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Hypertension and Sodium-Lithium Countertransport in Utah Pedigrees: Evidence for Major-Locus Inheritance

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Summary

Likelihood analysis was used to test for evidence that an allele at a major locus elevates rates of sodium-lithium countertransport (SLC) in a sample of 1,989 members of 89 Utah pedigrees. The pedigrees were ascertained through two or three sibs who died of stroke before age 74 years (stroke pedigrees), through hypertensive and normotensive probands of the Salt Lake Center of the Hypertension Detection and Followup Program (HDFP pedigrees), or through men who suffered a myocardial infarction before age 55 years (coronary pedigrees). Major-locus inheritance could be rejected in the total sample; transmission probability estimates of $\hat{\tau}_1 = .972$, $\hat{\tau}_2 = .520$, $\hat{\tau}_3 = .185$ differed significantly from Mendelian transmission specified by $\tau_1 = 1$, $\tau_2 = \frac{1}{2}$, $\tau_3 = 0$. However, heterogeneity between ascertainment groups was significant ($\chi^2_{(18)} = 40.06$, $P < .01$) and justified analysis within subsets of the sample. In the stroke pedigrees, evidence of major-locus inheritance was not found; polygenic heritability was estimated as .647. In the HDFP pedigrees, estimates of $\hat{\tau}_1 = .987$, $\hat{\tau}_2 = .430$, $\hat{\tau}_3 = .506$ differed significantly from Mendelian transmission; the inferred model consisted of a mixture of two distributions incompatible with both Mendelian and environmental transmission but compatible with polygenic inheritance within distributions. In the coronary pedigrees, the hypothesis of Mendelian transmission could not be rejected. In the coronary pedigrees, the evidence supported an incompletely recessive allele with a frequency of .227 which elevated the level of SLC to a mean of .530 mmol/liter RBC/h. The major locus explained 34.4% of the variation in SLC, and polygenic inheritance explained another 45.9%, for a total of 80.3% due to genetic factors; the remaining 19.7% was attributed to random environmental effects. Homozygosity for the allele was associated with a twofold increase in the frequency of hypertension and with age-dependent elevations of weight and triglyceride level.

Introduction

Intracellular sodium level and its rate of transport differ between controls and persons with essential hypertension (Hilton 1986). If a defect in sodium transport could be identified as a preclinical marker, then persons predisposed to the development of essential hypertension could be identified and clues to the underlying pathophysiological basis of the disease could be obtained (Blaustein 1984). One possible preclinical marker of essential hypertension is the in vitro rate of red blood cell sodium-lithium countertransport (SLC), one of several sodium transport systems in the cell. SLC is elevated in persons with essential hypertension (Canessa et al. 1980; Smith et al. 1984; Williams et al. 1984*b*); the absence of a similar elevation in persons with secondary hypertension suggests that the elevation does not result from high blood pressure (Canessa et al. 1980).

The possibility that SLC is inherited is supported by parent-offspring and sib-sib correlations >.3 and by nonsignificant spouse correlations (Dadone et al. 1984; Kagamimori et al. 1984, 1985; Boerwinkle et

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al. 1986). In addition, SLC is elevated in first-degree relatives of hypertensives (Canessa et al. 1980; Smith et al. 1984) and in normotensive teenage sons of two hypertensive parents (Woods et al. 1982; Woods and Watson 1984). However, others have not found SLC elevated in persons with a family history of hypertension (Sempos et al. 1984).

Subgroups with different mean levels apparently underly the population distribution of SLC (Dadone et al. 1984; Boerwinkle et al. 1984, 1986; Turner et al. 1985). These subgroups were identified as genotypes at a major locus on analysis of a random sample (Boerwinkle et al. 1984); deviations from Mendelian transmission, on further analysis, led to speculation about heterogeneity (Boerwinkle et al. 1986). On the other hand, Mendelian transmission was rejected in a sample of hypertension-prone pedigrees, and the identity of the subgroups could not be determined (Dadone et al. 1984).

We have extended our previous sample of 434 persons in 10 pedigrees (Dadone et al. 1984; Williams et al. 1984*b*) and present here an analysis of 1,989 persons in 89 pedigrees ascertained either through hypertensive probands, sibs who died of strokes, or probands with early coronary disease. Likelihood analysis was used to test for evidence that alleles at a major locus elevate SLC. Subsets of these pedigrees have been analyzed previously for total serum cholesterol (Williams et al. 1985; Leppert et al. 1986), HDL (Hasstedt et al. 1985, 1986), apolipoprotein A-I (Moll et al. 1986), and apolipoprotein B (Hasstedt et al. 1987).

