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# Genetic Variance and Heritability of Serum Cholesterol and Triglycerides Among Chinese Twin Neonates

**C.-J. Chen[1], M.-W. Yu[1], C.-J. Wang[1], S.-L. Tong[1], M. Tien[1], T.-Y. Lee[2], H.-C. Lue[2], F.-Y. Huang[3], C.-C. Lan[3], K.-H. Yang[4], H.-C. Wang[4], H.-Y. Shih[5], C.-Y. Liu[5], J.-S. Chen[2]**

*[1]Institute of Public Health, National Taiwan University College of Medicine; [2]National Taiwan University Hospital; [3]Mckay Memorial Hospital; [4]Taipei Municipal Maternal and Child Hospital; [5]National Nursing School Hospital, Taipei, Taiwan, Republic of China*

**Abstract.** In order to examine the genetic variance and heritability of serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides, a total of 349 pairs of same-sexed twin neonates born in four major general teaching hospitals in Taipei City were studied. Based on the placental pattern and 12 red blood cell antigens, 271 monozygotic (MZ) and 78 dizygotic (DZ) twin pairs were identified. There was a significant genetic variance for total cholesterol, HDL-C, LDL-C, and triglycerides both unadjusted and adjusted for sex, gestational age and placentation. The unadjusted heritability of total cholesterol, HDL-C, LDL-C, and triglycerides was 0.59, 0.30, 0.25 and 0.75, respectively; while the corresponding adjusted heritability was 0.74, 0.38, 0.31, and 0.49, respectively. Intrapair variance of serum lipids was not significantly different between monochorionic and dichorionic MZ twins.

**Key words: Heritability, Serum lipids, Neonates, Twins**

## INTRODUCTION

Cardiovascular diseases (CVDs) including cerebrovascular accidents and ischemic heart diseases are major causes of death in Taiwan [7]. The prevention and intervention of CVDs has become an important task in medical care and public health practice. As the progression of atherosclerosis starts in early childhood and becomes clinically manifested after age 30 [14], the prevention of CVDs should be

implemented in early life. It is important to explore possible risk factors associated with atherosclerosis for effective and efficient prevention of CVDs. Hyperlipidemia is one of the major risk factors of atherosclerosis. It is essential to elucidate the relative importance of genetic and environmental components in the determination of hyperlipidemia in order to evaluate the possibility of reducing the occurrence of hyperlipidemia through life-style changes.

Accumulating evidence suggests a familial aggregation of serum cholesterol and triglycerides levels [9,13,15-17]. The cause of familial aggregation of hyperlipidemia 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. Twin studies can provide useful information on the relative contribution of genetic and environmental components to diseases and their risk factors. The twin method has been used to estimate genetic variance and heritability of hyperlipidemia through the comparison of intrapair similarity between MZ and DZ twins [1,5,6,11,19]. We reported a significant genetic variance of serum cholesterol and triglycerides levels among Chinese adolescent twins, but the genetic variance was statistically significant only for cholesterol in boys after adjusting for dietary habit and lifestyle variables [2].

The specific aims of this report include: 1) the assessment of genetic variance and heritability of serum cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) levels of same-sexed Chinese twin neonates; and 2) the comparison of intrapair difference in levels of these serum lipids between monochorionic and dichorionic MZ twin neonates.

## MATERIALS AND METHODS

### Twin Subjects

Twin neonates delivered in four general teaching hospitals in Taipei City during the period from October 1, 1985 to December 31, 1988 were recruited as the study subjects. Among 844 twin pairs delivered, there were 63 pairs with one or both cotwins affected with stillbirth and/or congenital malformations. With regards to the sex distribution of 781 pairs with both cotwins alive, there were 643 same-sexed (318 male and 325 female) and 138 unlike-sexed pairs.

### Zygosity Determination

Zygosity of twin pairs was determined by placentation and 12 red cell antigens (A, B, C, D, E, c, e, M, N, $Le^a$, $Le^b$, and $P_1$). Monochorionic twin pairs and twin pairs concordant in all the above red cell antigens were classified as MZ, while dichorionic twin pairs and twin pairs who had no information on placental pattern were classified as DZ if they had one or more red cell antigens discordant. Among

349 same-sexed twin pairs whose cord blood samples were available, there were 271 MZ and 78 DZ twin pairs. The ratio of same-sexed MZ and DZ pairs was consistent with what we reported previously [3].

