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Genetic Variance and Heritability of Cardiovascular Risk Factors in Chinese Adolescent Twins

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Abstract. In order to estimate genetic variance and heritability of systolic blood pressure (SBP), diastolic blood pressure (DBP), serum cholesterol and triglyceride levels, a total of 235 (79 male and 82 female MZ, 41 male and 33 female DZ) twin pairs, recruited from 12 junior high schools in Taipei city, were studied. Statistically significant genetic variance observed for SBP, DBP, serum cholesterol and triglycerides persisted after adjustment for age and anthropometric characteristics. However, further adjustment for dietary preference, beverage consumption, and other host and environmental factors gave different results: genetic variance of adjusted SBP and DBP was still significant, while significance was found only in males for cholesterol and in neither males nor females for triglycerides. Heritability estimates of unadjusted SBP, DBP, cholesterol and triglycerides were 0.27, 0.45, 0.21 and 0.41, respectively, for males, and 0.15, 0.42, 0.41 and 0.82, respectively, for females. After adjustment for age, anthropometric characteristics, host and environmental factors, the heritability estimates of SBP, DBP and cholesterol were 0.64, 0.72 and 0.50, respectively, for males, and 0.40, 0.60 and 0.37, respectively, for females.

Key words: Blood pressure, Cholesterol, Triglycerides, Heritability, Adolescent twins

INTRODUCTION

Accumulating evidence suggests a familial aggregation of a cardiovascular disease (CVD), particularly where manifestation is in early life [15,23,35,51,56,61-63,66,69,71-74]. This familial aggregation of CVD may be the result of the aggregation of risk factors such as

high blood pressure, serum cholesterol and triglyceride levels [1,21,24,26,32,34,40,45-47, 52,64,67,68,75,84]. The cause of familial aggregation of these major CVD risk factors may be primarily genetic, environmental or an interaction of both. It is extremely difficult to distinguish the effects of shared environment from those of shared genes. Furthermore, certain environmental factors may even exhibit a pattern similar to mendelian segregation [37].

Twin studies can provide useful information on the relative contribution of genetic and environmental components in diseases and their risk factors [65,82]. Conventional twin method has been used to estimate genetic variance and heritability of CVD risk factors through the comparison of intrapair similarity between monozygotic (MZ) and dizygotic (DZ) twins [2-5,7,8,11,13,14,16,22,27-31,33,35,39,41-44,53,54,58,60,76, 77]. As the intrapair similarity of cotwins may simply be a reflection of similarity in anthropometric measurements, life style characteristics and/or other host and environmental factors, it is necessary to adjust for these factors while the genetic impact is evaluated.

In this report, both unadjusted and adjusted genetic variance and heritability of systolic blood pressure (SBP), diastolic blood pressure (DBP), serum cholesterol and triglyceride levels of 235 Chinese adolescent twins are described.

MATERIALS AND METHODS

Twin Sample

Adolescent twins aged 12 to 15 years, attending junior schools in Taipei city, were chosen as the study population. Through stratified cluster sampling using each junior high school as a sampling unit, a total of 328 twin pairs were found in 12 schools: of these, 254 pairs were same-sexed and aged 12 to 15 years. Among these eligible subjects, 224 (88.2%) agreed to participate with consents for analysis of their serum chemistry profiles, 11 (4.3%) agreed to participate but without a blood sample, and 19 (7.5%) refused to participate at all.

Zygosity Determination

For those 224 twin pairs who had blood sample drawn, zygosity was based on three red cell antigen systems (ABO, MNSs, Rh) and three continous characteristics of fingerprints. Antigens tested were A, A1, B, C, D, E, c, e, M, N, S and s (Ortho Diagnostics). If a twin pair was found to be discordant on any of the above antigens, the pair was classified as DZ. The fingerprint characteristics analyzed included total ridge count (TRC), total absolute difference in ridge count (TADRC), and total absolute difference in pattern type (TADPT) [6]. Each set of data was read by two of three readers blindly and independently. If any of the TADRC, TADPT or intrapair difference in TRC exceeded allowable limits, the twin pair was classified as DZ. The allowable limits were 37 for TADRC, 5 for TADPT and 18 for the intrapair difference in TRC. The 224 twin pairs were thus classified as 73 male MZ, 41 male DZ, 77 female MZ and 33 female DZ twin pairs.

