A Prospective Study of Sodium-Lithium Countertransport and Hypertension in Utah

Steven C. Hunt, Susan H. Stephenson, Paul N. Hopkins, Sandra J. Hasstedt, and Roger R. Williams

A 7-year prospective study of a cohort of 1,458 normotensive adults from Utah pedigrees, screened from 1980 to 1985, was done to determine whether baseline levels of sodium-lithium countertransport were associated with an increased risk of future hypertension. Subsequent new hypertension (n=39) was ascertained in 1989 from detailed follow-up medical questionnaires (67% response). Previous segregation analyses on a subset of these pedigree members who responded (n=342) using family relationships in addition to countertransport levels have shown statistically inferred major gene segregation of sodium-lithium countertransport levels. In the normotensive adults inferred by segregation analysis to carry the recessive major gene for high sodium-lithium countertransport, new-onset hypertension occurred in 18.8% (3 of 16) compared with 3.7% (12 of 326) in the low sodium-lithium countertransport genotype group (relative risk, 4.6 [1.6, 13.9]; p=0.03). However, an elevated baseline sodium-lithium countertransport level without genotype information from segregation analysis did not increase the risk of future hypertension in the complete cohort of adult pedigree members (relative risk, 1.02 [0.85, 1.22]). Adjustment for other risk factors reduced the relative risk to 0.90 (0.72, 1.11). We conclude that the presence of a major gene for sodium-lithium countertransport or another closely linked gene, rather than the actual level of sodium-lithium countertransport, may increase the risk of hypertension onset. High sodium-lithium countertransport levels do not increase the risk of future hypertension for individuals in whom only polygenic and environmental effects determine sodium-lithium countertransport level. Both longer follow-up to increase the number of events and studies in other populations are needed to verify these results. Further characterization of the biochemical and molecular nature of the underlying recessive gene trait is needed to understand how it may increase the risk of hypertension. (Hypertension 1991;17:1-7)

Sodium-lithium countertransport (SLC) is a ouabain-insensitive transport system that provides in vivo exchanges of sodium for sodium across cell membranes.1 It may also exchange other monovalent cations depending on intracellular and extracellular conditions.2 Usually measured in erythrocytes, SLC has shown elevated activity in hypertensive patients compared with normotensive individuals and has been proposed as a marker for risk of future hypertension.1,3,7

We have recently provided statistical evidence for a recessive major gene that affects SLC in large Utah pedigrees ascertained for early coronary heart disease (CHD).8 Others have also found evidence for major gene segregation of the phenotype.9,10 We estimated that in our coronary-ascertained pedigrees, a recessive major gene explained 34% of the variance of SLC and polygenes accounted for another 46% of the variance. Environmental factors accounted for the remaining 20% and may interact with the genetic factors. Only 5% of the population was homozygous for high levels of SLC. In our cross-sectional genetic study,8 individuals with a high probability of carrying the major gene for high SLC had twice the prevalence of hypertension, increased obesity, and elevated triglyceride levels as those without the high genotype.

Higher SLC in hypertensive patients, as well as increased prevalence of hypertension in individuals with a recessive gene reflected by segregating high SLC, suggest that SLC is closely associated with hypertension. However, prospective studies have not been done to show whether baseline SLC level
increases the risk of future hypertension or the hypertensive process itself alters the SLC activity. We present here a prospective study of SLC and hypertension, using pedigrees previously used for our cross-sectional studies. The possible prospective relation of the homozygous high SLC genotype to hypertension is also examined.

Methods
From 1980 to 1983 (visit 1), 2,500 individuals from 98 Utah pedigrees were screened at the Cardiovascular Genetics Clinic at the University of Utah. These pedigrees were ascertained from three sources: 1) descendants of sibships with two or more stroke deaths before age 75 (n = 542), 2) descendants of sibships with two or more coronary deaths (CHD) before age 55 (n = 1,202), and 3) first- and second-degree relatives of hypertensive and normotensive probands randomly selected from the Utah Hypertension Detection and Follow-up Program study (n = 756). The characteristics and details that concern these pedigree members are more fully described elsewhere. On an average of 2.5 years later (visit 2), 2,053 of the 2,500 individuals were rescreened along with 228 additional members of these pedigrees not originally screened at visit 1. The 228 new visit 2 and the 2,500 visit 1 individuals constitute the 2,728 individuals available for this study at baseline.

