Clinical Investigation and Reports

A Polymorphism of the Angiotensinogen Gene Associated With Variation in Blood Pressure in a Genetic Isolate

Robert A. Hegele, MD; J. Howard Brunt, PhD; Philip W. Connelly, PhD

**Background** The Hutterite Brethren are a genetic isolate characterized by high indices of relatedness and a communal agrarian lifestyle. We hypothesized that variation of the angiotensinogen (AGT) and angiotensin-converting enzyme (ACE) genes would be associated with variation in resting blood pressure in this group. We also hypothesized that the association would depend on the sex of the subjects.

**Methods and Results** In 741 Hutterites, we measured blood pressure in quadruplicate and analyzed DNA for genotypes of an insertion/deletion (I/D) polymorphism of ACE and of two protein polymorphisms of AGT, namely, M235T and T174M. We tested for association between variation in systolic and diastolic blood pressures and genotypic class. We observed that genotypes of AGT codon 174 were significantly associated with variation in systolic blood pressure. We also tested for an interaction between the AGT genotype and sex. We observed that genotypes of AGT codon 174 were significantly associated with variation in systolic blood pressure only in men. The AGT codon 174 polymorphism accounted for 3.1% of the total variation in systolic blood pressure in men.

**Conclusions** The association of AGT variation with resting blood pressure in men is consistent with the existence of important structural elements within, flanking, or proximal to the AGT gene, whose functional impact might be related to differences in sex. (Circulation. 1994;90:2207-2212.)

**Key Words** • hypertension • DNA • angiotensinogen

Complex quantitative traits such as blood pressure (BP) are considered to be influenced by both genetic and nongenetic factors. Approaches to analyze the genetic determinants of interindividual variation in BP must take into account both the number of gene products that contribute to pathogenesis and also the interactions of the gene products within biochemical and physiological pathways. The identification of major genetic determinants of BP should be easier in closely related subjects than in unrelated subjects for several reasons. First, members of a geographic or religious isolate have a similar genetic background and comprise a relatively homogeneous gene pool. This should permit experimental control over background genetic variation. Second, if the sample has arisen from a few founders, then the total number of alleles for a gene in the pool is expected to be small. This could help identify major genes that have a significant effect on BP, since the number of functionally relevant mutations in a genetic isolate is also expected to be small. Third, the high degree of relatedness between group members increases the likelihood that some subjects will carry an allele that is identical by descent. Thus, a recessive effect of a candidate gene on BP might be more easily identified. Finally, the sharing of environmental factors among group members should help reduce the nongenetic component of phenotypic variation.

The Hutterite Brethren are a North American religious genetic isolate. We have previously identified significant associations between candidate genes in lipoprotein metabolism and variation in plasma lipoproteins in the Hutterites. The Hutterites are a useful sample for the study of genetic determinants of quantitative traits such as plasma lipoproteins or BP because their founding gene pool is small and their indices of relatedness are high. DNA variation of the angiotensin-converting enzyme (ACE) gene in a noncoding region of the gene has been associated with variation in plasma ACE levels, coronary heart disease (CHD), and longevity. DNA variants of the angiotensinogen (AGT) gene underlying angiotensinogen protein polymorphism, particularly M235T and T174M, have been associated with hypertensive phenotypes. In addition, the genotype-phenotype association is modulated by gender since the expression of the hypertensive phenotype as preeclampsia in women was associated with the M235 variant of AGT. Therefore, we were also interested in determining the effect of gender on genotype-phenotype associations in the Hutterites. The current study had two major objectives: (1) to identify associations between either ACE or AGT genotypes and quantitative variation in systolic BP (SBP) and diastolic BP (DBP) and (2) to test whether these associations were dependent upon gender.

**Methods**

**Study Subjects** The Hutterite Brethren are an Anabaptist sect with approximately 30 000 members who live in Western Canada and the adjacent American states. They have an agrarian lifestyle and live on communal farms called colonies.
terites are descended from fewer than 100 founders who are considered to be unrelated to each other.\textsuperscript{3,11} The Hutterite terites have had a high intrinsic growth rate, and their population remains closed to immigration.\textsuperscript{11} They are subdivided into three endogamous sects: Dariusleut, Lerherleut, and Schmiedeleut.\textsuperscript{12} A high degree of consanguinity relative to the founders has accumulated over about 12 generations, with the average in-breeding coefficient of the current generation being 0.05.\textsuperscript{11} Hutterite society has a static inter- and intragenerational lifestyle.\textsuperscript{13} Colonies are effective surrogates for extended families; women marry between colonies, but men tend to remain within a colony.\textsuperscript{11} While the incidence of CHD in the Hutterites is unknown, the prevalence of risk factors appears to be comparable to that found in other populations.\textsuperscript{14} Smoking is forbidden, but alcohol is not.\textsuperscript{15} Major meals are taken communally, and the diet is high in animal fat.\textsuperscript{15} Mechanized farming techniques have reduced the amount of aerobic work-related exercise.\textsuperscript{14}