For those 11 pairs without blood samples, zygosity was based on fingerprints only, and all were classified as MZ. Amont the 224 pairs whose zygosity was based on bloodgroups and fingerprints, 20 (12%) out of 170 pairs with concordant fingerprint characteristics were DZ. Accordingly, only one or two ($11 \times 12\% = 1.3$) pairs may be expected to be DZ in these 11 pairs without blood samples.

Data Collection

Blood pressure was measured with a standard sphygmomanometer (Baumanometer Model 300). The recommendations of the National Heart, Lung and Blood Institute's Task Force on Blood Pressure Control in Children [49] were followed. Three measurements were taken to insure a relaxed state during the measurements, and the third reading was used for the analysis. Phase I and phase IV blood

pressure were recorded as systolic and diastolic blood pressure, respectively. Blood samples were collected in the early morning from each individual who had been fasting for more than 12 hours. Serum cholesterol and triglyceride levels were determined by Hitachi Model 716 Automatic Analyzer. Weight and height were measured with a standard medical balance beam scale with rigid vertical height measurements. As a measure of obesity, the ponderosity index (weight/height^3) was used.

Life style information on twin individuals was obtained through a self-administered questionnaire [6]. Included were questions pertaining to dietary preferences, beverage consumption, food frequencies, activity levels, and cigarette smoking. Personality characteristics were assessed with a revised Chinese edition of the Junior Eysenck Personality Inventory [18]. Both the life style questionnaire and the personality inventory were filled out by twins of a given school, in the same place, within the same period of time, to ensure that all the twins received similar instructions to answer the questions. Following a structured interview schedule, information on family background and early life experience of twin pairs were obtained from their parents in a home visit.

Methods of Analysis

Genetic variance and heritability of both unadjusted and adjusted values of SBP, DBP, serum cholesterol and triglycerides were calculated. In order to adjust for the possible effects of age, anthropometric characteristics, dietary preferences, beverage consumption, and other host and environmental factors, multiple regression equations were employed to provide the predicted values of these CVD risk factors for each twin individual. Data of only one twin from each pair were used to derive these regression equations. The adjusted value of the CVD risk factors for each individual was the residual value computed by subtracting predicted value from observed value.

The means of the CVD risk factors in MZ and DZ twins were first compared and tested by t' test [9,10]. If there were no significant differences between MZ and DZ twins, then the difference in total variance were tested by F' test [25]. In the case of no difference, within-pair genetic variance, G_{WT} [36], and Falconer's heritability index, h^2_F [19], were estimated. G_{WT} is simply the difference between within-pair mean squares of the trait in MZ and DZ twins ($G_{WT} = MSW_{DZ} - MSW_{MZ}$), while h^2_F is twice the difference between intrapair correlations (r's) in MZ and DZ twins, ($h^2_F = 2(r_{MZ} - r_{DZ})$). If the total variance of a trait was significantly different between MZ and DZ twins, the among-pair genetic variance [19] and Christian's heritability index [8,10] were used instead.

RESULTS

Means of CVD Risk Factors

Means and among-pair mean squares (MSA) of SBP, DBP, serum cholesterol and triglycerides in MZ and DZ twins are shown in Table 1. Mean levels of SBP, DBP and serum cholsterol were almost the same in male MZ and DZ twins, but slightly lower in female MZ than DZ twins. Mean triglyceride level was higher in male DZ than MZ twins, but lower in female DZ than MZ twins. However, differences in mean levels of these CVD risk factors between MZ and DZ twins were not statistically significant in either sex on t' test.

Unadjusted Genetic Variance and Heritability of CVD Risk Factors

Table 2 shows the MSA, MSW, r, G_{WT} and h^2_F values of SBP, DBP, serum cholesterol and triglyceride levels in MZ and DZ twins of both sexes. MSW were significanlty less than MSA values in each sex-zygosity group, all the F' tests being significant with $P < 0.001$, (except for triglycerides in female DZ twins where $P < 0.01$). In other words, intrapair differences were significantly smaller than interpair differences. All r values were greater than 0.50 (except for triglycerides of female DZ twins). MZ twins had greater r values than DZ twins in either sex.