At either visit 1 or visit 2, any individuals who were taking antihypertensive medications for high blood pressure, who had previously taken antihypertensive medications and had a current untreated sitting diastolic blood pressure of 90 mm Hg or above, or who had suffered a stroke were excluded from all analyses. Excluded from baseline as a result of having hypertension at visits 1 or 2 were 221 individuals. An additional 24 individuals were excluded because SLC was not measured at either visit 1 or visit 2. Because all new-onset hypertensive individuals were adults (ages 24–71 years), only the 1,458 adults (over age 17) were retained for analyses. Informed consent was obtained from all participants, and the study procedures followed the guidelines approved by an institutional review committee at the University of Utah.

In 1989, detailed medical questionnaires were sent to all previous participants that asked if they were presently taking antihypertensive medications for high blood pressure, how long, what the medication names were, if they had hypertension only during pregnancy, or if they had antihypertensive medication prescribed but had stopped taking it on their own or by their physician’s recommendations. New-onset hypertension was defined as the inception of taking antihypertensive medications after the visit 2 clinic visit or, if there were no visit 2, after the end of the visit 2 screening cycle (January 1986) and presently taking those medications. Therefore, only hypertension onset at least 2.5 years after the baseline SLC measurements were made was considered as new-onset hypertension in the prospective analyses. None of the adults who only attended the clinic for visit 2 had hypertension onset earlier than 2.5 years after that visit. Telephone calls were made to obtain medication names, dosages, and years taken from any person who claimed to be on blood pressure medication, without providing this information. At the end of 1989, the response rate for returning the questionnaire was 67% (n = 974) of the 1,458 adults. There were 40 individuals with new-onset hypertension, one of whom did not have SLC measured. Average length of follow-up from visit 1, or visit 2 if there were no visit 1, was 7.0 years.

Five subjects were never treated at either visit 1 or visit 2; their diastolic blood pressure was between 90 and 100 mm Hg. One of the five had an elevated mean of four measurements of diastolic blood pressure only at visit 1 and had a mean level less than 90 mm Hg at visit 2; three had an elevated level at visit 2 but were normotensive at visit 1. The fifth person had very labile blood pressure, with half of the four measurements under 90 and half over 90 mm Hg at each visit. Because the diagnosis of hypertension from three clinic visits is recommended, these subjects were considered normotensive at baseline. Analysis of the data showed that exclusion of these individuals from baseline did not affect the estimates or conclusions of this study.

SLC was measured as described by Canessa et al with the modifications of Smith et al. For the adults who attended visit 1 but did not have an SLC measurement (n = 93), the SLC level at visit 2 was used. The coefficient of daily variation in SLC from the same individuals was 9%, and the correlation of SLC from visit 1 to visit 2 was 0.7. Total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides were measured in plasma obtained after an overnight fast. Fasting plasma glucose was measured on an autoanalyzer (SMAC II Analyzer, Technicon Instruments Corp., Tarrytown, N.Y.). Body mass index was calculated as weight divided by height squared (kg/m²). A positive family history of hypertension was defined as a quantitative family history score greater than 1.0 based on at least two first-degree relatives with hypertension. The score is derived from comparing the observed number of events in the family with the expected number obtained from multiplying the age- and sex-specific Utah population hypertension incidence rates times the age- and sex-specific person-years in the family. This definition is highly predictive of future hypertension.

Plasma triglyceride was transformed by natural logarithm. All variables were adjusted for sex and a cubic polynomial in age, using a general linear model (SAS Institute, Cary, N.C.). The cubic polynomial in age was used because blood pressure, obesity, and lipids have nonlinear associations with age. Logistic regression on the residual variables was used for the prospective study analyses. Because these individuals belonged to pedigrees and were not independent observations, the logistic regression method of Rosner was also used to estimate the significance of the independent variables by controlling for the
Table 1. Baseline Means of New-Onset Hypertensive, Normotensive, and Nonresponder Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypertensive</th>
<th>Normotensive</th>
<th>Nonresponder</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (men/women)</td>
<td>22/17</td>
<td>449/486</td>
<td>254/230</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.5±11.1*</td>
<td>35.9±14.0</td>
<td>31.6±11.5*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.8±4.7*</td>
<td>24.9±4.5</td>
<td>24.5±4.8</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.6±13.7*</td>
<td>110.8±12.7</td>
<td>110.8±12.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75.0±9.3*</td>
<td>65.5±10.1</td>
<td>65.1±9.7</td>
</tr>
<tr>
<td>Sodium-lithium countertransport</td>
<td>0.273±0.118</td>
<td>0.265±0.104</td>
<td>0.267±0.112</td>
</tr>
<tr>
<td>(mmol/1 RBC/hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>210±31†</td>
<td>196±45</td>
<td>188±41*</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>149±69‡</td>
<td>109±78</td>
<td>104±72</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>46.3±14.6</td>
<td>48.1±12.0</td>
<td>47.9±12.1</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>106.4±19.0†</td>
<td>98.4±19.7</td>
<td>97.4±20.7</td>
</tr>
</tbody>
</table>

