

High Heritability of Ambulatory Blood Pressure in Families of East African Descent

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Abstract—We estimated the heritability of ambulatory systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) in east African families with at least 2 hypertensive siblings and living in the Seychelles islands (Indian Ocean). The sample consisted of 314 individuals (147 men and 167 women), both normotensive and hypertensive, from 76 pedigrees (mean±SD of 4.1±2.8 persons per pedigree). After a 2-week off-treatment period, daytime and nighttime ambulatory blood pressure (BP) was monitored. Office BP was measured with a standard mercury sphygmomanometer. We estimated by maximum likelihood the age- and sex-adjusted heritabilities from the additive polygenic component of the variance of the traits allowing for the presence of other familial correlations. We also adjusted for ascertainment (ie, for the fact that 2 siblings had to be hypertensive) and examined the effect of adjusting for body mass index, 24-hour urinary excretion of sodium and potassium, plasma renin activity, and plasma aldosterone concentration. Heritability estimates (±SE) for ambulatory SBP, DBP, and PP were, respectively, 0.37±0.12/0.24±0.12/0.54±0.12 for daytime and 0.34±0.13/ 0.37±0.15/0.47±0.12 for nighttime measurements ($P<0.05$ for all estimates). Heritability estimates for office SBP, DBP, and PP were, respectively, 0.20±0.11, 0.05±0.09, and 0.37±0.12. Heritability estimates for SBP varied markedly according to whether participants were treated for hypertension at baseline. The present data show that ambulatory BP and PP have a high heritability in families of African descent. They also demonstrate that antihypertensive treatment and the number of BP measurements have a major influence on the heritability estimates. (*Hypertension*. 2005;45:445-450.)

Key Words: blood pressure monitoring, ambulatory ■ genetics ■ ethnicity ■ blacks

Hypertension, which affects approximately one-third of the adult population in Western countries,¹ is now becoming a substantial burden in African countries as well, with prevalence ranging from 16% to 32% among adults.²⁻⁵ Because individuals of African descent are more prone to hypertension-related complications than whites,⁶⁻⁸ a better understanding of the familial aggregation of blood pressure (BP) in this ethnic group is of particular importance for unraveling the genetic variants influencing BP.

Heritability is a measure of familial aggregation caused by genetic factors. Narrow sense heritability is the proportion of the total phenotypic variance that is caused by the additive genetic variance (ie, that part of the genetic variance caused by the average effects of individual alleles, which reflects transmissible resemblance between relatives). A high heritability identifies good candidate phenotypes for further genetic studies. Studies conducted so far in Africa⁹⁻¹¹ used conventional BP measurement and found heritability estimates ranging from 0.34 to 0.45 for systolic BP (SBP) and from 0.29 to 0.43 for diastolic BP (DBP).

Two studies have measured the heritability of ambulatory BP in nontwins.^{12,13} Daytime heritability estimates for SBP/DBP were 0.32/0.25 in a study of black affected sibpairs¹² and 0.33/0.22 in a study of Swedish families.¹³ Nighttime heritability estimates for SBP/DBP were 0.69/0.51 in the former¹² and 0.37/0.32 in the latter.¹³ To date, only the Swedish study¹³ has reported the heritability of ambulatory pulse pressure (PP) (0.53/0.34 for daytime/nighttime).

We estimated the heritability of ambulatory SBP, DBP, and PP in families of African descent with at least 2 hypertensive siblings and living in the Seychelles islands (Indian Ocean), a country with very high prevalence of hypertension (ie, 30.8% for men and 24.3% for women, using a cutoff of 160/95 mm Hg).⁵ We also assessed the influence of the number of BP measurements on heritability estimates and the confounding effects of body mass index, sodium and potassium excretion in 24-hour urine, and plasma aldosterone.

Methods

The selection criteria for the study have been described elsewhere.¹⁴ In brief, participants were recruited between August 1999 and

Received September 27, 2004; first decision October 13, 2004; revision accepted January 10, 2005.

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Hypertension is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000156538.59873.86

January 2002 in the Seychelles islands. Families were selected from the ongoing hypertension register if there were ≥ 2 full siblings with hypertension ($\geq 140/90$ mm Hg, average of 3 office measures using a standard mercury sphygmomanometer with a cuff adapted to the participant's arm circumference or on current antihypertensive treatment) and if there were ≥ 2 other first-degree relatives (full siblings or parents) irrespective of their BP status. Seventy-six of the 135 screened families were found to be eligible.

