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Evidence of a Rare Gene for Low Systolic Blood Pressure in the Framingham Heart Study

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Key Words. Blood pressure · Family studies · Unified model · Segregation analysis · Heritability

Abstract. A major risk factor for coronary heart disease in both men and women is elevated systolic blood pressure (SBP). We performed segregation analysis on age, sex-adjusted, and transformed systolic blood pressure data on 1,141 families from the Framingham cohort-offspring study using the segregation analysis program POINTER. The results of hypothesis testing revealed: (1) these data are consistent with familial transmission; (2) there is evidence for the transmission of a rare, major gene for low SBP with a gene frequency of $q = 0.02$; and (3) most of the transmissible component to SBP can be attributed to the polygenic background with $H = 0.31$.

Introduction

The importance of elevated blood pressure as a direct contributor to morbidity and mortality from the major cardiovascular diseases has long been recognized [Dawber, 1980; Havlik et al., 1980]. Prospective studies such as the Framingham Study which were designed to measure predisposing antecedent factors in disease-free populations and monitor them over time for the subsequent occurrence of clinical disease, have shed light on the true relation between high blood pressure and cardiovascular disease. In the Framingham Study, the relation between the prevalence of coronary heart disease and

systolic blood pressure (SBP) was found, at baseline, to be direct and significant for both sexes and in all age groups [Dawber, 1980]. This relation was shown to be independent of other known risk factors, and directly proportional to the degree of blood pressure elevation. Contrary to clinical concepts in vogue, the risk of cardiovascular sequelae in the Framingham Study is as closely related to SBP as to diastolic pressure, and even isolated systolic elevations have prognostic value. Elevated SBP is a consistent predictor of cardiovascular disease in virtually every society.

SBP was chosen as the variable of interest because very little formal segregation analysis has been performed on this ather-

Table 1. Means and standard deviation of SBP levels in 1,141 Framingham families

Sex	Group	Observations, n	SBP	
			mean	SD
Male	parents	1,141	135.60	18.37
	offspring	1,230	125.21	14.33
Female	parents	1,141	130.91	22.30
	offspring	1,267	115.83	14.38

ogenic trait. The Framingham cohort is ideal to study because it is population-based and thus less biased, and the age structures of the parental and offspring cohorts are similar at the time they were examined. Past studies of hypertension have consistently found familial aggregation but little or no evidence for major gene segregation [Schull et al., 1977; Chakraborty et al., 1977; Feinleib et al., 1979; Havlik et al., 1979; Morton et al., 1980; Krieger et al., 1980; Annett et al., 1983; Carter, 1984]. Formal segregation analysis of this trait can provide insight into the sources of familial variation in blood pressure.

Methods

Data

The Framingham Study consists of data on a cohort of men and women, ages 30-59, who lived in Framingham, Mass., USA, and were examined biennially beginning in 1948; and their offspring who were examined beginning in 1971. Details of the Framingham Heart Study sampling scheme and cohort characteristics have been reviewed elsewhere [Higgins, 1983]. For this study, 1,141 families with a total of 4,779 individuals were available.

An average of three SBP readings, taken at base-

line, both the parental and offspring studies, constitute the blood pressure data. SBP was age- and sex-adjusted separately in parents and offspring using regression techniques. SBP was regressed on a polynomial function of age in a stepwise method retaining only significant terms, in each sex for the parental and offspring data. The means and standard deviations are presented, by sex and generation, in table 1.

Commingling Analysis

We examined commingling and skewness in the age and sex adjusted SBP values using the FORTRAN computer program SKUMIX [MacLean et al., 1976; Morton et al., 1983]. This program, which ignores family structure, enables tests for the presence of up to three commingled distributions. Parameters used in SKUMIX include: u , the overall mean of the quantitative variable; V , the variance of each component distribution; t , the distance in standard deviation units between the means of the two outermost distribution; d , the displacement of the middle distribution; q , and F , which give the proportions of admixture (when $F = 0$, the proportions are constrained to be in Hardy-Weinberg equilibrium). In addition, p , the value of the power transform proposed in MacLean et al. [1976] to remove skewness may be estimated. The power transform is given by:

$$y = \frac{6}{p} \left[\left(\frac{x}{6} + 1 \right)^p - 1 \right]$$

where x is the standardized quantitative variable to be transformed, y is the power transformed variable and r is set such that $(x/r + 1)$ is always positive (in these analyses r was fixed at 6.0). Nested hypotheses may be tested using the likelihood ratio criterion.