Values are mean±SD. RBC, red blood cells; HDL, high density lipoprotein.

*p<0.001; †p<0.05; ‡p<0.01, comparison of the hypertensive or nonresponder groups with the normotensive group.

Results

Table 1 shows the baseline characteristics of the new-onset hypertensive, normotensive, and nonresponder groups. The subjects who became hypertensive were significantly older, more obese, and had higher total cholesterol, triglyceride, fasting glucose, and sitting blood pressure levels. Blood pressure increases between visits 1 and 2 were the same for each group (4/5 mm Hg in the new-onset hypertensive and 5/4 mm Hg in the normotensive groups). HDL cholesterol and SLC levels were not significantly different. The nonresponder group was very similar to the normotensive group although statistically slightly younger with lower total cholesterol. No evidence of a response bias between the two groups is apparent. Figure 1 shows the distribution of the percent of normotensive and hypertensive subjects across the SLC category. They look very similar despite the variability in the hypertensive group because of small numbers of subjects.

The relative risk of hypertension was 1.02 (0.85, 1.22), \( p = 0.42 \) (Table 2), assuming an SLC difference between hypertensive and normotensive individuals of 0.070 mmol/l red blood cells (RBC)/hr (found in a previous cross-sectional study using these pedigrees). A difference between hypertensive and normotensive individuals of as large as 0.200 mmol/l RBC/hr would give a relative risk of only 1.06 (logistic regression coefficient, 0.31±1.6). Controlling for the familial dependence within households did not change the standard error estimate. Therefore, SLC level showed no predictive value for hypertension in the group as a whole.

Controlling for age (\( p = 0.0001 \)) and sex- and age-adjusted plasma triglyceride (\( p = 0.02 \)), HDL cholesterol (\( p = 0.42 \)), fasting glucose (\( p = 0.11 \)), family history of hypertension (\( p = 0.005 \)), body mass index (\( p = 0.02 \)), and baseline diastolic blood pressure (\( p = 0.0009 \)) reduced the relative risk (relative risk, 0.90 [0.72, 1.11]).

Familial dependence within sibships. The power of the study to detect mean differences similar to our published cross-sectional differences was determined using a t test between the SLC means of the normotensive versus hypertensive individuals who were hypertensive at baseline.

To test whether the presence of a major gene for high SLC was associated with new-onset hypertension, individuals from the coronary-ascertained pedigrees were assigned probabilities of being homozygous for the gene associated with high SLC levels, using the best fitting model from maximum likelihood pedigree analysis. Sixteen individuals had probabilities of greater than 50% of having the homozygous high SLC genotype and 326 with probabilities less than 50% of having both alleles (i.e., heterozygous and homozygous low SLC genotypes). Because high SLC has been cross sectionally associated with hypertension, one-sided 95% confidence intervals for the relative risks were used.

![Figure 1. Line graph showing distribution of percent of 39 new-onset hypertensive (HBP) and 935 normotensive (NBP) individuals within each sodium-lithium countertransport (SLC) category level. Marks on horizontal axis are lower limits of each category of 0.05 mmol/l red blood cells (RBC)/hr SLC.](http://hyper.ahajournals.org/)
TABLE 2. Relative Risk of Hypertension Within Risk Factor Groups for Sodium-Lithium Countertransport

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative risk*</th>
<th>One-sided 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.02</td>
<td>(0.85, 1.22)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.90</td>
<td>(0.72, 1.11)</td>
</tr>
<tr>
<td>Ascertainment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD pedigrees</td>
<td>1.01</td>
<td>(0.79, 1.29)</td>
</tr>
<tr>
<td>Non-CHD pedigrees</td>
<td>1.05</td>
<td>(0.81, 1.36)</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.27</td>
<td>(0.90, 1.78)</td>
</tr>
<tr>
<td>Negative</td>
<td>0.95</td>
<td>(0.76, 1.18)</td>
</tr>
</tbody>
</table>

CHD, Coronary heart disease ascertained.