Antihypertensive therapy, if any, was stopped for 2 weeks before performing the ambulatory BP monitoring. Two sets of triplicate office BP measurements (one during treatment and the other after a 2-week treatment washout) were taken in the morning between 7:00 and 10:30 AM, for subjects who had been sitting quietly for at least 10 minutes, by trained health professionals using a standard mercury sphygmomanometer with a triple-bladder cuff (Tricuff) that automatically adjusts bladder width to arm circumference, as previously used in the Seychelles.¹⁵ Ambulatory BP was monitored using electronic Diasys devices (DIASYS integra; Novacor SA, Rueil-Malmaison, France) placed on the left arm with an appropriately sized cuff. Measurements were based on the auscultatory mode, relayed by the oscillometric mode in case of failure of the auscultatory mode, and recorded every 20 minutes during the day and every 30 minutes during the night. We considered as invalid any values of SBP < 50 mm Hg or > 250 mm Hg; DBP < 30 mm Hg or > 150 mm Hg; PP (SBP-DBP) < 10 mm Hg or > 150 mm Hg, and pulse < 35 bpm or > 250 bpm. In total, 0.6% of the ambulatory BP values were invalid and discarded. We used the actual awake and asleep periods, as reported by participants, to define day and night. The ambulatory devices were previously validated for both the auscultatory and oscillometric modes.^{16,17} In addition, for each participant, we compared 2 measurements taken in the office with the ambulatory device in auscultatory mode with 2 standard sphygmomanometer readings: the mean (standard error [SE]) absolute differences were 2.18(0.60)/1.99(0.50) mm Hg for the first comparison and 0.61(0.59)/1.46(0.47) mm Hg for the second comparison, for SBP/DBP.

After overnight fasting, investigations began between 7:00 and 8:00 AM in a quiet room with the subject lying on a bed for 1 hour. All analyses (except for blood glucose) were conducted at the laboratories of the University Hospital of Lausanne. Plasma renin activity and plasma aldosterone were measured using radioimmunoassays, as described previously.¹⁸ Participants were given plastic containers to collect urine for 24 hours during their usual diet during the same day that ambulatory BP was monitored. Urinary and plasma sodium and potassium concentrations were measured by flame photometry (IL-943; Instrumentation Laboratory, Milan, Italy), and creatinine concentration was measured by the picric acid method (Cobas-Mira; Riche, Basel, Switzerland). Body mass index was calculated as weight (kg) divided by squared height (m²).

Statistical Analyses

The heritability estimates were obtained using the ASSOC program in Statistical Analysis in Genetic Epidemiology.¹⁹ The age- and sex-adjusted narrow sense heritability of the various traits was estimated by maximum likelihood assuming multivariate normality after a simultaneously estimated power transformation. To estimate heritability, we used a linear regression model in which the total residual variance, after regressing out covariates, is partitioned into the sum of an additive polygenic component, an additional common sibship component, and an individual-specific random component; heritability was estimated as the polygenic component divided by the total residual variance. Thus, ASSOC calculates the additive polygenic component of the variance of a trait from pedigree data in the presence of other familial correlations. All models were analyzed with and without a common sibship component, which can represent either a dominance component or a common sibship environmental component. Families were ascertained on the basis of the baseline hypertension status of their members. Correction for ascertainment aims to determine what would have been the results had the investigators not ascertained this way and should therefore use a variable that most reasonably reflects the event that triggered the

family to enter the study. We therefore corrected for BP ascertainment by including as a covariate an indicator variable whose value was 1 if the participant had an average of 3 office readings $\geq 140/90$ mm Hg (for the first set of readings) or was using current antihypertensive treatment and whose value was 0 otherwise. For traits other than BP, this method of ascertainment correction leads to very similar heritability estimates (ie, $\approx 1\%$ difference), as does conservatively adjusting for baseline office SBP and DBP. We conducted sensitivity analyses to see whether removal of oscillometric readings, adjustment for body mass index, sodium and potassium in 24-hour urine, plasma renin activity, or aldosterone modified the heritability of the various BP phenotypes. We only analyzed participants with at least 20 valid daytime and 10 valid nighttime BP measurements. To assess the effect of the number of ambulatory BP readings on heritability, we randomly selected 1, 2, 5, or 10 SBP/DBP/PP measures, separately during the day and night, and calculated the heritability estimates for the averages of each set of measures and for all available measures. Two plasma renin activity and aldosterone values lying > 4 standard deviations (SDs) beyond the mean were considered as outliers and eliminated from the analysis.

