD score of 5.66 for gout at the same chromosomal location. In our study, we failed to find any evidence for linkage of serum uric acid on chromosomes 2q, 4q, and 15q except for suggestive linkage on chromosome 4q at 211 cM (Figure 1), which is approximately 87 cM telomeric to the region identified by Cheng et al.15 for gout and serum uric acid.

The identification of linkage for serum uric acid at 133 cM on chromosome 6q22–23 in this study is significant because this genetic region has already been localized for diabetes-, cardiovascular-, and kidney-related phenotypes. The implicated 6q chromosomal region (110 to 140 cM) harboring potential susceptibility genes is shown in Table 5. It is interesting to note a few examples from Table 5, such as the linkage of IgA nephropathy (IGAN1; MIM 161950), which has been localized to the same genetic location16 where we observed linkage of serum uric acid on 6q. Hyperuricemia is known as a risk factor for renal progression in IgAN.17 Immunohistochemical methods clearly demonstrate that serum levels of uric acid correlate with inflammatory cell infiltration both in glomeruli and in renal interstitium.17 There also exists independent association
between serum uric acid and tubular atrophy and interstitial fibrosis, characteristics of IgAN. Using data from other Mexican American cohorts, Hanis et al. localized a chromosomal region on 6q22 for type 2 diabetes. Furthermore, this genetic location has been shown to be linked with type 2 diabetes in Pima Indians and with obesity in a French population cohort.

Our uric acid linkage markers D6S474 and D6S1040 span approximately 18 Mb on chromosome 6q encompassing many potential candidate genes, including connective tissue growth factor (CTGF); plasma cell glycoprotein 1 (PC-1), also known as ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1); and serum/glucocorticoid regulated kinase 1 (SGK1). CTGF has been implicated in the pathogenesis of diabetic nephropathy because of its integral role in extracellular matrix remodeling, mesangial cell hypertrophy, and fibrosis in the glomerulus and elsewhere in the renal cortex. The overexpression of membrane glycoprotein PC-1 may reduce insulin-stimulated tyrosine kinase activity and decrease glucose uptake, indicating a role of PC-1 in insulin resistance or type 2 diabetes. K121Q polymorphism in exon 4 of the ENPP1 gene is associated with insulin resistance, increased susceptibility to type 2 diabetes, atherosclerotic vascular disease, myocardial infarction, and hypertension in adulthood and decreased renal function and accelerated progression of nephropathy in patients with diabetes. Genetic variation in SGK1 has been reported to be associated with high BP, and SGK1 is involved in the pathogenesis of diabetic nephropathy.

We also observed a suggestive linkage (LOD scores $\geq 2.0$) of serum uric acid to a region on chromosome 4q at 211 cM (Figure 1). Matthews et al. localized a region 4q QTL at 189.38 cM for familial psoriasis 3 (PSORS3), which is approximately 21 cM telomeric to the region where we observed a linkage of uric acid. Elevated serum uric acid level is a frequent finding in psoriasis, and it is believed that the rapid epidermal turnover in psoriasis might lead to an increased purine breakdown that in turn influences the serum levels of uric acid.

In summary, this study presents the first genome-wide search for QTL influencing variation in serum uric acid in a Mexican American population. We observed a major locus for serum uric acid level on chromosome 6q22–23, a region that was already shown to be linked with type 2 diabetes, obesity, and IgAN. It suggests either that this genetic region harbors multiple susceptibility genes influencing the different phenotypes or that a common gene on 6q influences all of these phenotypes.

CONCISE METHODS

The study participants were from the SAFHS, the first and one of the largest population-based genetic studies of CVD risk factors in Mexican Americans. The details of the SAFHS have been described elsewhere. Briefly, the probands were selected randomly regardless of any preexisting medical conditions from a census tract that consisted of a low-income Mexican American barrio in San Antonio. The inclusion criteria of selected probands were being 40 to 60 yr of age, having a spouse who was willing to participate, and having had at least six offspring and/or siblings who were $\pm 16$ yr of age. Relatives of the proband and of his or her spouse, aged $\geq 16$ yr of age, were also invited to participate. Pregnant women and individuals who were not able to give informed consent were excluded. All participants gave informed consent, and the institutional review board of the University of Texas Health Science Center at San Antonio approved the study protocols.