Subjects from 21 colonies of the Alberta Dariusleut and Lerherleut sects took part in the Canadian Heart Health Survey screening for CHD risk factors.\textsuperscript{16,17} Physical examination included determination of body mass index (BMI) defined as weight divided by height squared (kg/m\textsuperscript{2}) and four separate BP determinations. All patients answered a questionnaire indicating whether or not they had been diagnosed as having hypertension. Those who answered in the affirmative were asked whether or not they were currently taking medication prescribed for hypertension. Plasma samples from 846 Hutterites were obtained with informed consent. Exclusion criteria included an inadequate blood sample available for all biochemical and/or genetic determinations. The study was approved by ethical review panels of the Universities of Alberta and Toronto.

Genetic Analyses

Leukocyte DNA was prepared as described\textsuperscript{4} and was used for genotype analysis with the Taq polymerase chain reaction (PCR). Sufficient DNA and phenotypic information was obtained for analysis from 741 Hutterites. Genotypes for the DNA polymorphisms underlying the ACE insertion/deletion (I/D) polymorphism were determined as described.\textsuperscript{7} Genotypes for AGT codon 235 were determined as described.\textsuperscript{18} Genotypes for AGT codon 174 were determined using PCR. Amplifiers AGT174-5 and AGT174-3 were used, and had the sequences 5'–CAGGGCCCTGATAGCAGCAGCA–3', and 5'–GAGAGCCAGCCCTGACACAA–3', respectively. These were subjected to 30 cycles of PCR using 60°C as the annealing temperature. The PCR products were digested with endonuclease NlaIII (Bethesda Research Laboratories), using the manufacturer's recommendations. The digested fragments were electrophoresed in 8% polyacrylamide gels that were stained with ethidium bromide. Using this isotyping system, the larger (100 bp) and smaller (67 and 33 bp) fragments were represented by T174 and M174 variants, respectively.

Statistical Analysis

SAS software (version 6) was used for all statistical comparisons.\textsuperscript{20} The distribution of SBP and DBP was significantly nonnormal in this data set. Therefore, for parametric statistical analyses, each variable was transformed and subjected to analysis of normality. The reciprocal of the square root was used for SBP and the natural logarithm was used for DBP. After these transformations, the distribution of the variables was not significantly different from normal (data not shown). The transformed variables were used for parametric statistical analyses, but the nontransformed values are presented in the tables.

ANOVA was performed using the general linear models (GLM) procedure to determine the sources of variation for biochemical traits, with F tests computed from the type III sums of squares.\textsuperscript{20} This form of sum of squares is applicable to unbalanced study designs. Dependent variables were transformed for SBP and DBP. Independent variables included in the ANOVA were age, log BMI, current treatment status with antihypertensive agents ("treatment" or "no treatment"), and colony of origin, with the latter variable included to correct for contribution to variation that was related to other shared genetic and environmental factors. Also included as independent variables were genotypes of ACE I/D and AGT codons 235 and 174. Since we wished to identify significant genotype-gender interactions, we included interaction terms with gender for each genotype system.

When a significant association was identified within the whole group, baseline traits among individuals classified by genotype were subsequently compared using a nonparametric test for significant differences between groups (Kruskal-Wallis test, \(\chi^2\) approximation, NPARIWAY routine\textsuperscript{20}).

When a significant genotype-gender interaction term was identified within the whole group, the ANOVA was repeated for each sex separately using the GLM procedure to determine the sources of variation for biochemical traits, with F tests computed of the I/D sums of squares. Genotype-gender interaction terms were transformed SBP and DBP. Independent variables included in the ANOVA were age, log BMI, treatment with antihypertensive agents, and colony of origin. Any significant genotype-phenotype association that was detected by ANOVA was tested independently using \(\chi^2\) analysis. Subjects were classified as being hypertensive by fulfilling either of the following criteria: (1) current treatment with an antihypertensive agent or (2) an SBP exceeding 140 mm Hg. The classification of "hypertensive" or "not hypertensive" was used as the first variable for \(\chi^2\) analysis. Genotypic class was used as the second variable. \(\chi^2\) analysis was also used to test for deviation of genotype frequencies from those predicted by the Hardy-Weinberg law.