Results

From the 402 eligible participants who underwent ambulatory BP measurements, 40 were excluded because of an insufficient number of daytime (< 20) and/or nighttime (< 10) ambulatory BP measurements, 38 because of missing 24-hour urine collection and 10 because of missing plasma renin activity, aldosterone, or other laboratory measurements. Our final sample in this study consisted of 314 individuals, 147 men and 167 women, from 76 pedigrees of mean size (SD) 4.13 (2.82) that included 544 sibling pairs, 87 parent-offspring pairs, 69 avuncular pairs (ie, uncle/aunt-niece/nephew pairs), 30 first cousin pairs, and 4 grandparent-grandchild pairs. One hundred fifteen participants reported to be using antihypertensive treatment at baseline and 199 did not. Participant characteristics are listed in Table 1. The average plasma renin activity and sodium excretion in 24-hour urine was low in all presented subgroups. Given the reasonable volume and creatinine excretion in the 24-hour urine, we can be confident that the low urinary sodium excretion was not mainly caused by incomplete urine collection. The mean (SD) differences in ambulatory BP after removing the oscillometric measures (23%) were 0.05 (5.51), -0.61 (4.41), and 0.66 (4.48) mm Hg for daytime SBP, DBP, and PP, and -0.09 (4.14), -0.20 (2.58), and -0.30 (4.20) mm Hg for nighttime SBP, DBP, and PP.

Table 2 shows office and ambulatory BP values for men and women by antihypertensive treatment status. Both men and women, treated and untreated, demonstrated a significant nighttime BP decrease for SBP, DBP, and PP.

A significant heritability was found for office and ambulatory SBP and PP (Table 3), whereas the heritability of DBP was only statistically significant for ambulatory BP. Allowing for an additional sibling correlation did not substantially modify (< 1 SE difference) the heritability estimates for SBP and DBP because the sibship component either was estimated to be zero or was not significant. Heritability estimates for PP were slightly lower when allowing for a sibship component of variance that was, however, not significant at the 5% level. Except for nighttime BP, all traits showed higher heritability when only untreated individuals were analyzed, ie, when the

TABLE 1. Descriptive Statistics by Sex and Antihypertensive Treatment Status

	Men		Women	
	Untreated, n=106	Treated, n=41	Untreated, n=93	Treated, n=74
Age, y	42.6 (10.3)	51.4 (10.4)	43.4 (10.4)	52.3 (12.8)
BMI, kg/m ²	25.8 (4.5)	26.4 (4.9)	26.9 (5.0)	28.1 (4.8)
Plasma				
Sodium, mmol/L	139.5 (2.9)	139.4 (3.0)	140.0 (3.6)	139.4 (3.9)
Potassium, mmol/L	3.86 (0.23)	3.81 (0.24)	3.73 (0.17)	3.58 (0.28)
Creatinine, μ mol/L	83.2 (17.1)	84.4 (19.3)	70.5 (10.0)	72.5 (14.1)
Renin activity, ng/h/L	0.48 (0.45)	0.57 (0.38)	0.43 (0.42)	0.43 (0.77)
Aldosterone, pg/mL	56.0 (25.8)	62.1 (24.4)	53.5 (16.5)	63.0 (24.1)
Urine				
Sodium, mmol/24 h	109.7 (56.9)	99.9 (63.5)	102.4 (43.6)	97.3 (51.1)
Potassium, mmol/24 h	46.5 (17.9)	43.4 (22.6)	42.2 (16.9)	43.9 (23.1)
Creatinine, mmol/24 h	15.1 (4.2)	12.9 (3.8)	10.5 (2.6)	9.7 (2.3)
Volume, L/24 h	1.9 (1.1)	2.0 (1.2)	2.1 (1.3)	1.8 (0.8)

All values are mean \pm SD.

phenotypes of previously treated individuals were considered to be missing. For the 277 individuals with at least 10 daytime and 10 nighttime auscultatory readings, excluding oscillometric measures resulted in similar (<1 SE difference) and significant heritability estimates for daytime and nighttime SBP and DBP. Heritability estimates (SE) for daytime and nighttime PP were different with [0.42 (0.13) and 0.28 (0.13), respectively] and without [0.22 (0.11) and 0.46 (0.14), respectively] oscillometric measures.