*Estimated from the logistic regression coefficient for a difference of 0.070 mmol/l RBC/hr in countertransport levels, which was the difference found between hypertensive and normotensive patients in previous studies. See text for definition of positive family history.

**A** Adjusted for baseline age, diastolic blood pressure, body mass index, plasma triglycerides, HDL cholesterol, plasma glucose level, and family history of hypertension.

Analyses on subgroups of positive and negative family history of hypertension, or CHD and non-CHD-ascertained pedigrees, also showed no predictive value of SLC (Table 2). The association between hypertension and SLC was higher but still not significant for those with a positive family history of hypertension (relative risk, 1.27) compared with those with a negative family history (relative risk, 0.95).

The power to detect a significant result was calculated by use of the mean differences and standard deviations for the hypertensive and normotensive groups analyzed in a previous study. In that study, the hypertensive and normotensive SLC values were 0.338 and 0.268 mmol/l RBC/hr, respectively, with a pooled standard deviation of 0.105. Therefore, the difference between the two groups was 0.667 standard deviation units. The harmonic mean of the sample sizes of the two groups (39 and 935) was 75. With this sample size of 75 in each group, we had a 99% power of detecting the previously found significant difference of 0.667 (one-sided α=0.05) between groups. The observed difference between new hypertensive and normotensive patients in this study was only 0.074 standard deviation units.

Because the SLC phenotype apparently could not predict future hypertension in individuals in whom 95% had SLC determined by polygenes and environmental influences, the subset of pedigree members in whom evidence for major gene segregation was found were analyzed. There were 342 members of coronary-ascertained pedigrees that could be assigned to one of the SLC genotypes, which was based on maximum likelihood segregation analysis of their SLC levels and the levels of their relatives (Table 3). Sixteen of these people had a probability greater than 0.5 (mean probability, 0.88±0.14) of being homozygous for high SLC. Of these 16 labeled with a high SLC genotype, 18.8% (n=3) became hypertensive compared with 3.7% (12 of 326) of those who had less than a 50% chance (mean probability, 0.02±0.07) of being homozygous for high SLC. The unadjusted relative risk was 4.6, with a one-sided 95% confidence interval (1.6, 13.9). Significance from a one-sided Fisher's Exact Test was p=0.033. Fitting a backwards elimination logistic model to the onset of hypertension and controlling for baseline age (p=0.0001), diastolic blood pressure (p=0.002), HDL cholesterol (p=0.004), and family history of hypertension (p=0.05), the risk of hypertension was 5.3 (1.3, 21.5) times higher for the high SLC genotype than the low one. Body mass index, triglycerides, and plasma glucose were not significant (p>0.05) and were removed from the model.

To further demonstrate the SLC association with hypertension only in individuals in whom a major gene for high SLC levels is present, the incidence of hypertension was calculated for those with an SLC above and below 0.4 mmol/l RBC/hr within the genotype. In those with an SLC lower than 0.4 mmol/l RBC/hr (all had the low genotype), 3.7% (32 of 872) became hypertensive. In those with an SLC higher than 0.4 mmol/l RBC/hr who did not have the high SLC genotype, only 4.7% (4 of 86) became hypertensive (relative risk, 1.3; p=0.41), again suggesting that the SLC level itself is not associated with an increased risk of hypertension. In those with an SLC higher than 0.4, the incidence of hypertension was 18.8% (3 of 16) in the high SLC genotype group compared with 4.7% in the low genotype group (relative risk, 4.0; p=0.075). The mean SLC levels were 0.56 and 0.26 mmol/l RBC/hr for the high and low SLC genotypes, respectively.