Material and Methods

As part of ongoing studies of the genetic epidemiology of hypertension (Williams et al. 1984*a*) and coronary heart disease (Williams et al. 1979) in Utah families, members of 96 pedigrees have been studied. The pedigrees were ascertained through three types of probands: (1) two or three sibs who died of stroke before age 74 years (stroke pedigrees), (2) hypertensive and normotensive probands at the Salt Lake Center of the Hypertension Detection and Followup Program (HDFP pedigrees), and (3) men with onset of coronary disease before age 55 years (coronary pedigrees). Each local relative who agreed to participate completed a questionnaire detailing life-style and medical information, donated blood and urine for laboratory tests, and was examined for cardiovascular disease.

By the method of Canessa et al. (1980) as adapted by Smith et al. (1982), SLC was measured as the rate of sodium-dependent lithium efflux from lithium-loaded red blood cells. Measurements made on women who were either pregnant or taking contraceptive or menopausal estrogens at the time of blood drawing were eliminated from the sample, since SLC is elevated by oral contraceptive use (Beuckelmann and Erdmann 1984) and rises during pregnancy (Worley et al. 1982). Measurements on medicated hypertensives were not removed from the sample since treated and untreated hypertensives do not differ significantly (Williams et al. 1983, 1984*b*; Kagamimori et al. 1984), and hypertensives were possibly the most informative observations in our sample. The resulting sample consisted of 493 (224 male, 269 female) members of eight stroke pedigrees, 698 (338 male, 360 female) members of 64 HDFP pedigrees, and 798 (359 male, 439 female) members of 17 coronary pedigrees, for a total of 1,989 members of 89 pedigrees. With anyone being treated with hypertensive medications being designated as hypertensive, the stroke pedigrees contained 39 hypertensives, the HDFP pedigrees contained 81 hypertensives, and the coronary pedigrees contained 46 hypertensives, for a total of 166 hypertensives in the sample. Included among the HDFP pedigrees were 12 pedigrees (71 persons) ascertained through normotensive probands. The five hypertensive members of these pedigrees included the spouses of two probands and three supposedly normotensive probands who were hypertensive on examination in our clinic. SLC for each person was adjusted for age and sex by using coefficients produced by linear regression, which explained 5.8% of the variance in SLC.

Systolic blood pressure (SBP) and fourth-phase diastolic blood pressure (DBP) measurements were made, with the subjects in a sitting position, by using a random-zero mercury sphygmomanometer. Weight was measured in pounds by using a medical scale accurate to one-half pound. Triglyceride level was measured using a coupled enzymatic method and commercial reagents (Cal Biochem, La Jolla) (Wahlefeld 1974). *Z*-scores for SBP and DBP, for weight, and for triglyceride level were formed by subtracting the mean and dividing by the SD within sex-specific age groups in our data. The age groups used were 2-year intervals to age 19 years, 5-year intervals to age 39 years, 10-year intervals to age 59 years, and all >59 years of age.

Likelihood analysis (Elston and Stewart 1971) was

used to test for evidence that an allele at a major locus determines high SLC. Likelihoods were computed using PAP (Hasstedt and Cartwright 1981) and the maxima obtained with GEMINI (Lalouel 1979). No ascertainment correction was made because the pedigrees were ascertained through patients with a variety of disorders that may or may not be related to SLC level. Inference about the population at large is limited by the absence of a correction. Hypothesis testing was performed by comparing the likelihood of a submodel to the likelihood of a more general model. χ^2 Statistics were computed as -2 multiplied by the natural logarithm of the ratio of the likelihoods. The assumptions required for the use of χ^2 statistics in pedigree analysis are discussed by Cannings et al. (1980). First, the data must consist of a large number of independent and identically distributed observations. If the sampling unit is an individual, these assumptions are not satisfied because the observations are not independent. If the sampling unit is a pedigree, the observations are independent but are not identically distributed, since the pedigree structures vary. The second restriction is the requirement that comparisons be made between a submodel and a more general model. We comply with this restriction. The third restriction is that the true parameter values should not lie on a boundary. We consider models in which this occurs. Although violating the assumptions probably does not invalidate the likelihood-ratio test, the χ^2 test statistics should be interpreted with caution. The df for the χ^2 statistic are the difference in the number of parameters estimated in the submodel and the number estimated in the general model.