The average ambulatory SBP, DBP, and PP for 1, 2, 5, and 10 randomly selected measures and for all measures varied,

respectively, from 130.2 to 132.5, 84.2 to 84.8, and 46.0 to 48.3 for daytime, and from 117.9 to 118.5, 75.7 to 76.1, and 42.0 to 42.5 for nighttime (Table 4). The total number of measurements varied from 20 to 50 for daytime ambulatory BP and from 10 to 23 for nighttime ambulatory BP. The heritability of ambulatory daytime and nighttime SBP, DBP, and PP increased when the number of randomly selected measures that were averaged increased, especially for daytime estimates. For all the results presented in Table 4, adding body mass index, sodium and potassium in 24-hour urine, plasma renin activity, or plasma aldosterone as covariates

TABLE 2. Blood Pressure by Sex and Antihypertensive Treatment Status

			Men		Women	
			Untreated	Treated	Untreated	Treated
Office BP	Week -2 *	SBP	132.9 (21.8)	148.2 (17.8)	127.4 (21.1)	135.7 (16.1)
		DBP	84.2 (11.8)	91.5 (11.7)	81.2 (13.0)	83.9 (9.4)
		PP	48.7 (15.1)	56.7 (13.7)	46.2 (13.0)	51.8 (13.0)
Office BP	Week 0*	SBP	128.1 (16.9)	151.3 (15.6)	121.4 (18.7)	143.3 (15.3)
		DBP	82.3 (11.3)	94.9 (11.1)	78.9 (12.2)	87.3 (9.7)
		PP	44.7 (11.9)	53.9 (10.9)	42.2 (10.6)	55.6 (12.9)
Ambulatory BP†	Daytime	SBP	128.4 (13.6)	144.7 (15.0)	120.9 (14.3)	139.3 (15.5)
		DBP	83.6 (9.5)	94.3 (10.3)	78.8 (10.1)	88.2 (9.8)
		PP	44.9 (9.6)	50.4 (11.0)	42.1 (8.3)	51.1 (11.0)
	Nighttime	SBP	114.9 (14.5)	129.9 (17.6)	110.1 (14.1)	125.2 (14.9)
		DBP	74.1 (10.5)	85.2 (12.2)	70.7 (10.4)	79.0 (9.4)
		PP	40.8 (10.0)	44.7 (12.2)	39.5 (9.0)	46.2 (11.0)

All data are mean (SD).

*Office BP values are for the average of 3 sitting measures using a standard mercury sphygmomanometer. Values measured at week -2 were under treatment for treated patients. At week 0, office and ambulatory BP were measured off-treatment.

BP indicates blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

†Ambulatory BP values were comparable when calculated based on 10 values randomly selected from all such values.

TABLE 3. Heritabilities of Office and Ambulatory BP

		All Participants, N=314			Untreated Individuals, N=199		
		h ² (SE)	P	λ ₁	h ² (SE)	P	λ ₁
Office BP week -2	SBP	0.28 (0.12)	0.02	-0.45	0.47 (0.15)	0.002	-0.35
	DBP	0.18 (0.10)	0.08	0.48	0.24 (0.18)	0.19	1.02
	PP	0.38 (0.12)	0.002	-0.23	0.48 (0.16)	0.002	-0.31
Office BP week 0*	SBP	0.20 (0.11)	0.08	-0.22	0.26 (0.14)	0.07	-0.74
	DBP	0.05 (0.09)	0.54	0.22	0.09 (0.14)	0.49	0.10
	PP	0.37 (0.12)	0.002	0.12	0.43 (0.16)	0.007	-0.14
Ambulatory							
Daytime	SBP	0.37 (0.12)	0.003	-0.46	0.57 (0.16)	<0.001	-0.14
	DBP	0.24 (0.12)	0.05	-0.38	0.32 (0.17)	0.07	-0.14
	PP	0.54 (0.12)	<0.001	-0.09	0.57 (0.15)	<0.001	-0.08
Nighttime	SBP	0.34 (0.13)	0.01	-0.48	0.29 (0.16)	0.07	-0.59
	DBP	0.37 (0.15)	0.01	-0.29	0.31 (0.20)	0.13	-0.14
	PP	0.47 (0.12)	<0.001	0.16	0.40 (0.16)	0.01	0.29
24-h	SBP	0.40 (0.13)	0.002	-0.56	0.52 (0.16)	0.001	-0.06
	DBP	0.28 (0.13)	0.03	-0.49	0.34 (0.19)	0.07	-0.33
	PP	0.53 (0.11)	<0.001	-0.07	0.55 (0.16)	<0.001	-0.07