**Discussion**

In this prospective study, we demonstrated that in pedigree members selected for the presence of cardiovascular disease, the SLC level alone is not associated with an increased risk of hypertension. How-
ever, in individuals with the high SLC genotype (inferred from levels of relatives in addition to the individual's level), the risk of hypertension was four-fold higher than for those who had the low genotype whose SLC level was determined only by polygenic and environmental influences. This result was based on small numbers of new-incidence cases of hypertension and requires confirmation after longer follow-up. The increased risk with the SLC genotype and not the SLC level suggests that the cause of an increased SLC level is the most important factor that determines hypertension risk, not the level itself. The defect associated with the major gene that causes elevated SLC seems different from the polygenic and environmental influences that elevate SLC. The major gene defect may affect both SLC and other pathophysiological processes that increase blood pressure (Figure 2), and the polygenic and environmental determinants of SLC are apparently not associated with hypertension. In addition, the SLC major gene may be closely linked in linkage disequilibrium to another gene that is responsible for hypertension onset. Established essential hypertension may also cause compensatory elevations in SLC, resulting in an association between hypertension and SLC in those without the major gene for SLC.

Even in those with the major gene for high SLC, a genetic background of polygenes or strong environmental influences for low SLC could lower the SLC level into the range of normotensive values, and the person would still have an increased risk of hypertension. The availability of SLC levels in close relatives becomes important in determining the probability of carrying the major gene for high SLC and the risk of hypertension.

The weak positive family history relation with SLC in normotensive persons may be much stronger if analyses could be limited to those families in which the major gene for high levels is present. The likelihood of differentiating families in whom the alleles for high SLC are present may be less because of different definitions of a positive family history and different family or individual sampling protocols. These factors may explain the variable results published that concern whether family history of hypertension is associated with SLC\(^{21-26}\). The strongest evidence for an SLC association with a positive family history of hypertension came from the study of Woods et al.\(^{22}\) who used the offspring of two hypertensive parents. If SLC is recessively inherited and the high genotype is associated with hypertension, the chances are greater for the offspring of two hypertensive parents to have the high SLC genotype than offspring of only one parent with hypertension. From a short-term (25-40-month) follow-up on most of the subjects in Woods's study,\(^{27}\) the offspring of two hypertensive parents had significantly greater increases in blood pressure than the other offspring. However, the lack of a correlation between blood pressure change and SLC that they found may arise from a lack of power resulting from the use of only 35 subjects. In addition, SLC seems more strongly related to hypertension as a dichotomous trait than to blood pressure itself.

**Characteristics of the High Sodium-Lithium Countertransport Genotype**

Our previous cross-sectional genetic study that characterized the SLC genotypes found that there was twice as much hypertension in those with the high SLC genotype, that plasma triglyceride levels were elevated, and the individuals were more obese. We have also described a familial syndrome that comprises early-onset hypertension and lipid abnormalities (primarily elevated triglyceride levels) that is related to obesity and increased fasting insulin levels.\(^{28,29}\) In sibships with this syndrome, SLC was significantly elevated compared with levels in normolipidemic hypertensive individuals and was significantly correlated with triglycerides, insulin levels, and obesity.\(^{30}\) These sibships are being expanded into larger pedigrees for more detailed genetic analyses that relate SLC to these variables. These observed correlations extend longitudinally as well as cross sectionally, as changes in SLC over 2.5 years correlated with changes in triglyceride levels and obesity independent of the baseline

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**Figure 2. Suggested model showing contribution of individual components of sodium-lithium countertransport (SLC) determination in Utah pedigrees (major gene, polygenic, and environment) to final SLC level and onset of hypertension.**

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**Legend:**

- **Major Gene (30%)**
- **Polygenic (40%)**
- **Environmental (20%)**

**Results:**

- Hypertension Onset
- SLC Determination

**Conclusion:** The model illustrates the complex interplay between genetic and environmental factors in determining SLC levels and the likelihood of developing hypertension.
levels. The major gene responsible for the increased SLC level and hypertension risk may be an underlying factor for these manifestations of a single syndrome. Further studies are required to determine what this underlying defect is and how it may influence these various metabolic processes.

Possible Study Weaknesses

Possible biases in the results may have occurred from at least three sources. First, only 67% of the participants responded. If the decision to return the questionnaire was not associated with hypertension status or SLC level, then there was no bias from this source because inclusion of the nonresponding individuals in the analysis as normotensives did not change the results (relative risk, 1.02 [0.85, 1.21]). There were also no baseline differences in blood pressure, body mass index, triglycerides, or SLC level between those who did and did not respond, suggesting that response was not related to any of the variables associated with SLC or with SLC alone.