Finally, regression analysis was performed, and partial regression coefficients\textsuperscript{20} were used to estimate the percent of phenotypic variation that was accounted for by genotypic variation.

Results

Allele and Genotype Frequencies

The allele frequencies of ACE alleles I and D were 0.40 and 0.60, respectively. The genotype frequencies of the I/I, I/D and D/D genotypes were 0.29, 0.22, and 0.49, respectively. While allele frequencies were similar to those reported in other Caucasian populations,\textsuperscript{5-7} there was a significant deviation of ACE I/D genotype frequencies from those predicted by the Hardy-Weinberg law in this sample of Hutterites (\(\chi^2=111\), \(P<.0001\)).

The frequencies of AGT alleles M235 and T235 were 0.59 and 0.41, respectively. The genotype frequencies of the M235/M235, M235/T235, and T235/T235 genotypes were 0.33, 0.52, and 0.15, respectively. The allele frequencies were similar to those reported in other normotensive populations.\textsuperscript{8} There was no deviation of the genotype frequencies from those predicted by the Hardy-Weinberg law in this sample of Hutterites (\(\chi^2=0.76\), NS).

The frequencies of AGT alleles T174 and M174 were 0.82 and 0.18, respectively. The genotype frequencies of the T174/T174, T174/M174, and M174/M174 genotypes were 0.66, 0.32, and 0.02, respectively. The allele frequency of M174 was somewhat higher than that reported in other normotensive samples.\textsuperscript{9} There was a tendency for these genotype frequencies to deviate from those predicted by the Hardy-Weinberg law in this sample of Hutterites (\(\chi^2=2.20, P=0.07\)). Significant linkage disequilibrium was detected between alleles of the two polymor-
TABLE 1. ANOVA in Hutterite Subjects

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>df</th>
<th>F</th>
<th>P&gt;F</th>
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<tr>
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<td>23.8</td>
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</tr>
<tr>
<td>Sex</td>
<td>1</td>
<td>10.1</td>
<td>.0015</td>
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<tr>
<td>Log BMI</td>
<td>1</td>
<td>58.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>1</td>
<td>68.5</td>
<td>&lt;.0001</td>
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<tr>
<td>Colony</td>
<td>20</td>
<td>3.15</td>
<td>&lt;.0001</td>
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<td>ACE I/D genotype</td>
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<td>NS (.75)</td>
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<tr>
<td>AGT codon 235 genotype</td>
<td>2</td>
<td>2.02</td>
<td>NS (.13)</td>
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<tr>
<td>AGT codon 174 genotype</td>
<td>2</td>
<td>3.58</td>
<td>.028</td>
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<tr>
<td>ACE I/D–gender interaction</td>
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<td>0.56</td>
<td>NS (.57)</td>
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<tr>
<td>AGT 235–gender interaction</td>
<td>2</td>
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<td>NS (.47)</td>
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<tr>
<td>AGT 174–gender interaction</td>
<td>2</td>
<td>3.64</td>
<td>.027</td>
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TABLE 2. ANOVA in Hutterite Subjects Classified by Sex

<table>
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<th>P&gt;F</th>
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<tr>
<td>Antihypertensive medication</td>
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<td>3.04</td>
<td>.0493</td>
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<tr>
<td>Colony</td>
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<td>1.98</td>
<td>.0081</td>
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<td>ACE I/D</td>
<td>2</td>
<td>0.12</td>
<td>NS (.88)</td>
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<tr>
<td>AGT codon 235 genotype</td>
<td>2</td>
<td>0.69</td>
<td>NS (.50)</td>
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<tr>
<td>AGT codon 174 genotype</td>
<td>2</td>
<td>6.07</td>
<td>.0026</td>
</tr>
</tbody>
</table>

Determinants of Variation in SBP and DBP

The ANOVA is shown in Table 1. Significant associations were identified between transformed SBP and the independent variables of age, sex, log BMI, treatment with antihypertensive agents, and colony of origin. SBP was significantly associated with AGT codon 174 genotype but not with ACE I/D or AGT codon 235 genotype. SBP was also significantly associated with the AGT codon 174 genotype–gender interaction term but not with the ACE I/D–gender or AGT codon 235 genotype–gender interaction terms.