### Serum Lipids Examination

Serum levels of total cholesterol, HDL-C, LDL-C and triglycerides were determined blindly by autoanalyzer in the Clinical Pathology Laboratory of the National Taiwan University Hospital according to the standard protocol [18]. For those cord blood sample of small quantity, serum levels of lipids were examined in the following sequence: total cholesterol, triglycerides, HDL-C and LDL-C. In other words, some twin pairs had no information on HDL-C and LDL-C due to the lack of serum specimens. The number of pairs with both cotwins examined for cholesterol, triglycerides, HDL-C and LDL-C was 271, 269, 163 and 158, respectively, for MZ twins, 78, 73, 44 and 40, respectively, for DZ twins.

### Methods of Analysis

Genetic variance and heritability of both unadjusted and adjusted levels of serum cholesterol, triglycerides, HDL-C and LDL-C were calculated. In order to adjust for the possible effect of sex, gestational week, and placental pattern, multiple regression equations were employed to provide the predicted values of these serum lipids for each twin individual. Data of one twin randomly selected from each pair were used to derive the regression equations. The adjusted value of the serum lipids for each individual was the residual value computed by subtracting predicted value from observed value.

The mean levels of serum lipids in MZ and DZ twins were first compared and tested by $t'$ test [4]. If there was no significant difference in mean levels between MZ and DZ twins, then the difference in total variance was tested by $F'$ test [10]. In case of no difference, within-pair genetic variance, $G_{WT}$ [12], and Falconer's heritability index [8], $h^2$, were estimated. The within-pair genetic variance is simply the difference between within-pair mean squares (MSWs) of the trait in MZ and DZ twins, ie, $G_{WT} = MSW_{DZ} - MSW_{MZ}$. The Falconer's heritability is twice the difference in intrapair correlations between MZ and DZ twins, ie, $h^2 = 2(r_{MZ} - r_{DZ})$.

## RESULTS

### Mean Levels of Serum Lipids

The mean levels of serum total cholesterol, triglycerides, HDL-C, and LDL-C were

75.7, 31.1, 28.8, and 20.2, respectively, among monochorionic MZ (MZ-M) twins; 70.4, 30.4, 30.5, and 17.4 among dichorionic MZ (MZ-D) twins; and 75.1, 30.4, 30.6 and 17.4 among DZ twins as shown in Table 1. The mean levels of these serum lipids were not significantly different either between MZ-M and MZ-D twins or between MZ and DZ twins.

## MSWs and Genetic Variance of Serum Lipids

Table 2 shows MSWs and among-pair mean squares (MSAs) of serum total cholesterol, triglycerides, HDL-C and LDL-C of MZ and DZ twin pairs. MSWs of these serum lipids were significantly smaller than MSAs for both MZ and DZ twins. As there was no significant difference in total variance of these serum lipids between MZ and DZ twins, the significance of $G_{WT}$ for each serum lipid was examined by F test. There was a significant genetic variance for serum total cholesterol, triglycerides, HDL-C and LDL-C. The total variance and MSW of serum lipids were not significantly different between MZ-M and MZ-D twins as indicated in Table 3.

## MSWs and Genetic Variance of Adjusted Serum Lipids

MSWs and MSAs of serum cholesterol, triglycerides, HDL-C, and LDL-C levels adjusted for sex, gestational age and placentation among MZ and DZ twins are illustrated in Table 4. MSWs of adjusted serum lipids were significantly smaller than their MSAs in both MZ and DZ twins. The total veriance of adjusted serum lipids was not significantly different between MZ and DZ twins. F test showed a significant $G_{WT}$ for adjusted serum total cholesterol, triglycerides, HDL-C and LDL-C. Table 5 shows similar total variance and MSW of these serum lipids among MZ-M and MZ-D twins.