Second, exclusion of individuals who were normotensive at visit 1 but hypertensive at visit 2 could have been too conservative. However, repetition of the analysis, including the 19 individuals who became hypertensive between visits 1 and 2, still did not alter the results (relative risk, 1.03 [0.89, 1.19]). Third, misclassification of true new-onset hypertension as normotension that resulted from not measuring actual blood pressure could have masked a real association. Some misclassification of the end points seems certain because many individuals may not have seen their physician since their visit to our clinic. If a large number of true, undiagnosed hypertensive individuals were misclassified as normotensive and SLC is prospectively associated with hypertension, then the elevated SLC levels of these persons may have been enough to hide a true association in our study. Although only direct measurement of current blood pressure in the study cohort will enable us to overcome this limitation, we believe that it did not severely bias the results. No difference in baseline SLC between the definite hypertensive and the self-reported normotensive individuals was observed. If the undetected hypertensive persons were similar to the detected ones, the mean levels of the two groups would remain the same. Even if the undetected hypertensive individuals were different from the detected ones, the normotensive mean would not change when they were reclassified because of the extremely large normotensive sample. The hypertensive mean could possibly be changed with the addition of more hypertensive individuals if a large difference in such variables as body mass index, which might reflect different SLC levels between diagnosed and undiagnosed hypertensive persons were observed, but we have no evidence of this effect. Additionally, any possible misclassification did not prevent detection of a significant risk of hypertension when the SLC genotype rather than the level was used. If a true association with both level and genotype did exist, one would probably expect misclassification to similarly affect both.

Misclassification of baseline hypertensive status could have occurred. However, the exclusion of the five new-onset hypertensive individuals with questionable baseline hypertension status at visits 1 or 2 did not change the results of the entire cohort. In addition, all five of them had an estimated zero probability of carrying the major gene associated with high SLC, and their exclusion from the major gene analysis would increase the estimate of the relative risk and the significance of the result (relative risk, 7.5; one-sided Fisher's Exact Test, p = 0.009).

Misassignment of genotype could have occurred from two sources. First, if many individuals were not clearly one genotype or the other (e.g., genotypic probabilities in the 30-70% range for any genotype), the use of a 0.5 probability arbitrary cut-off could have misclassified some individuals. However, as shown in the Results section, the genotype probabilities were very dichotomous, with few individuals in the 30-70% probability range (only one person in the high genotype group had a less than 70% probability of being the high genotype). Second, the genetic model itself may not adequately describe the genetic determination of SLC. The polygenic heritability estimate of 46% shown in Figure 2 is similar to the 45-48% and 42% found by the other genetic studies. However, the estimated frequency of high homozygotes in the Michigan study was around 25% and the frequency estimate of 7% for the high genotype in the Seattle data was much closer to that found in our study (5%). The mean values for the high and low genotypes in Seattle were very similar to ours: 0.60 and 0.29 in Seattle versus 0.56 and 0.26 mmol/l rbc/hr in Utah. Both the Michigan investigation and our study had difficulties showing that the estimates of the allele transmission from parents to offspring were Mendelian. Mendelian estimates were obtained for only our coronary-ascertained pedigrees. This determination indicates probable heterogeneity in the populations or the presence of environmental factors that confound the SLC level. Until some of the genetic modeling problems are overcome, we do not know the extent of genotype misclassification but hope that the wide separation in genotype probabilities under the current model provides a robustness to these probabilities under other possible, analogous models.

In conclusion, despite the possible weaknesses of this study, we believe the results support our principal conclusion: SLC levels per se are not prospectively associated with an increased risk of hypertension, but individuals with the major gene for high SLC have a fourfold higher risk of hypertension. Although based on small numbers, this finding suggests two possibilities: either the major gene-determined mechanism of elevating SLC is different from the polygenic or environmental mechanisms, or the gene influences other factors associated with becoming hypertensive in addition to the level of SLC. The
major gene defect represented by segregating high levels of SLC is expressed before the development of hypertension, and molecular identification of the genetic defect is important to understand the pathophysiology leading to hypertension onset. Continued follow-up of these pedigree members along with prospective results from other populations are needed to confirm these results.

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References


KEY WORDS • blood pressure • epidemiology • genetics • red blood cells
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