Significant associations were identified between transformed DBP and the independent variables of age, sex, treatment with antihypertensive medications, log BMI, and colony of origin. However, DBP was not significantly associated with either ACE I/D, AGT codon 235, or codon 174 genotypes. ANOVA also found that DBP was not significantly associated with any genotype–gender interaction term.

Determinants of SBP in Subjects Divided by Gender

Significant phenotype-genotype associations were identified after adjustment for the covariates of age, log BMI, treatment with antihypertensive medications, and colony of origin. For both SBP and DBP, the independent variable of sex was significantly associated with variation, with P always <.0001 (Table 1). Also, the genotype–gender interaction term for AGT codon 174 genotype and SBP as the dependent variable was significant. As a consequence, to test the effects of genotypes of ACE I/D and AGT codons 235 and 174 on SBP, ANOVA was performed separately for men and women. The results of the ANOVA are shown in Table 2.

In men, SBP was significantly associated with log BMI, treatment with antihypertensive medications, and colony. Furthermore, in men, SBP was significantly associated with AGT codon 174 genotype (P=.0026). In women, SBP was significantly associated with age, log BMI, treatment with antihypertensive medications, and colony. However, in women, SBP was not significantly associated with any genotypic variable. There were no other significant associations with any other genotype in either sex (data not shown).

See Table 1 for abbreviations.
SBP and DBP in Subjects Divided by Gender and Classified by AGT Codon 174 Genotype

Among men classified by AGT codon 174 genotype, there were no significant between-group differences in age, BMI, or mean DBP. However, there was a significant between-group difference in SBP (P = .028). There was a consistent dose-related increase in both SBP and DBP in men, with T174/T174 homozygotes having lowest mean values, T174/M174 heterozygotes having intermediate mean values, and M174/M174 homozygotes having the highest mean values. (See Table 3.) Among women classified by AGT codon 174 genotype, there were no significant between-group differences in age, BMI, SBP, or DBP. However, T174/T174 homozygotes had the lowest mean SBP and DBP, T174/M174 heterozygotes had intermediate mean SBP and DBP, and M174/M174 homozygotes had the highest mean SBP and DBP. This was similar to the trend observed in men, although the between-group differences were not significant. (See Table 4.)

Regression analysis using a standard linear model was performed in men to estimate the percent of phenotypic variation that was determined by genetic variation. The model applied in men using age, BMI, treatment with antihypertensive medications, colony of origin, and genotypes of AGT codon 174 was able to account for 35% of the total variation in SBP. In men, 31% of the total variation in SBP was accounted for by genetic variation of AGT codon 174. This compared with 53% of total variation in SBP that was accounted for by BMI, 0% that was accounted for by age, 16% that was accounted for by treatment with antihypertensive medication, and 7.9% that was accounted for by colony of origin.

Association of Hypertension With AGT Codon 174 Variation

Subjects were classified as being hypertensive either by a history of current antihypertensive medication intake or a mean SBP exceeding 140 mm Hg. Using these criteria, 22.4% of men and 17.2% of women were classified as being hypertensive.

In men, the M174 allele was significantly associated with a diagnosis of hypertension (x² = 5.99, P = .05). The frequency of hypertension among T174/T174 homozygotes, T174/M174 heterozygotes, and M174/M174 homozygotes was 19% (46 of 242), 28% (36 of 111), and 50% (2 of 4), respectively. In women, the M174 allele was not significantly associated with a diagnosis of hypertension (x² = .383, P = .83). The frequency of hypertension among T174/T174 homozygotes, T174/M174 heterozygotes, and M174/M174 homozygotes was 18% (52 of 295), 15% (21 of 133), and 22% (2 of 7), respectively.

Discussion

The principal finding of this study in Hutterites is the identification of an association between AGT genetic variation and differences in SBP that appear to be gender specific. We found a significant association between variation of SBP within the normal range and variation of AGT codon 174 in men but not in women from a genetically isolated population that was ascertained from CHD risk factor screening. We also found that while the AGT M174 variant was significantly associated with hypertension in male subjects, it was not associated with hypertension in female subjects.

The AGT M174 variant has been found at higher frequency in hypertensive subjects than in normal control subjects in North American and Parisian hypertensive sibling pairs. In both groups, the frequency in severely hypertensive index cases was approximately double the frequency in control subjects, namely, 0.17 versus 0.08. This is completely consistent with our findings in a predominantly normotensive Hutterite sample. The highest mean SBP level was found in four men homozygous for the AGT M174 variant, with an intermediate mean SBP level in men heterozygous for the AGT M174 and T174 variants and the lowest mean SBP level in men with the T174/T174 genotype.