The mixed model (Elston and Stewart 1971; Morton and MacLean 1974), with parameterized transmission probabilities (Boyle and Elston 1979; Lalouel et al. 1983), was used to test for the presence of a major locus. The model assumed that the phenotype was independently determined by a major locus with a large effect, additive polygenes each with a small effect, and random environmental factors specific to the individual. The major locus was assumed to have two alleles. The polygenic and random environmental components were assumed to be normally distributed. The transformation $y = 6/P[(x/6 + 1)^P - 1]$ (MacLean et al. 1976) was used to transform the standardized variable to approximate normality within genotypes. Hardy-Weinberg equilibrium determined the genotypic probabilities for each individual without parents in the pedigree; products of transmission probabilities determined the genotypic probabilities for individuals with parents in the pedigree. Likelihoods of the mixed model were approximated (Hasstedt 1982).

The parameters of the model were q, the frequency of the allele for high levels; μ_1, μ_2, μ_3, ($\mu_1 \leq \mu_2 \leq \mu_3$), the means of the three major-locus genotypes; H_p, the polygenic heritability; σ, the phenotypic SD within major-locus genotypes; P, the power of the transformation; and τ_1, τ_2, τ_3, the probabilities of transmitting, from each of the three genotypes, the allele determining high levels of SLC. H_p is the proportion of the variance, within each major-locus genotype, attributed to polygenes. $\mu_1 = \mu_2$ Designates recessivity; $\mu_2 = \mu_3$ designates dominance of the allele determining elevated levels of SLC. $\mu_1 \neq \mu_2 \neq \mu_3$ Designates codominance, which may correspond to incomplete recessivity ($\mu_1 \sim \mu_2$) or to incomplete dominance ($\mu_2 \sim \mu_3$).

To test the first hypothesis, absence of a major locus ($q = 0$ or $\mu_1 = \mu_2 = \mu_3$), the likelihood of the codominant mixed model was compared with the likelihood of the polygenic model. To test the hypotheses of recessivity and dominance ($\mu_1 = \mu_2$ and $\mu_2 = \mu_3$, respectively), the likelihood of the codominant mixed model was compared with likelihoods of the recessive mixed and dominant mixed models, respectively. Any restriction on the means resulting from this test held for all subsequent tests. To test the hypothesis of Mendelian transmission ($\tau_1 = 1$, $\tau_2 = \frac{1}{2}$, $\tau_3 = 0$), the likelihood of the mixed model with estimated transmission probabilities was compared with the likelihood of the same model with Mendelian transmission assumed. To test the hypothesis of an environmental mixture of distributions ($1 - q = \tau_1 = \tau_2 = \tau_3$), the likelihood of the mixed model with estimated transmission probabilities was compared with the likelihood of the mixed model with equal transmission probabilities. A major locus was inferred by rejecting the hypothesis of environmental transmission but not rejecting the hypothesis of Mendelian transmission. To test the hypothesis of homogeneity between ascertainment groups, the product of the maximized likelihoods within groups was compared with the maximized likelihood for the sample as a whole (Morton 1956). The mixed model with estimated transmission probabilities was used in the heterogeneity test.

For each observation, we computed the genotypic probability, $\hat{P}_{ij}$, the probability that individual i has genotype j. The parameters of the genetic model were

Table 1

Number (*N*) and Mean ± SD SLC and Related Variables, within Ascertainment Groups and in Total Sample

Ascertainment Group	Age		SLC		SBP		DBP		Weight		Triglyceride Level	
	N	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD
Stroke	493	30 ± 19	493	.281 ± .096	444	112 ± 10	440	73 ± 9	487	183 ± 33	403	114 ± 62
HDFP	698	31 ± 19	698	.276 ± .106	614	112 ± 9	612	77 ± 10	689	183 ± 32	529	118 ± 66
Coronary	798	27 ± 17	798	.275 ± .104	756	113 ± 9	738	76 ± 9	784	178 ± 30	783	127 ± 96
Total	1,989	29 ± 18	1,989	.277 ± .103	1,797	112 ± 9	1,790	76 ± 9	1,960	181 ± 32	1,715	121 ± 81

fixed at their maximum-likelihood estimates. $\hat{P}_{ij}$ was computed as the likelihood of the model conditioned on individual i having genotype j, divided by the unconditional likelihood of the model.