All values are mean (SD).

*2 weeks off treatment for the treated patients.

h² indicates heritability; λ₁, power transformation estimated to normalize the residuals.

All estimates were corrected for ascertainment. SBP and PP were adjusted for age and sex, DBP for age, age², and sex. For ambulatory BP phenotypes, calculation based on 10 values were comparable.

modified the heritability of BP by not >50% of 1 SE (data not shown), without any systematic direction; hence, none of these covariates substantially affected the heritability of BP in our sample. Heritability estimates increased with increased number of measures even after excluding oscillometric measures (data not shown).

For the results in Tables 3 and 4, ascertainment correction only slightly affected the heritability of BP (usually by less than half the SE) without any systematic direction.

Discussion

We found a statistically significant heritability of ambulatory SBP, DBP, and PP in our sample of families of African descent in the Seychelles islands and heritability estimates of BP were higher when based on ambulatory BP than on office BP. Noticeably, our population was characterized by low plasma potassium and renin levels and low average urinary sodium excretion. Similar to the study conducted in Nigerian Yoruba families,⁹ adjustment for body mass index did not substantially alter the BP heritability estimates (this latter study used conventional BP). Likewise, neither plasma renin activity nor plasma aldosterone significantly modified the heritability of BP when added as covariates. The exclusion of ambulatory oscillometric measures mainly affected PP heritability estimates.

The 2 previous nontwin studies^{12,13} that have reported the heritability of ambulatory BP included different sample sizes, study designs, and populations. Like Fava et al,¹³ we also found ambulatory BP to be more heritable than office BP. If

we compare our heritability estimates among untreated individuals with those of the untreated Swedish siblings,¹³ we have slightly higher daytime and slightly lower nighttime estimates for both SBP and DBP. Differences in heritability estimates between the 2 studies are not surprising because of the very different genetic and environmental backgrounds (Swedish versus East Africans). Compared with the black affected sibpairs taken off treatment,¹² our heritability estimates among individuals taken off treatment are lower. But the small sample size of the former study¹² resulted in large standard errors, so that their daytime estimates (0.32±0.23 for SBP and of 0.25±0.26 for DBP) are not significantly different from zero. Unlike the study in blacks, our nighttime estimates were not significantly different from 0 for either SBP or DBP, even after a 2-week washout period. Our study provides new evidence of the heritability of ambulatory BP in families of African descent.

In our study, treated participants were taken off treatment for 2 weeks under close clinical supervision. Restricting the analysis to individuals who were untreated at baseline substantially reduced the sample size, but heritability estimates (±SE) increased from 38% (±12) to 61% (±16) for daytime SBP and from 25% (±12) to 37% (±18) for daytime DBP, suggesting that previous treatment plays a role in obscuring familial aggregation of BP. A similar effect was noted for office BP but not for ambulatory nighttime BP. Cui et al argued that treated hypertensive individuals should not be excluded from the analysis because of their important contribution to the familial component of BP variance.²⁰ The

TABLE 4. Heritability of Average Ambulatory BP According to the Number of Randomly Selected Measures Averaged