Table 3. Clinical Features of Men Classified by AGT Codon 174 Genotype (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>T/T</th>
<th>T/M</th>
<th>M/M</th>
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<tbody>
<tr>
<td>n</td>
<td>230</td>
<td>103</td>
<td>4</td>
<td></td>
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<tr>
<td>Age, y</td>
<td>37.7 ± 13.7</td>
<td>36.6 ± 15.3</td>
<td>38.0 ± 13.5</td>
<td>NS (.57)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>28.3 ± 3.7</td>
<td>27.7 ± 3.56</td>
<td>30.4 ± 0.90</td>
<td>NS (.22)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127.4 ± 13.40</td>
<td>131.8 ± 15.00</td>
<td>136.0 ± 13.50</td>
<td>.028</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82.2 ± 10.00</td>
<td>84.3 ± 10.80</td>
<td>89.3 ± 12.70</td>
<td>NS (.11)</td>
</tr>
</tbody>
</table>

Table 4. Clinical Features of Women Classified by AGT Codon 174 Genotype (Mean ± SD)

<table>
<thead>
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<th>T/M</th>
<th>M/M</th>
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<tr>
<td>n</td>
<td>279</td>
<td>123</td>
<td>8</td>
<td></td>
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<tr>
<td>Age, y</td>
<td>37.8 ± 15.30</td>
<td>37.0 ± 15.20</td>
<td>38.7 ± 11.10</td>
<td>NS (.75)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>27.9 ± 5.70</td>
<td>28.9 ± 6.00</td>
<td>29.0 ± 6.60</td>
<td>NS (.28)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>121.8 ± 15.30</td>
<td>122.1 ± 15.20</td>
<td>125.2 ± 14.50</td>
<td>NS (.70)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75.6 ± 9.10</td>
<td>76.1 ± 9.30</td>
<td>80.3 ± 9.80</td>
<td>NS (.42)</td>
</tr>
</tbody>
</table>

See Tables 1 and 3 for definitions of abbreviations.
SBP level in men homozygous for the AGT T174 variant. Thus, the AGT M174 variant was associated with a higher baseline BP within the normal range and has a codominant effect with T174 on resting BP. Its significant association with hypertension in the Hutterites and also in study samples from Paris and Salt Lake City suggest that it might predispose carriers to a slightly higher baseline BP. Phenotypic hypertension might then develop in AGT M174 carriers when secondary genetic or environmental factors are present.

Jeunemaître et al found that variation of AGT codon 235 was also strongly associated with severe hypertension. They demonstrated that the AGT T235 variant was significantly more frequent in severely hypertensive index cases compared with normotensive control subjects (0.51 versus 0.36). Bennett et al subsequently found in a case-control study in Caucasians with severe familial essential hypertension that the AGT T235 variant was not significantly increased compared with normotensive control subjects. Thus, the results of Jeunemaître et al contrast with whereas the results of Bennett et al are consistent with our finding that variation of AGT codon 235 was not significantly associated with BP in a predominantly normotensive Hutterite sample. The reasons for these discrepancies may relate to fundamental genetic differences in the study samples, within which subjects were ascertained using different criteria. The strong association of T235 with hypertension in the Paris and Salt Lake City samples suggests that it is may be a factor predisposing to hypertension in carriers. Our results suggest that such predisposition might not be evident by studying resting BP. Also, the expression of phenotypic hypertension in AGT T235 carriers might also require the presence of secondary genetic or environmental factors that were absent in our sample. Alternatively, since there can be strong linkage disequilibrium between alleles at AGT codons 235 and 174, the significance of any allelic association with phenotype could be due to linkage disequilibrium with another functionally relevant allele. While we demonstrated strong linkage disequilibrium between alleles of codons 235 and 174 in our Hutterite sample, only alleles of codon 174 were significantly associated with variation in resting BP, suggesting that in this group alleles at codon 235 were not associated with resting BP either independently or through linkage with codon 174. However, the linkage disequilibrium was not complete and was due to a higher than expected frequency of the M235 and T174 alleles and not between the other alleles that have been associated with higher BP.