Genotypic probability estimators (GPEs) are asymptotically unbiased under certain assumptions (S. J. Hasstedt and P. P. Moll, unpublished data). Intuitively, GPEs partially assign individuals to genotypic classes by using their genotypic probabilities. The GPE of the frequency of genotype j is $\hat{f}_j = \Sigma_{i=1}^{n} \hat{P}_{ij}/n$, where n is the number in the sample; the GPE of the mean of variable Y for genotype j is $\hat{\mu}_{Yj} = \Sigma_{i=1}^{n} \hat{P}_{ij}\, Y_i/\hat{n}_j$, where Y_i is a quantitative variable measured on person i and $\hat{n}_j = n\hat{f}_j$; the GPE of the variance of Y due to the major locus is $\sigma^2_{ML} = \Sigma_{j=1}^{J} \hat{f}_j (\hat{\mu}_{Yj} - \mu_Y)^2$, where μ_Y is the sample mean and J is the number of genotypes; the GPE of the prevalence for genotype j is $\hat{\phi}_j = \Sigma_{i=1}^{n} \hat{P}_{ij}\, z_i/\hat{n}_j$, where $z_i = 0$ if individual i is unaffected and 1 if individual i is affected; and the GPE of the SE of the prevalence for genotype j is $\sqrt{\hat{\phi}\,(1 - \hat{\phi})/\hat{n}_j}$. The displacement of variable Y is computed as $(\hat{\mu}_{Y3} - \hat{\mu}_{Y1})/\sqrt{\mathrm{Var}(Y)}$.

The analysis provided maximum-likelihood estimates of the genotypic frequencies, genotypic means and common SD of transformed SLC, and the heritability of the polygenic component. We wanted genotypic means of SLC in the original scale but could not obtain the moments of the untransformed variable in terms of moments of a normally distributed, power-transformed variable; therefore, we computed GPEs of the genotypic mean levels of SLC in the original scale. We wanted to confirm that the allele was expressed across the age range, but analysis within subgroups of the sample by age would have produced poor estimates; therefore, we computed GPEs of the genotypic frequencies within age groups. We wanted to estimate the effect of the SLC major locus on other variables, but bivariate analysis of SLC with each related variable would require prohibitive effort and univariate analysis of the related variable might not reveal this major locus; therefore, we computed GPEs of the genotypic mean levels, the variance due to the major locus of SBP, DBP, weight, triglyceride level, and the genotypic prevalence, with SE, of hypertension.

Results

Means ± SDs of SLC, blood pressures, weight, and triglyceride level within ascertainment groups are presented in table 1. Because of large sample sizes, the differences between ascertainment groups in mean levels, while not striking, are significant (by analysis of variance) for age ($F = 8.138$, $P = .0003$), DBP ($F = 33.762$, $P < .00005$), weight ($F = 6.509$, $P = .0015$), and triglyceride level ($F = 4.302$, $P = .0137$). Only SLC and SBP did not differ between groups.

Table 2 presents χ^2 statistics to test, for the total sample, major-locus hypotheses about SLC. The hypothesis of no major locus ($q = 0$) was rejected. Since recessivity ($\mu_1 = \mu_2$) and dominance ($\mu_2 = \mu_3$) were also rejected, codominant inheritance was indicated. However, for confirmation of the presence of a major locus, we tested the hypothesis of Mendelian transmission ($\tau_1 = 1$, $\tau_2 = \frac{1}{2}$, $\tau_3 = 0$). This hypothesis was rejected with estimates of $\hat{\tau}_1 = .972 \pm .024$, $\hat{\tau}_2 = .520 \pm .068$, $\hat{\tau}_3 = .185 \pm .111$. In addition, we rejected the environmental model ($1 - q = \tau_1 = \tau_2 = \tau_3$).