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Table 1 - Means and Among-Pairs Mean Squares of Blood Pressure, Serum Cholesterol and Triglyceride Levels

	Male pairs					Female pairs				
	MZ (n = 73 pairs)		DZ (n = 41 pairs)		t'	MZ (n = 77 pairs)		DZ (n = 33 pairs)		t'
	Mean	MSA	Mean	MSA		Mean	MSA	Mean	MSA	
Systolic BP (mm Hg)[1]	111.3	305.5	110.3	302.5	0.43	106.7	258.5	109.2	245.5	−1.09
Diastolic BP (mm Hg)[1]	68.3	237.9	69.0	288.8	−0.30	68.5	182.6	70.2	226.0	−0.80
Serum cholesterol (mg%)	133.6	1020.5	132.6	1077.2	0.24	144.5	721.6	148.0	882.7	−0.84
Serum triglyceride (mg%)	73.2	1223.7	79.1	1469.3	−1.15	77.4	1314.0	74.1	1066.7	0.66

[1] Sample including 6 male and 5 female additional MZ pairs without serum chemistry data.

$$t' = (\bar{Y}_{MZ} - \bar{Y}_{DZ}) / \sqrt{\frac{MSA_{MZ}}{2n_{MZ}} + \frac{MSA_{DZ}}{2n_{DZ}}}$$, where $\bar{Y}$'s are means and n's are numbers of twin pairs.

Table 2 - Genetic Variance and Heritability of Crude Blood Pressure, Serum Cholesterol and Triglycerides

	MZ pairs (n = 150)				DZ pairs (n = 74)					
	MSA	MSW	r_I	n	MSA	MSW	r_I	n	G_{WT}	h^2_F
Male pairs										
Diastolic BP[1]	237.85	26.44***	0.80	79	288.81	58.01***	0.67	41	31.58**	0.27
Systolic BP[1]	305.50	30.81***	0.82	79	302.50	77.50***	0.59	41	46.69***	0.45
Cholesterol	1020.49	92.05***	0.83	73	1077.20	169.27***	0.73	41	77.21*	0.21
Triglyceride	1223.67	82.75***	0.87	73	1469.31	293.95***	0.67	41	211.20**	0.41
Female pairs										
Diastolic BP[1]	182.64	24.16***	0.77	82	226.02	41.17***	0.69	33	17.01*	0.15
Systolic BP[1]	258.49	21.03***	0.85	82	245.50	53.55***	0.64	33	32.52**	0.42
Cholesterol	721.63	75.46***	0.81	77	882.65	215.12***	0.61	33	139.66***	0.41
Triglyceride	1314.02	151.97***	0.79	77	1066.73	478.74**	0.38	33	326.78***	0.82

[1] See note to Table 1.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 3 - Genetic Variance and Heritability of Age-Anthropometry-Adjusted Blood Pressure, Serum Cholesterol and Triglycerides

CVD risk factors	MZ pairs (n = 150)				DZ pairs (n = 74)				G_{WT}	h^2_F
	MSA	MSW	r_I	n	MSA	MSW	r_I	n		
Male pairs										
Diastolic BP[1]	242.05	26.10***	0.81	79	247.15	58.05***	0.62	41	31.96**	0.37
Systolic BP[1]	242.92	32.36***	0.76	79	231.44	88.91**	0.44	41	56.55***	0.64
Cholesterol	950.45	100.57***	0.81	73	1101.38	191.88***	0.70	41	91.31*	0.21
Triglyceride	1239.25	83.79***	0.87	73	1403.10	287.60***	0.66	41	203.81***	0.43
Female pairs										
Diastolic BP[1]	177.82	21.84***	0.78	82	191.78	46.58***	0.61	33	24.73**	0.34
Systolic BP[1]	236.77	24.03***	0.82	82	179.36	57.89***	0.51	33	33.86**	0.61
Cholesterol	708.46	73.26***	0.81	77	875.83	237.33***	0.57	33	164.07***	0.48
Triglyceride	1255.09	148.16***	0.79	77	924.65	461.88**	0.33	33	313.72***	0.91