Unified Mixed Model Analyses

The FORTRAN computer program POINTER which incorporates the unified mixed model of complex segregation analysis [Lalouel et al., 1983] was used for segregation analyses of these data. Under this model, phenotypic variation in a quantitative trait may be attributable to variation due to a major locus, a multifactorial/polygenic component, and/or random environment.

Parameters for the model include: the mean (μ) and variance (V) of the quantitative trait; the heritability in children (H) and adults (HZ); the frequency

Table 2. Admixture analysis of SBP

Parameter	Component distributions, n							
	untransformed				transformed (p)			
	1	2	3	3 _F	1	2	3	3 _F
v	0.99	0.72	0.51	0.55	0.90	0.75	0.59	0.62
u	0.00	0.00	-0.00	0.00	-0.12	-0.07	-0.05	-0.04
d			0.33	0.37			0.30	0.40
t		3.41	4.65	4.62		2.74	3.64	3.92
q		0.16	0.08	0.06		0.15	0.11	0.05
p	(1) ^a	(1) ^a	(1) ^a	(1) ^a	-0.63	0.08	0.35	0.49
F				0.13				0.16
-2 ln L + C	6779.11 (L1)	6449.22 (L2)	6397.10 (L3)	6384.89 (L4)	6425.96 (L5)	6378.10 (L6)	6378.76 (L7)	6372.76 (L8)

χ^2 tests of hypotheses:

- (1) skewness in a single distribution: L1-L5, $\chi^2 = 353$, 1 d.f.;
- (2) two distributions fit better than one: L1-L2, $\chi^2 = 330$, 2 d.f.;
- (3) skewness in two distributions: L2-L6, $\chi^2 = 71$, 1 d.f.;
- (4) three distributions fit better than two: L2-L3, $\chi^2 = 52.12$, 1 d.f.;
- (5) skewness in three distributions: L3-L7, $\chi^2 = 18.34$, 1 d.f.;
- (6) three distributions in Hardy-Weinberg proportions: L3-L4, $\chi^2 = 12.21$, 1 d.f.

^a Fixed parameter.

(q) of the allele specifying higher values of the trait; the distance (t) in standard deviation units between the two homozygote means; the displacement of the heterozygote mean (d); and the transmission probabilities (^TAAA, ^TAaA, and ^TaaA). The major locus is assumed to be diallelic and in Hardy-Weinberg equilibrium. We report results obtained using conditional likelihoods (i.e., conditional on parental phenotypes); results obtained using joint likelihoods were similar. Nested hypotheses were tested using the likelihood ratio criterion.

Results

Commingling Analyses

The results of commingling analyses are presented in table 2. There is evidence

for skewness in the single distribution ($\chi^2 = 353$, 1 d.f.) and allowing for two distributions provides a significantly better fit to the data than allowing for only one ($\chi^2 = 330$, 2 d.f.). In addition there was significant residual skewness in the two-distribution model ($\chi^2 = 71$, 1 d.f.). Three distributions fit the data better than two ($\chi^2 = 52$, 1 d.f.) and there was evidence for skewness ($\chi^2 = 18$, 1 d.f.). The distributions were not in Hardy-Weinberg proportion, however, ($\chi^2 = 12$, 1 d.f.). In order to reduce the chance of obtaining false evidence for a major locus, we chose the conservative approach of transforming the data using the estimate of p obtained un-

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Table 3. Tests of hypotheses for SBP using conditional likelihood and assuming one component in the distribution ($p = -0.627$)

Hypothesis	Parameter estimates									
	V	u	d	t	q	H	T ₁	T ₂	T ₃	-2 ln L + C
L1 No familial effect (d = t = q = H = 0)	0.900	-0.125	0 ^a	0 ^a	0 ^a	0 ^a				6,822.51
L2 No major locus (d = t = q = 0)	0.890	-0.137	0 ^a	0 ^a	0 ^a	0.388				6,563.91
L3 No polygenic effect (H = 0)	0.893	-0.131	0.539	1.57	0.643	0 ^a	(1.0) ^a	(0.5) ^a	(0) ^a	6,616.73
L4 Mixed model	0.888	-0.134	0.654	3.91	0.982	0.309	(1.0) ^a	(0.5) ^a	(0) ^a	6,546.40
Test on transmission probabilities:										
L5 Unrestricted transmission probabilities	0.884	-0.130	0.657	3.91	0.983	0.309	1 ^b	0.526	0 ^b	6,546.39

