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Consistency of genetic inheritance mode and heritability patterns of triglyceride vs. high density lipoprotein cholesterol ratio in two Taiwanese family samples

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Abstract

Background: Triglyceride/HDL cholesterol ratio (TG/HDL-C) is considered as a risk factor for cardiovascular events. Genetic components were important in controlling the variation in western countries. But the mode of inheritance and family aggregation patterns were still unknown among Asian-Pacific countries. This study, based on families recruited from community and hospital, is aimed to investigate the mode of inheritance, heritability and shared environmental factors in controlling TG/HDL-C.

Results: Two populations, one from community-based families (n = 988, 894 parent-offspring and 453 sibling pairs) and the other from hospital-based families (n = 1313, 76 parent-offspring and 52 sibling pairs) were sampled. The population in hospital-based families had higher mean age values than community-based families (54.7 vs. 34.0). Logarithmic transformed TG/ HDL-C values, after adjusted by age, gender and body mass index, were for genetic analyses. Significant parent-offspring and sibling correlations were also found in both samples. The parent-offspring correlation coefficient was higher in the hospital-based families than in the community-based families. Genetic heritability was higher in community-based families (0.338 ± 0.114 , $p = 0.002$), but the common shared environmental factor was higher in hospital-based families (0.203 ± 0.042 , $p < 0.001$). Commingling analyses showed that more than one-component distribution models were the best-fit models to explain the variance in both populations. Complex segregation analysis by regressive models revealed that in both samples the best-fit model of TG/HDL-C was the model of environmental effects plus familial correlation, in which significant parent-offspring and sibling correlations were demonstrated. Models of major gene effects were rejected in both samples.

Conclusion: Variations of TG/HDL-C in the normal ranges were likely to be influenced by multiple factors, including environmental and genetic components. Higher genetic factors were proved in younger community-based families than in older hospital-based families.

Background

Triglyceride and high density lipoprotein (HDL) cholesterol are important components in insulin resistance syndrome and are considered as risk factors for cardiovascular diseases [1–4]. Atherogenic dyslipidemia, including hypertriglyceridemia and low HDL cholesterol levels are the targets for primary prevention by lifestyle intervention in Adult Treat Panel III guidelines [5]. The ratio of triglyceride vs. HDL cholesterol (TG/HDL-C) can be considered a single phenotype trait for cardiovascular risk [6,7]. TG/HDL-C is a simple, readily calculated measurement about atherogenic plasma lipoproteins, and related to lipoprotein particle sizes [8]. Shared gene and environmental factors were reported to influence HDL cholesterol and triglyceride levels simultaneously [9]. Also, pleiotropic effects on low HDL cholesterol and high triglyceride were evident among families [7,9,10]. Extensive genomic scanning study on this combined trait was also reported to linkage with chromosome 7 [11].

Many factors were associated with HDL cholesterol and triglyceride levels, such as age, gender, lifestyle activities, and obesity. But the proportion of TG/HDL-C variances explained by known factors was small. Genetic factors was considered as a significant role in determining serum levels [12]. Even linkage results of TG/HDL-C were reported in Framingham families [11], there were inconsistent study results about the mode of inheritance of TG/HDL-C, especially for HDL cholesterol phenotype. The reasons of inconsistency were due to different ascertainment strategies and study population characteristics [13–21]. In brief, most studies on the mode of inheritance of HDL cholesterol demonstrated major gene effects. Amos et al. showed major gene effect existed in a multiple generation pedigree family [13]. Also, Borecki et al demonstrated that HDL cholesterol was controlled by the major gene effect [22]. The allele frequency of autonomic recessive gene in the Jerusalem families was 0.06 [23]. Coresh et al. [17] proved one autosomal dominant gene with allele frequency of 0.25. Mahaney et al. also demonstrated in Mexican American population, HDL cholesterol was controlled by a major dominant recessive gene [20]. In the other side, Cupples et al. cannot demonstrate the major gene effect in Berkeley families [18]. Moll et al. [24] and Prenger et al. [21] cannot define the major gene effect in HDL cholesterol levels among high risk probands of coronary heart disease. The controversial results about the mode of inheritance of HDL cholesterol implied that complex pathogenesis mechanisms existed. Furthermore, genetic factors controlling TG/HDL-C ratio were more complicated. Although several disorders of dyslipidemia were identified by candidate-gene studies and positional cloning experiments, there remain many problems still remain to be resolved.