[1] See note to Table 1.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 4 - Genetic Variance and Heritability of Overall-Adjusted Blood Pressure, Serum Cholesterol and Triglycerides

	MZ pairs (n = 150)				DZ pairs (n = 74)				G_{WT}	h^2_F
	MSA	MSW	r_I	n	MSA	MSW	r_I	n		
Male pairs										
Diastolic BP	222.98	58.30**	0.59	73	162.22	94.18*	0.27	41	35.88*	0.64
Systolic BP	231.75	35.59***	0.73	73	215.85	98.51**	0.37	41	62.91***	0.72
Cholesterol	583.88	182.52***	0.52	73	526.02	303.00*	0.27	41	120.48*	0.51
Triglyceride	866.92	345.66**	0.43	73	963.02	593.03	0.24	41	?	?
Female pairs										
Diastolic BP	124.54	40.74***	0.51	77	130.04	69.24*	0.31	33	28.50*	0.40
Systolic BP	235.09	57.19***	0.61	77	191.06	100.87*	0.31	33	43.69*	0.60
Cholesterol	641.24	199.93***	0.52	77	575.80	284.39*	0.34	33	84.46	0.37
Triglyceride	940.25	310.76***	0.50	77	892.13	565.31	0.22	33	?	?

?: Genetic variance and heritability were not estimated because MSW was not significantly less than MSA in DZ twins.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

As total variance in CVD risk factors was not significantly different between MZ and DZ twins, G_{WT} and h_F^2 were calculated. Significant genetic variance was found for all traits in males and females. The h_F^2 for SBP and DBP was 0.45 and 0.27, respectively, in males, and 0.42 and 0.15, respectively, in females. The h_F^2 for serum cholesterol and triglycerides was 0.21 and 0.41, respectively, in males, and 0.41 and 0.82, respectively, in females.

Adjusted Genetic Variance and Heritability of CVD Risk Factors

Age and anthropometric characteristics were considered to exclude their possible confounding effects on SBP, DBP, serum cholesterol and triglyceride levels. In most cases, MSW increased and MSA decreased after the adjustment for age and anthropometric characteristics. The adjusted MSW was still significantly less than adjusted MSA with $P < 0.01$ or 0.001 on F' test for all sex-zigosity groups. The r values remained the same or decreased after the adjustment. The G_{WT} changed only slightly after adjustment and remained statistically significant. The h_F^2 for adjusted SBP and DBP was 0.64 and 0.37, respectively, in males, and 0.61 and 0.34, respectively, in females. The h_F^2 for adjusted serum cholesterol and triglycerides was 0.21 and 0.43, respectively, in males, and 0.48 and 0.91, respectively, in females (Table 3).

Besides age and anthropometric characteristics, other host and environmental factors, such as dietary preferences, beverage consumptions, activity levels, might also influence the genetic variance and heritability of the CVD risk factors. Further adjustment for these variables was carried out, and the MSA, MSW, r, G_{WT} and h_F^2 of such overall-adjusted levels of SBP, DBP, serum cholesterol and triglycerides in each sex-zygosity group are shown in Table 4. After the overall adjustment, MSA decreased and MSW increased, MSW being still significantly less than MSA for SBP, DBP and serum cholesterol in each sex-zygosity group and for triglycerides in MZ twins of both sexes. However, in DZ twins, MSW was no longer less than MSA for triglycerides in males and females. All the r values decreased after the overall adjustment. Significant and slightly increased G_{WT} was observed for DBP and SBP in males and females, but for cholesterol in males only. Since the MSW of overall-adjusted triglycerides was not significantly less than its MSA, the G_{WT} and h_F^2 of triglycerides were not estimated. The h_F^2 of overall-adjusted levels of SBP, DBP and cholesterol was 0.72, 0.64 and 0.51, respectively, in males, and 0.60, 0.40 and 0.37, respectively, in females.