To test for heterogeneity, the likelihood was maximized separately for each ascertainment group. Table 3 presents the estimates of the transmission probabilities. Estimates on the coronary pedigrees deviate the least from Mendelian probabilities, and estimates on the stroke pedigrees deviate the most from Mendelian probabilities. The hypothesis of homogeneity due to the method of ascertainment was re-

Table 2

χ^2 Statistics to Test Major-Locus Hypotheses, in the Total Sample and within Ascertainment Groups

Hypothesis[a]	Total	Ascertainment Group[b]			
		Stroke	HDFP	Coronary	df
$q = 0$ (No Major Locus)	59.68**	2.58	22.61**	42.32**	3
$\mu_1 = \mu_2$ (Recessivity)	4.51**	1.43	1.20	4.70*	1
$\mu_2 = \mu_3$ (Dominance)	37.07**	2.26	11.10**	29.33**	1
$\tau_1 = 1, \tau_2 = \frac{1}{2}, \tau_3 = 0$ (Genetic)	14.97**	...	15.29**	5.62	3
$1 - q = \tau_1 = \tau_2 = \tau_3$ (Environmental)	16.85**	...	8.47*	8.80*	3

[a] See text for definition of the parameters.
[b] See text for definition.
* $P < .05$.
** $P < .01$.

Table 3

Estimate ± SE of the Transmission Probabilities within Ascertainment Groups

Ascertainment Group[a]	Transmission Probability		
	τ_1	τ_2	τ_3
Stroke	.645 ± .067	.657 ± .070	.358 ± .135
HDFP	.978 ± .030	.393 ± .113	.439 ± .271
Coronary	.977 ± .021	.541 ± .104	.096 ± .106

[a] See text for definition.

jected ($\chi^2_{(18)} = 40.06, P < .01$). Table 2 presents, for each of the three ascertainment groups, tests of major-locus hypotheses. In the stroke pedigrees, the hypothesis of no major locus could not be rejected; the most likely model was polygenic inheritance with estimated heritability of $\hat{H}_p = h^2 = .647$. In the HDFP pedigrees, both genetic and environmental transmission were rejected; the most likely model had two modes, non-Mendelian transmission probabilities and an estimated polygenic heritability within modes of $\hat{H}_p = .637$. In the coronary pedigrees, major-locus inheritance was suggested by rejection of the environmental model in conjunction with failure to reject the genetic model.

The most likely genetic model for the coronary pedigrees was an incompletely recessive allele with an estimated frequency of $\hat{q} = .227 \pm .031$. Polygenic heritability was estimated as $\hat{H}_p = .700 \pm .064$. The major locus accounted for 34.4% of the variance; polygenes accounted for 45.9%; random environmental factors accounted for the remaining 19.7%. Genotypic probabilities were computed for members of the coronary pedigree by using this genetic model. The GPEs of the genotypic mean levels of SLC (mmol/liter RBC/h) were $\hat{\mu}_1 = .245$, $\hat{\mu}_2 = .286$, and $\hat{\mu}_3 = .530$.

Table 4 presents GPEs of the prevalence of hypertension within genotypes at the SLC locus in mem-

Table 4

Estimate ± SE of Prevalence of Hypertension by SLC Genotype, within Sex and Age Groups, in Coronary Pedigrees

Group[a]	N	Genotype[b]			
		All	1	2	3
Men aged 30–49 years	137	.044 ± .017	.041 ± .022	.032 ± .027	.092 ± .075
Men aged 50+ years	47	.255 ± .064	.228 ± .081	.279 ± .111	.357 ± .258
Women aged 50+ years	49	.429 ± .071	.381 ± .087	.465 ± .127	.823 ± .249

[a] There were no hypertensive women in the 30–49-year-old age group.
[b] Genotypes 1, 2, and 3 designate low homozygotes, heterozygotes, and high homozygotes, respectively.

Table 5

Estimated Frequency and Displacement of SLC, SBP, DBP, Weight, and Triglyceride Level by Genotype, within Age Groups, in Coronary Pedigrees

Age (Years)	N	Frequency[a]			Displacement[b]				
		1	2	3	SLC	SBP	DBP	Weight	Trig
5–9	132	.559	.395	.046	3.003	.271	−.562	−.431	−.701
10–19	177	.612	.364	.024	2.757	.099	.149	.179	.446
20–29	148	.590	.357	.053	2.868	.600	.564	.548	.663
30–39	186	.607	.307	.087	2.541	.581	.503	1.106	.989
40+	154	.627	.316	.057	2.503	.164	−.083	.240	1.287
Total	797	.601	.345	.054	2.751	.424	.329	.593	.911

[a] Genotypes 1, 2, and 3 designate low homozygotes, heterozygotes, and high homozygotes, respectively.
[b] Difference between the means in high vs. low homozygotes divided by the SD in the sample.

bers of the coronary pedigrees. The prevalence within the sample agrees roughly with incidence figures for Utah (Hunt et al. 1986*a*). Within age and sex categories, high homozygotes have approximately twice the prevalence estimated for low homozygotes. However, because so few persons fall within each group, the SEs of the estimates are large.