No. Measures	Daytime			Nighttime		
	h^2 (SE)	P	λ_1	h^2 (SE)	P	λ_1
SBP						
1	0.06 (0.09)	0.47	-0.14	0.18 (0.11)	0.13	0.08
2	0.19 (0.10)	0.06	-0.56	0.14 (0.11)	0.18	-0.30
5	0.37 (0.12)	0.003	0.05	0.26 (0.13)	0.04	-0.40
10	0.38 (0.12)	0.002	-0.38	0.34 (0.14)	0.01	-0.48
All	0.37 (0.12)	0.003	-0.46	0.34 (0.13)	0.01	-0.48
DBP						
1	0.05 (0.09)	0.55	0.43	0.29 (0.13)	0.03	0.20
2	0.19 (0.13)	0.14	-0.48	0.17 (0.12)	0.15	0.08
5	0.18 (0.12)	0.14	0.11	0.37 (0.14)	0.01	-0.26
10	0.25 (0.12)	0.04	-0.16	0.34 (0.15)	0.02	-0.26
All	0.24 (0.12)	0.05	-0.38	0.37 (0.15)	0.01	-0.29
PP						
1	0.12 (0.10)	0.26	0.55	0.21 (0.13)	0.10	0.77
2	0.11 (0.10)	0.27	0.54	0.23 (0.11)	0.04	0.40
5	0.43 (0.12)	0.0004	0.36	0.34 (0.12)	0.003	0.44
10	0.55 (0.13)	0.00002	0.17	0.45 (0.12)	0.0003	0.15
All	0.54 (0.12)	0.00002	-0.09	0.47 (0.12)	0.0001	0.16

SBP was adjusted for age and sex; DBP for age, age², and sex; and PP for age and age².

1, 2, 5, and 10 SBP, DBP, and PP measures were randomly selected and averaged for each period, daytime or nighttime.

The number of ambulatory measurements varied from 20 to 50 for daytime BP and from 10 to 23 for nighttime BP. All presented results were corrected for ascertainment.



2-week washout period in our study might not have been long enough to fully eliminate the confounding effect of treatment. Our results clearly illustrate the potential confounding effect of antihypertensive treatment on BP heritability.

We were also interested in assessing the effect of the number of BP measurements on heritability estimates. Ambulatory measurements were chosen at random to minimize biases associated with a specific period of the day, with physical activity (for daytime) or with sleep quality (for nighttime). We confirm the findings of Kotchen et al¹² who found heritability estimates to be higher for multiple measurements averaged over 24 hours than for measurements at a single point in time. Our results illustrate the expected attenuation that arises when heritability estimates are based on only a few BP readings. Ambulatory BP offers the advantage of being based on multiple BP readings. Considering only the number of measurements, one could argue that multiple office BP readings could serve the same purpose as ambulatory BP. Nevertheless, office BP may represent a different phenotype than BP measured out of the office, even if similar heritability estimates are obtained. Because ambulatory BP better-predicts cardiovascular outcomes than conventional office BP,²¹⁻²³ it might represent a more relevant phenotype than conventional BP to study the genetic determinants of BP.

Heritability estimates are population-specific. Because heritability is the ratio of the additive genetic variance to the total phenotypic variance, a variation in environmental factors per

se (eg, salt intake at a population level, which has rarely been accounted for in heritability studies) can either increase or decrease heritability, even if genetic factors are equal. In our study, controlling for urinary sodium and potassium excretion did not significantly affect our heritability estimates. Our results were obtained in a setting with a low average sodium excretion and our findings may therefore not be generalizable to populations with higher dietary salt intake. Furthermore, the method used to measure BP and the number of averaged BP readings used to assess the BP phenotype are important factors, as demonstrated in our study. Finally, the high intra-individual BP variability (a factor that can be partially controlled by increasing the number of measurements) further complicates the precise phenotypic characterization of BP.

Perspectives

The present data show that ambulatory BP has a high heritability in families of African descent with low renin status and low average urinary sodium excretion. They also demonstrate that antihypertensive treatment and the number of BP measurements have a major influence on the heritability estimates. Finally, our results suggest a substantial genetic component in ambulatory PP. Today, numerous studies are investigating the genetic aspects of essential hypertension and many of these studies are, for practical reasons, based on a few isolated office BP measurements. Our results suggest that this may not be the ideal methodological approach, and that for future studies ambulatory BP, which provides a larger

number of values, may be represent a more appropriate phenotype to look for genes involved in BP control.

Acknowledgments

The study benefited from a grant from the Swiss National Science Foundation (TANDEM number 31-51115.97). This work was supported in part by a US Public Health Service Resource Grant (RR03655) from the National Center for Research Resources and Research Grant (GM28356) from the National Institute of General Medical Sciences. We thank the Ministry of Health in the Seychelles for logistic support.

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