## Intrapair Correlation and Heritability

Intrapair correlation and heritability of unadjusted and adjusted levels of serum lipids are shown in Table 6. The intrapair correlations of unadjusted total cholesterol, triglycerides, HDL-C and LDL-C were 0.82, 0.77, 0.78, and 0.84, respectively, for MZ twins, and 0.53, 0.40, 0.63, and 0.72, respectively, for DZ twins. The corresponding heritability indices of these serum lipids were 0.59, 0.75, 0.30, and 0.25, respectively. The intrapair correlations of adjusted total cholesterol, triglycerides, HDL-C and LDL-C were 0.81, 0.73, 0.78, and 0.84, respectively, for MZ twins, and 0.44, 0.48, 0.59, and 0.69, respectively, for DZ twins. The corresponding heritability indices of these serum lipids were 0.74, 0.49, 0.38, and 0.31, respectively.

**Table 1 - Mean levels of serum cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) of monochorionic MZ (MZ-M), dichorionic MZ (MZ-D) and DZ twin pairs**

| | MZ | | | | | | DZ | | t′ test | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Monochorionic | | Dichorionic | | Total | | | | | |
| | N | Mean | N | Mean | N | Mean | N | Mean | MZ-M vs MZ-D | MZ vs DZ |
| Cholesterol | 197 | 75.7 | 62 | 70.4 | 271 | 74.3 | 78 | 75.1 | 1.60 ns | − 0.29 ns |
| Triglycerides | 195 | 31.1 | 62 | 30.4 | 269 | 31.0 | 73 | 30.4 | 0.36 ns | 0.40 ns |
| HDL-C | 114 | 28.8 | 40 | 30.5 | 163 | 29.5 | 44 | 30.6 | 0.87 ns | − 0.68 ns |
| LDL-C | 112 | 20.2 | 38 | 17.4 | 158 | 19.6 | 40 | 17.4 | 1.14 ns | 1.08 ns |

ns = nonsignificant.

**Table 2 - Within-pair mean squares (MSW) and among-pair mean squares (MSA) of serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) of MZ and DZ twin pairs**

| | MZ | | | DZ | | | F′ test for total variance | F test for genetic variance |
|---|---|---|---|---|---|---|---|---|
| | N | MSW | MSA | N | MSW | MSA | | |
| Cholesterol | 271 | 97.9 | 1012.2 | 78 | 217.4 | 703.3 | 0.83 ns | 2.22** |
| Triglycerides | 269 | 46.7 | 358.4 | 73 | 81.9 | 189.2 | 0.67 ns | 1.76** |
| HDL-C | 163 | 26.2 | 211.2 | 44 | 43.6 | 193.2 | 0.90 ns | 1.67* |
| LDL-C | 158 | 26.0 | 329.2 | 40 | 42.6 | 260.4 | 0.85 ns | 1.64* |

ns = nonsignificant; * = $P < 0.05$, ** = $P < 0.01$.

**Table 3 - Within-pair mean squares (MSW) and among-pair mean squares (MSA) of serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) of monochorionic and dichorionic MZ twin pairs**

| | MZ-M | | | DZ-D | | | F′ test for | F test for within- |
|---|---|---|---|---|---|---|---|---|
| | N | MSW | MSA | N | MSW | MSA | total variance | -pair mean square |
| Cholesterol | 197 | 87.6 | 993.0 | 62 | 140.1 | 1057.7 | 1.11 ns | 1.60 ns |
| Triglycerides | 195 | 49.3 | 302.3 | 62 | 46.2 | 361.6 | 1.16 ns | 0.94 ns |
| HDL-C | 114 | 26.2 | 196.5 | 40 | 26.4 | 239.6 | 1.19 ns | 1.01 ns |
| LDL-C | 112 | 25.3 | 303.6 | 38 | 28.2 | 354.4 | 1.16 ns | 1.11 ns |

ns = nonsignificant.

**Table 4 - Within-pair mean squares (MSW) and among-pair mean squares (MSA) of serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) adjusted for sex, gestational age and placentation of MZ and DZ twin pairs**

| | MZ | | | DZ | | | F′ test for | F test for |
|---|---|---|---|---|---|---|---|---|
| | N | MSW | MSA | N | MSW | MSA | total variance | genetic variance |
| Cholesterol | 258 | 100.4 | 940.5 | 70 | 219.3 | 561.6 | 0.75 ns | 2.18** |
| Triglycerides | 256 | 48.7 | 310.5 | 65 | 66.4 | 189.7 | 0.71 ns | 1.36* |
| HDL-C | 154 | 26.2 | 211.4 | 38 | 46.9 | 181.6 | 0.96 ns | 1.79** |
| LDL-C | 150 | 26.0 | 307.2 | 35 | 48.0 | 258.1 | 0.92 ns | 1.84** |

ns = nonsignificant; * = $P < 0.05$, ** = $P < 0.01$.