Phenotyping

The phenotypic and demographic data were collected from 644 Mexican Americans who participated in the third cycle of the SAFHS. The proband and all recruited first-, second-, and third-degree relatives underwent a physical examination and were subjected to an extensive data-gathering protocol in which information on sociodemographic

Table 5. Summary of linkage findings of the phenotypes on chromosome 6q22–23 (110 to 140 cM)

<table>
<thead>
<tr>
<th>Population</th>
<th>Phenotype</th>
<th>Chromosomal Band</th>
<th>Markers</th>
<th>Position (cM)</th>
<th>LOD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish</td>
<td>Type 2 diabetes</td>
<td>6q16.3-q23.2</td>
<td>D6S287-D6S262</td>
<td>112.50</td>
<td>3.17</td>
<td>44</td>
</tr>
<tr>
<td>Mexican American</td>
<td>Type 2 diabetes</td>
<td>6q</td>
<td>D6S262</td>
<td>114.20</td>
<td>0.77</td>
<td>18</td>
</tr>
<tr>
<td>Finnish</td>
<td>Insulin</td>
<td>6q</td>
<td></td>
<td>119.50</td>
<td>1.85</td>
<td>45</td>
</tr>
<tr>
<td>White</td>
<td>IgAN</td>
<td>6q22–23</td>
<td>D6S474-D6S1040</td>
<td>118.00 to 129.00</td>
<td>5.60</td>
<td>16</td>
</tr>
<tr>
<td>Pima Indians</td>
<td>Type 2 diabetes</td>
<td>6q</td>
<td>D6S1009-D6S1003</td>
<td>128.00</td>
<td>3.00</td>
<td>19</td>
</tr>
<tr>
<td>Chinese</td>
<td>Type 2 diabetes</td>
<td>6q21-q23</td>
<td>D6S1040</td>
<td>128.90</td>
<td>6.23</td>
<td>46</td>
</tr>
<tr>
<td>French</td>
<td>Obesity</td>
<td>6q22.31-q23.2</td>
<td>D6S462-D6S441</td>
<td>129.76</td>
<td>4.06</td>
<td>20</td>
</tr>
<tr>
<td>Japanese</td>
<td>Type 2 diabetes</td>
<td>6q</td>
<td>D6S1009</td>
<td>137.70</td>
<td>1.91</td>
<td>47</td>
</tr>
<tr>
<td>Mexican American</td>
<td>Fasting insulin/leptin/</td>
<td>6q</td>
<td>D6S403</td>
<td>142.90</td>
<td>4.20</td>
<td>48</td>
</tr>
<tr>
<td>GENOA*</td>
<td>SBP</td>
<td>6q23.1</td>
<td>D6S1009-D6S1003</td>
<td>143.00 to 146.00</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>BMI</td>
<td>6q23–25</td>
<td>GATA184A08</td>
<td>144.40</td>
<td>4.64</td>
<td>50</td>
</tr>
</tbody>
</table>

*GENOA, Genetic Epidemiology Network of Arteriopathy. Black, Mexican American, and white.
characteristics, cigarette smoking, alcohol consumption, and medications was obtained. Data were also collected on phenotypes related to obesity, diabetes, and CVD. Anthropometrics and BP were measured according to standardized methods. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the midpoint between the lower ribs and ilioc crest with no clothes around the waist and the participant in erect posture. Waist and hip circumferences were measured with a nonstretchable measuring tape at the widest circumference to the nearest 0.1 cm. BP was measured three times, with an appropriate arm cuff, using a random zero sphygmomanometer (Gelman-Hawksley Ltd., Sussex, England). The first measurement of the SBP and diastolic BP was omitted, and the mean of the second and third readings was used in the analyses. Pulse pressure was calculated as the difference between SBP and diastolic BP.

Blood was collected after an overnight fast and stored at −80°C until analyzed. Serum glucose was analyzed by the oxidase method (Abbott Laboratories, Abbott Park, IL). A homogeneous method for direct measurement of HDL cholesterol in serum was used. Serum triglyceride levels were determined by the enzymatic colorimetric method using an autoanalyzer (Express Plus; Bayer Diagnostics, Pittsburgh, PA). Fasting serum uric acid was oxidized in the presence of uricase to form hydrogen peroxide, which was measured photometrically.32 Serum creatinine was estimated by modified kinetic Jaffe reaction (Beckman Synchron LX System, Beckman Coulter, Fullerton, CA). Type 2 diabetes was diagnosed according to the World Health Organization criteria.33 Individuals who reported a history of diabetes and stated that they were receiving insulin or oral hypoglycemic agent were also considered to have diabetes.

Genotyping
Genomic DNA was prepared from lymphocytes collected from all participants using a standard protocol34 and amplified by PCR using fluorescently labeled primers from MapPairs 6 and 8 Linkage Screening Sets (Research Genetics, Huntsville, AL). The PCR products were pooled and typed using the ABI 377 and GeneScan and Genotyper software (Applied Biosystems, Foster City, CA). All family members were genotyped for 417 microsatellite markers spaced at an average interval of 10 cM. In addition, polymorphic markers in candidate genes were included in the map as described previously.35 The screening set and genotyping protocols are available at the web site of the Center for Medical Genetics Marshfield Medical Research Foundation (http://research.marshfieldclinic.org/genetics). Genotypic data were cleaned for verification of family relationships and Mendelian inconsistencies. Data were searched for spurious double recombination, and those reflected by a high posterior probability of genotyping error were corrected. This correction significantly reduced the map expansion and led to the calculation of more accurate multipoint identity-by-descent (IBD) probabilities.