Gender differences in AGT-associated hypertension have been reported. Both AGT T235 and M174 were significantly more prevalent in female hypertensive subjects than in control subjects, but no linkage with either variant was found among sibling pairs of female hypertensive subjects. The authors did not use a statistical model that would specifically identify a gender-specific modulation of the AGT-associated predisposition. However, they hypothesized that AGT contributes to hypertension indirectly in women. They postulated that an estrogen-related factor might mediate the impact of the AGT-associated genetic predisposition. The contention that gender and sex hormones could modulate the expression of AGT-associated hypertension was supported by the subsequent observation that AGT T235 was significantly more frequent in Caucasian women with preeclampsia and pregnancy-induced hypertension compared with normotensive pregnant control subjects (0.65 versus 0.40). Taken together, these data suggest that gender appears to modulate the expression of both AGT-associated hypertension and AGT-associated variation in normal BP.

Variation at AGT codon 235 has also been associated with variation in plasma angiotensinogen level, providing a possible biochemical mechanism linking the genomic DNA variation with the hypertension phenotype. Among all subjects with hypertension, AGT M235/M235 homozygotes had the lowest mean plasma angiotensinogen levels, AGT M235/T235 heterozygotes had intermediate mean plasma angiotensinogen levels, and AGT T235/T235 homozygotes had the highest mean plasma angiotensinogen levels. When men and women were analyzed separately, the difference between genotypic classes was much more remarkable and statistically significant in women. These data further support the notion that gender modulates the impact of AGT genetic variation on both intermediate phenotypes, such as plasma angiotensinogen levels, and distant phenotypes, such as BP.

It has been postulated that elevations in plasma or tissue levels of AGT associated with specific structural AGT variants might result in increased baseline production of angiotensin II. Chronically high levels of angiotensin II might increase vascular tone, resulting in an increase in resting BP. Our data would suggest that gender might have an impact on the association between AGT-associated variation in resting BP. Jeunemaître et al have also postulated that elevated baseline angiotensinogen levels might also affect the reactivity of the renin-angiotensin system with an altered homeostatic setpoint in predisposed individuals. In the presence of additional pathophysiological stresses such as hypervolemia, increased sympathetic nervous system stimulation, or increased cardiac output, this predisposition might lead to the development of overt clinical hypertension.

The effect of sex hormones on angiotensinogen is complex. Estrogens have been shown to stimulate transcription of hepatic angiotensinogen. In contrast, androgens have been reported to increase transcription of renal angiotensinogen. It is thus possible that the mechanism for the gender-specific associations between AGT genetic variation and both intermediate and distant phenotypes is hormonally mediated. However, such hormonal mediation may be tissue specific, providing an additional level of complexity of AGT gene regulation for any particular subject.

The absence of association between genetic variation of ACE and BP in the Hutterites is consistent with other observations that have ruled out a significant relation between this locus and human hypertension. The deviation of observed ACE I/D genotype frequencies from those expected according to the Hardy-Weinberg distribution is undoubtedly related to the unusual genetic features of this isolate, including the mating patterns and high degree of relatedness. We have previously observed deviations from expected allelic and genotypic frequencies for other loci in this study sample.
Regression analysis determined that 3.1% of the total variation in SBP was accounted for by genetic variation of AGT codon 174. This was comparable to the proportion of total variation in SBP that was accounted for by BMI, which was 5.3%. However, it was less than the proportion of variation that was accounted for by medication status and colony of origin, which were 16.9% and 7.9%, respectively. The genetic contribution to interindividual variation in BP has been estimated at 20% to 40%. Thus, in these Hutterite men, a substantial part of the genetic component of interindividual variation in BP appears to have been determined by genetic variation of AGT. The relatively high proportion of variation attributable to colony of origin, namely, 7.9%, could reflect additional shared genetic or environmental factors that determine interindividual variation in BP in this study sample.

Summary

We have observed that genetic variation in AGT was associated with interindividual variation in SBP only in men. This provides support for the previous observations of association between structural variation in AGT and BP-related phenotypes such as plasma angiotensinogen levels and overt hypertension. Studies using highly related subjects can help apportion the relative contribution of various genetic factors to a complex phenotype like BP. Newer approaches to rapidly screen for regions of genomic DNA that are identical by descent and to perform combined segregation and linkage analysis in highly related populations could further help to identify new genes that are important in polygenic diseases such as hypertension and help to identify high-risk individuals who are candidates for interventions.

Acknowledgments

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A polymorphism of the angiotensinogen gene associated with variation in blood pressure in a genetic isolate.

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