χ^2 tests of hypotheses (L1-L5 are the likelihoods associated with hypotheses 1-5):

- (1) no familial effect: L1-L4, $\chi^2 = 276$, 4 d.f.; $p < 0.0001$;
- (2) no major locus: L2-L4, $\chi^2 = 17.5$, 3 d.f.; $p < 0.001$;
- (3) no polygenic effect: L3-L4, $\chi^2 = 70.3$, 1 d.f.; $p < 0.0001$;
- (4) Mendelian transmission: L4-L5, $\chi^2 = 0.01$, 1 d.f., n.s.

^a Parameter fixed.

^b Parameter converged to bound.

der single distribution ($p = -0.627$) prior to segregation analysis. Analyses were carried out on data transformed using the value of p obtained under a two-distribution model ($p = 0.08$) as well, and these will be mentioned below.

Although a power transformation was used to correct for skewness, residual kurtosis remained ($B^2 = 4.01$) and may have influenced the results. Williams et al. [1983] show evidence that kurtosis can have a dramatic effect on results of segre-

gation analyses in an application to blood glucose.

Unified Mixed Model Analyses

Table 3 presents the results of complex segregation analysis of age- and sex-adjusted, power-transformed SBP in the 1,141 nuclear families of the Framingham Heart Study. The hypotheses of no transmission of SBP can be rejected ($\chi^2 = 276$, 4 d.f.) as can the hypotheses of no major effect ($\chi^2 = 17.51$, 3 d.f.) and no polygenic

component ($\chi^2 = 70.3$, 1 d.f.). The transmission probabilities were not significantly different from their Mendelian expectations ($\chi^2 = 0.01$, 3 d.f.), indicating that the transmission of the major effect is not significantly different from that of a major gene locus.

While there was evidence for 2 and 3 commingled distributions, the proportions of admixture suggested by results of SKUMIX ($0.05 \leq q \leq 0.2$) were not comparable to the allele frequency estimate obtained using POINTER ($0.6 = 1 = 0.98$). Repeated efforts using SKUMIX to uncover evidence for more than one distribution with a $q \geq 0.9$ were unsuccessful. Similarly, analyses using POINTER on the data power transformed under the assumption of one distribution ($p = -0.63$) failed to uncover any evidence of a major locus with a value of q in the range of 0.05 to 0.02. When the data were transformed using the value of p obtained from the two-distribution model ($p = 0.08$), we found some evidence for a major locus with $q = 0.16$. Since we were unable to detect a locus with similar characteristics in the data transformed to eliminate skewness, we feel these results are questionable.

Discussion

Despite the fact that the adult children's SBP values were assessed some 30 years after parental values, there was significant evidence for transmission of SBP in this population. This is rather compelling support for the influence of genetic factors in SBP, since the family members in the study no longer shared households, diets, etc., although it is possible that early

shared environment increases familial resemblance for SBP. While previous studies have also found evidence for a polygenic component to SBP with $H = 0.22$ [Morton et al., 1980], evidence for a major locus influencing SBP values has not previously been reported. In these data, a polygenic component with $H = 0.31$ accounts for 27% of the total variance in SBP while a rare major gene ($q = 0.02$) accounts for 7% of the variance.

We were able to determine, through point likelihood estimation techniques, which families contributed most to the evidence of this rare gene. The evidence for the major gene predisposing to low systolic blood pressure comes from a small number of individuals in a few families. Families providing most of the evidence for the major gene are summarized in table 4. Many more families must be contributing to the evidence for this gene but small family sizes make discrimination of these families difficult.