Statistical Genetic Methods
We performed a pedigree-based multipoint variance-components analysis to test for linkage between marker loci and the serum uric acid values, using a maximum-likelihood method implemented in the software program Sequential Oligogenic Linkage Analysis Routines (SOLAR).36 To locate specific QTL influencing serum uric acid values, we first estimated the proportion of the total phenotypic variance attributable to additive genetic effects. According to classical quantitative genetics principles, the total phenotypic variance (σ²y) can be decomposed into the genetic components (σ²g) and nongenetic or environmental components (σ²e): σ²y = σ²g + σ²e.

As a first step in the genetic analysis, h² of serum uric acid values was estimated. The h² of a phenotype refers to the ratio of the variance attributable to additive genetic components to the total phenotypic variance and is expressed as h² = σ²g/σ²y.38

A variance components linkage method uses information from all possible pedigree relationships simultaneously and assumes that the genetic covariance between relative pairs in a pedigree is a function of the proportion of genes IBD at a marker.39 If a locus on a chromosome is linked to the quantitative trait (e.g., serum uric acid), then the expected genetic covariances between family members can be expressed as a function of the IBD relationships at that marker locus. The overall expected IBD relationship between relative pairs is twice the kinship (Φ), which is defined as the probability that two homologous genes drawn at random, one from each individual, will be IBD. IBD at the specific QTL locus (I) is estimated using genetic marker data. The covariance matrix is expressed as Ω = Ι + 2Φσ²g + ΙΦσ²e, where Ω is the covariance matrix of the entire family; Ι is a matrix of the proportions of the specific QTL that the relative pairs share as IBD; σ²g is the additive genetic effect of the specific QTL; Φ is the kinship matrix; σ²e is the residual or non-QTL genetic effect; I is an identity matrix; and σ²e represents the random environmental effect.

The null hypothesis is that the additive genetic variance of the specific QTL (σ²q) for the trait equals zero. The likelihood of the null hypothesis (H₀), where σ²q is constrained to zero, is compared with the likelihood of the alternative hypothesis (H₁), where the σ²q is estimated. Twice the difference between the log likelihood of the two models yields a test statistic. This test statistic is asymptotically distributed as a mixture of a χ² distribution with 1 degree of freedom and a point mass at zero.40 The LOD score is used to demonstrate the significance of the test. It is calculated as follows: LOD = log 10 (likelihood of H₁) − log 10 (likelihood of H₀). The calculations of locus-specific IBD for relative pairs and the multipoint linkage analysis were performed using the SOLAR program.41 LOD scores were interpreted using common thresholds to define genome-wide significance.41

For meeting the assumption of normal distribution of the variance component linkage method, the distributions of all phenotypes were examined and log-transformed when necessary. Data ≥±4 SD from the means were blanked out. The kurtoses of all phenotypes were reexamined, and additional outliers were removed so that the kurtosis for each of the traits was ≤±1.9, thereby avoiding an inflation of type 1 error.42

We also performed bivariate genetic analysis to examine the genetic correlation between serum uric acid and selected CVD risk factors. The genetic correlation indicates the extent of genes shared between a pair of traits (pleiotropy). The correlation (ρp) between two phenotypes is expressed in terms of its core genetic and environmental correlations and expressed as Pp = ρg (\sqrt{h_1^2} \sqrt{h_2^2}) + ρe (\sqrt{(1− h_1^2)} \sqrt{(1− h_2^2)}), where h_1^2 and h_2^2 are the heritabilities of the two phenotypes of interest and ρg and ρe are the additive genetic and environmental correlations between the traits, respectively.43 Because
of the skewed distributions of many phenotypes, they were log-transformed to normalize and the log-transformed values were used in the analysis.

ACKNOWLEDGMENTS

This work was supported in part by NHLBI grant P01 HL45522, National Institute of Mental Health grant MH59490, and the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases George O’Brien Kidney Research Center grant (P50-DK-061597). S.D.N. is supported by an American Heart Association Postdoctoral Fellowship (0525206Y); F.T. is supported by the Scientist Development Grant award from the American Heart Association (0530059N). We also acknowledge the Fredric C. Barter General Clinical Research Center, University of Texas Health Science Center at San Antonio (San Antonio, TX), supported by M01-RR01346, which provided clinical support to this project.

DISCLOSURES

None.

REFERENCES

21. McKnight AJ, Savage DA, Patterson CC, Brady HR, Maxwell AP: Rhesus allele of the K121Q polymorphism of the plasminogen activator type 1 receptor gene is linked to CHD in two New Zealand aboriginal populations. J Hum Genet 49: 291–296, 2004
23. Kubaszk MC, Paykaran A, Eriksson JG, Forsen T, Osmond C, Barker DJ, Laakso M: The association of the K121Q polymorphism of the plasma cell glycoprotein-1 gene with type 2 diabetes and hyperten-
sion depends on size at birth. J Clin Endocrinol Metab 89: 2044–2047, 2004