**Table 5 - Within-pair mean squares (MSW) and among-pair mean squares (MSA) of serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) adjusted for sex, gestational age and placentation of monochorionic and dichorionic MZ twin pairs**

| | MZ-M | | | DZ-D | | | F′ test for | F test for within- |
|---|---|---|---|---|---|---|---|---|
| | N | MSW | MSA | N | MSW | MSA | total variance | -pair mean square |
| Cholesterol | 196 | 87.9 | 936.9 | 61 | 141.7 | 934.1 | 1.05 ns | 1.62 ns |
| Triglycerides | 194 | 49.6 | 301.6 | 61 | 46.8 | 346.3 | 1.12 ns | 0.94 ns |
| HDL-C | 113 | 26.0 | 189.4 | 40 | 26.4 | 251.9 | 1.29 ns | 1.02 ns |
| LDL-C | 111 | 25.5 | 289.7 | 38 | 28.2 | 360.4 | 1.23 ns | 1.11 ns |

ns = nonsignificant.

**Table 6 - Unadjusted and adjusted intrapair correlation ($r_{MZ}$ and $r_{DZ}$) and heritability ($h^2$) of serum cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)**

| | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|
| | $r_{MZ}$ | $r_{DZ}$ | $h^2$ | $r_{MZ}$ | $r_{DZ}$ | $h^2$ |
| Cholesterol | 0.82 | 0.53 | 0.59 | 0.81 | 0.44 | 0.74 |
| Triglycerides | 0.77 | 0.40 | 0.75 | 0.73 | 0.48 | 0.49 |
| HDL-C | 0.78 | 0.63 | 0.30 | 0.78 | 0.59 | 0.38 |
| LDL-C | 0.84 | 0.72 | 0.25 | 0.84 | 0.69 | 0.31 |

## DISCUSSION

A significant genetic variance was observed for serum total cholesterol, triglycerides, HDL-C and LDL-C among Chinese neonate twins in this study. These findings are consistent with those of several twin studies on serum lipids [1,5,6,11,19]. In our previous study, we found a significant genetic variance for serum cholesterol and triglycerides among Chinese adolescent twins [2]. However, a basic but debatable assumption of the conventional MZ-DZ comparison method used to examine the relative importance of genetic and environmental components in the determination of a given trait is the equality of intrapair environmental correlation in MZ and DZ twins. It is essential to adjust for effects of environmental factors which may be different between cotwins of a given pair. We reported a significant genetic variance for serum cholesterol level after adjustment for dietary preference and lifestyle variables of twin individuals, but not for adjusted level of triglycerides in adolescent twins. In this study, we observed a significant genetic variance of serum total cholesterol, triglycerides, HDL-C and LDL-C in neonatal twins after adjustment for sex, gestational age and placentation.

As two neonatal twins of a pair are given birth by the same mother, their levels of serum lipids should be similar. The findings that MSWs of serum lipids were significantly smaller than MSAs in both MZ and DZ twins reflects the intrapair similarity. However, the similarity may be due to the similar intrauterine environment, genetic composition or both. As MSWs of serum lipids in MZ twins were significantly smaller than those in DZ twins, it suggests the importance of the genetic composition in the determination of these serum lipids at the perinatal stage. The finding that monochorionic and dichorionic MZ twins had similar MSWs of serum lipids suggests that the placental pattern has little effect on the similarity between MZ cotwins. This further supports the conclusion that genetic factors play an important role in the determination of serum lipids of neonates.

Further studies on the chronological changes of the similarity in serum lipids between MZ and DZ twins will improve the understanding of the development of hyperlipidemia in early childhood and clarify the relative and interactive effects of genetic and environmental components in the determination of hyperlipidemia. This will in turn help the implementation of an intervention program to reduce the adverse effect of hyperlipidemia.

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**Correspondence:** Prof. Chien-Jen Chen, Institute of Public Health, National Taiwan University College of Medicine, 1, Jen-Ai Road Section 1, Taipei 10018, Taiwan, Republic of China.