The first two families might be characterized as 'low' \times 'low' homozygote matings in which the offspring are also 'low'. The last three families appear to have one homozygous 'low' parent and one heterozygous parent, with at least two children in each family who have segregated the 'low' phenotype. While the transmission of low SBP in these families is consistent with the segregation of a major locus, a variety of factors that we did not examine might also have given rise to these observations. If, for example, SBP were adjusted for other physical variables such as pulse rate, weight, height, it is possible that the transmission of low SBP in these families would no longer be apparent. Havlik et al. [1979] found that after adjust-

Table 4. Families providing evidence for the SBP gene in these analyses

Number	Family likelihood	Position	Sex	Age at Exam	SBP	Power-transformed, standardized, age- and sex-adjusted SBP
1	8.19	FA	M	53	113	-1.92
		MO	F	57	117	-2.55
		CH	F	55	121	-1.18
		CH	F	50	92	-4.37
2	6.71	FA	M	51	113	-1.83
		MO	F	48	106	-2.31
		CH	M	54	98	-4.15
		CH	M	52	113	-1.82
3	3.64	FA	M	47	101	-2.77
		MO	F	43	133	0.00
		CH	M	46	119	-0.87
		CH	M	42	105	-2.16
		CH	F	47	93	-3.57
		CH	F	43	111	-0.81
4	3.61	FA	M	59	97	-3.98
		MO	F	55	149	-0.07
		CH	M	51	129	-0.27
		CH	M	48	154	1.36
		CH	M	49	110	-1.99
		CH	F	54	105	-2.96
5	3.25	FA	M	59	133	-0.57
		MO	F	59	103	-4.47
		CH	M	51	115	-1.54
		CH	F	57	109	-2.97
		CH	F	53	120	-0.98

ment for known SBP correlates such as age, pulse, weight and alcohol consumption, significant partial correlations were still present. These authors conclude that either the presence of additional environmental blood pressure determinants in families or a separate genetic component is needed to explain the familial aggregation. They contend that the absence of

spouse correlation for blood pressure indicates that heredity is the more likely explanation for the aggregation of blood pressure in families, but did not address the question of major locus versus polygenic components to transmission.

These results suggest that approximately 7% of the variability in systolic blood pressure might be due to a rare gene

with a gene frequency of $q = 0.02$. If confirmed in other studies, future investigations might be targeted towards identification of DNA markers linked to this rare allele for systolic blood pressure.

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Anti-Gerbich Antibodies and Gerbich-Negative Dantu-Positive Red Blood Cells in a Woman from South Africa

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Abstract. Anti-Gerbich type anti-Ge₃ antibodies were identified in the serum of a woman of mixed ethnic origin from Cape Town. The woman had type Ge₂,-₃ (Gerbich) red cells on which there was no evidence of weakened Kell antigens. Her red cells were also Dantu-positive.

Since Rosenfield et al. [1] reported in 1960 three antibodies that defined the very common red blood cell antigen Gerbich, rare Gerbich(Ge)-negative red cells have been identified in people of European, Mexican, South American, Indian, Negro and Oriental origin [2]. Two types of Ge-negative red cell membranes, Gerbich and Leach, are known [2]. In the Gerbich type, the sialoglycoproteins β (β -SGP) and γ (γ -SGP), important for maintaining cell shape, are absent. The membranes instead contain an abnormal β -related SGP which apparently fulfils a similar support function [3]. In the Leach type, the β -SGP, γ -SGP and the β -related SGP are absent and the red cells are elliptocytic and/or echinocytic [2]. Ge-negative red cells which give negative results with both anti-Ge₂ and anti-Ge₃ antibodies are known as the Gerbich type and those giving negative results

with anti-Ge₂ but positive results with anti-Ge₃ as the Yus type. Red cells with Leach type membranes also give negative results with anti-Ge₂ and anti-Ge₃ antibodies. The Kell and para-Kell antigens are often expressed weakly on Ge-negative red cells of the Gerbich and Leach types but are usually expressed normally on those of the Yus type [4-6]. Anti-Ge₂ antibodies are found more often than anti-Ge_{2,3} antibodies in persons with Ge₂,-₃ (Gerbich) red cells [4].

Dantu is a low-frequency red cell antigen of the MNSs system found so far mainly in people of Negro origin [7]. The membranes of the cells contain a hybrid δ - α form of SGP of which two variants, Ph and NE, are known [7]. The antigens besides Dantu encoded by the *Dantu* gene complex are variable strength M and N, no or very weak U and an unusual form of