DISCUSSION

A significant genetic variance was found for unadjusted SBP, DBP, serum cholesterol and triglyceride levels in this study. These findings are consistent with those of several twin studies on CVD risk factors [2-5,7,8,11,13,14,16,22,27-31,33,35,39,41-44,53,54, 57,58,60,76,77]. However, it is difficult to compare the present observations with those of other studies because of different cultural and ethnic background and of considerable variation in approach and design methods. Volunteer twin subjects were recruited through newspaper, poster, radio and other mass media in some studies [10,19,22,40]. In certain population-based twin studies, the participation rates were at best about 60% [3,6]. Small sample size was another problem in some studies [2,37,56]. In case of volunteer subjects or of low participation rate in population-based studies, self-selection was the issue and

representativeness of the twin sample might be questioned. Cotwins who are similar are more likely to agree jointly to participate than dissimilar cotwins. The genetic variance and heritability thus estimated will be biased.

Age distribution was considerably different in MZ and DZ twins of some studies [31]. As both twins of a given pair are of the same age, it is generally assumed that age is already controlled in a twin study. This is true in the case of MSW and G_{WT}, but not for heritability estimation where MSA is involved. If heritability is estimated, among-pair variation in age should be taken into consideration. This is particularly necessary when MZ and DZ twins differ in age distribution and the trait tends to change with age. For example, when the age distribution is broader in MZ than DZ twins, the MSA will be biased upward in MZ relative to DZ twins. The heritability of the trait will thus be overestimated. Some investigators used physical similarity as the main criterion for zygosity determination [24]. Genetic variance and heritability will also be overestimated under this circumstance. As age and anthropometric characteristics were different in our MZ and DZ twins, they were adjusted first. This resulted in the decrease of all r values, implying that part of the similarity was explained by the anthropometric characteristics, especially for SBP and DBP in DZ twins.

A basic but debatable assumption of the conventional twin method is the equality of intrapair environmental correlations in MZ and DZ twins. This assumption has long been challenged [17,38,70]. Environmental correlation was usually found significantly higher in MZ than DZ twins. The higher similarity in MZ than DZ twins may thus be the result of more similar genetic and/or environmental components in MZ twins. It is essential to adjust for environemntal factors if they are associated with the trait and differently distributed in MZ and DZ twins. However, most of the twin studies aimed to estimate genetic variance and heritability of CVD risk factors failed to do so.

In this study, r values of all CVD risk factors decreased in all classes of twins after the overall adjustment of age, anthropometric characteristics, dietary preferences, beverage consumption, and other host and environmental factors. It is obvious that part of the similarity was due to these variables. After adjustment, G_{WT} was still significant for SBP and DBP in males and females, and for serum cholesterol level in males. The adjusted h_F^2 of SBP, DBP, and serum cholesterol was greater than the unadjusted one. This suggests that the residual variation in these CVD risk factors had a greater genetic component than unadjusted variation. Another interesting finding is that heritability estimates were higher for males than females after adjustment. This may be attributed to the greater similarity in unknown environmental factors and/or non-additive genetic variance in males than females. As to cholesterol, menstrual cycle and its related hormonal changes may be one of the major reasons for such sex difference. The r values in triglycerides of DZ twins of both sexes were no longer significant after adjustment. As two memebrs of a given DZ pair still share common genes, the absence of intrapair correlations suggests that genetic components might not be important in the determination of serum triglyceride level in Chinese adolescent twins and, by inference, in the Chinese population.

Although many reports have suggested a genetic component in blood pressure, little is known about either the biochemical mechanism or its genetic basis in man. However, two potential loci have been identified in animal studies of hypertension [59, 83]. While some studies indicate that the activity of enzymes in the metabolism of

norepinephrine is genetically determined [50,78,79], the relation of these enzymes with SBP and DBP remains to be determined. Studies on urinary concentration of the renal enzyme kallikrein revealed a familial aggregation and an association with SBP [85]. Some genetic markers have also been found to be associated with higher blood pressure [12,48, 55,80,81], but there are no obvious biochemical-physiological relationships between these markers and blood pressure. Numerous functional and structural proteins are involved in the vasoregulatory system, and a better understanding of human essential hypertension requires a detailed description of the genetic loci involved.

Major genes have been found to be associated with high serum cholesterol and some of their biochemical mechanisms have been indicated [20]. However, there must be many genes involved in the absorption, metabolism and monitoring of serum lipids. A continuing search for loci which have segregating alleles with measurable effects should be carried out. Meanwhile, progress is likely to result from a better understanding of lipoprotein metabolism and the determination of the consequences of different kinds of environmental changes.

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