Table 5 presents age-specific GPEs of the frequency and displacement of SLC, of blood pressure, of weight, and of triglyceride level for members of the coronary pedigrees. Similar frequencies and displacements for SLC across age groups demonstrate the expression of elevated SLC in homozygotes at no later than age 5 years. The displacement for SLC decreases slightly with age; the opposite trend is seen for triglyceride level and possibly also for weight; little effect is seen for blood pressure at any age. The SLC locus accounts for .98% of the variance in SBP, .54% of the variance in DBP, 1.93% of the variance in weight, and 4.02% of the variance in triglyceride level.

Lithium ratio, which is highly inversely correlated with SLC, is elevated in some patients having manic-depressive illness (Ostrow et al. 1978). Segregation of elevated lithium ratio has weak support in some pedigrees (Dorus et al. 1983; unpublished studies cited by Egeland et al. [1984]) but not in others (Shaughnessy et al. 1985). In our sample, we rejected the hypothesis of no major locus, on the basis of evidence for a rare ($\hat{q}$ = .003) recessive allele for low levels of SLC (corresponding to high lithium ratio). This frequency would predict that approximately 10 persons in our sample have the low homozygous genotype. With this small sample size of potential homozygotes, neither Mendelian nor environmental transmission could be rejected.

Discussion

Homozygotes for an allele at a major locus were shown to have elevated SLC and an increased prevalence of hypertension. Although the SLC elevation is substantial, the hypertension association is not complete; that is, some homozygotes fail to develop hypertension and some nonhomozygotes do develop hypertension. This locus is therefore a susceptibility gene, rather than a disease gene for hypertension. There are probably other susceptibility genes present in the population, a circumstance that would give the appearance of polygenic inheritance of hypertension.

With a frequency of 5% for the homozygous genotype, elevated SLC is a common trait. The frequency in the general population may be lower than this estimate obtained from our pedigrees, since we made no correction for the ascertainment through cases of coronary disease. However, even higher frequencies for the upper distribution, frequencies ranging from 14% to 28%, have been estimated in a random sample (Boerwinkle et al. 1984, 1986; Turner et al. 1985). The paucity of high levels of SLC in juveniles has led to speculation that elevated levels may not be expressed until adulthood (Williams et al. 1983). However, in the present analysis, high homozygotes are just as common in youth as in adults, and Boerwinkle et al. (1986) found bimodality within children.

Despite its association with hypertension, this locus explained <1% of the variance in blood pres-

sure. For weight, the estimates were 1.93% overall and a maximum of 9.29% in the 30–39-year-old age group. For triglyceride level, the estimates were 4.02% overall and a maximum of 8.74% in the 40+-year-old age group. These estimates generally agree with correlations of .27 for SLC and weight (Williams et al. 1983) and of .35 for SLC and triglyceride level (Hunt et al. 1986*b*). In addition, higher SLC is found in obese persons (Miilumpalo et al. 1985) and in persons with hyperlipidemia (Corrocher et al. 1985).

One expects pedigrees ascertained through hypertensives to include homozygotes for a common allele such as this—and possibly at a higher frequency. However, major-locus inheritance was rejected in pedigrees selected through hypertensives or stroke deaths, both in the present analysis and in a previous analysis of a subset of these pedigrees (Dadone et al. 1984). One possible explanation is that other factors, either genetic or environmental, also elevate SLC in these pedigrees and thereby distort the transmission of the major locus.

In summary, homozygosity for a common recessive allele is associated with an increased risk of hypertension and is expressed as high levels of SLC in ~5% of both juveniles and adults. Elevated SLC caused by something other than this major locus apparently obscured the transmission at this locus in pedigrees ascertained through probands with hypertension or stroke.

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