Different mechanisms exist between special monogenic hyperlipidemia and general population. For example, more than 600 low density lipoprotein (LDL) receptor mutations underlie familial hypercholesterolemia type, but no single LDL receptor single nucleotide polymorphism has been associated with variation of plasma lipoproteins in the general population [12]. Also, it is still unclear whether common genetic variant can help to predict risk of CHD in general population. So we should define homogeneous and low-risk general population samples to elucidate the genetic roles in controlling TG/HDL-C. This study, based on two samples, one from rather young families in community-based population, another from older adult subjects undertaking health screening in hospital-based population, was designed to estimate the roles of genetic components and the mode of inheritance in TG/HDL-C among Taiwanese.

Results

Hospital-based family members had higher mean age values than community-based families (34.0 vs. 54.7, respectively, Table 1). Also, there were higher total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol and lower TG/HDL-C values in hospital-based families than those in community based families, with smaller standard deviation values (Table 1). High values of skewness and kurtosis were found in both of triglyceride and TG/HDL-C ratio, and the logarithm transformed TG/HDL-C had near zero values of skewness and kurtosis, indicating compatible with normal distribution. We adjusted logarithm transformed TG/HDL-C in linear model by age, gender and body mass index, and residual values were for further genetic analyses. The explained variability of TG/HDL-C by gender, age, interaction of age and gender, and body mass index were 24.1% in the community-based sample and 19.4% in hospital-based one. Age had significant effects only among younger community families, but not among older hospital-based families. Body mass index had significant positive effects on TG/HDL-C in both samples (Table 2).

The commingling distributions of two populations were compatible with more than one-component normal distribution (Table 3). In younger community-based families, the best-fit model of explaining TG/HDL-C variance was the 2-component model, whose component means, variances, and proportions were (-0.256, 0.754), (0.609, 1.389), and (74.7%, 25.3%), respectively. The χ^2 for comparing the 2-component with 1-component distribution was 6.46 (degree of freedom [df] = 3, $p = 0.091$). For hospital-based families, the best-fit model was the 3-component model ($\chi^2 = 3.27$, $df = 3$, $p = 0.353$, compared with 4-component model). We found in older hospital-based families, there were wider range of mean estimates and

Table 1: Various lipid profiles in the two study population samples

	Community-based (N= 988)				Hospital-based (N= 1313)			
	Mean	SD	Skewness	Kurtosis	Mean	SD	Skewness	Kurtosis
Age (years)	34.0	20.1	0.80	-0.47	54.7	11.5	-0.27	0.14
Total cholesterol (mg/dL)	182.4	39.7	0.74	2.15	194.4	36.2	0.25	1.37
Triglyceride (mg/dL)	117.5	93.3	3.61	18.23	130.4	79.3	2.26	8.05
HDL cholesterol (mg/dL)	42.9	10.5	0.53	0.34	52.8	14.6	0.81	0.88
LDL cholesterol (mg/dL)	103.0	41.6	0.53	0.41	116.2	31.2	0.55	0.55
Triglyceride vs. HDL ratio	3.15	3.53	5.45	48.53	2.86	2.37	2.55	9.30
Logarithm of triglyceride vs. HDL-C ratio	0.85	0.70	0.76	0.89	0.80	0.70	0.22	-0.19

Abbreviations: SD: standard deviation, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol

Table 2: Estimated parameter, standard error and explained variability in the linear regression models for logarithm transformed TG/HDL ratio values in two samples.

Variables	Community based			Hospital based		
	Estimated parameter	Standard error	P	Estimated parameter	Standard error	P
Intercept	-0.710	0.144	<.0001	0.071	0.403	0.860
Gender (women/men)	-0.040	0.068	0.5529	-0.876	0.173	<.0001
Age	0.022	0.005	<.0001	-0.014	0.011	0.212
Gender*Age	-0.004	0.002	0.038	0.012	0.003	<.0001
Body mass index	0.056	0.005	<.0001	0.076	0.006	<.0001
R square	24.1%			19.4%		

Table 3: Commingling analysis of adjusted log TG/HDL ratio in two population samples.

I. Community-based:													
Components	Component means			Component variances			Component proportions (%)				-2ln(l)+c	χ^2	P
	μ_1	μ_2	μ_3	σ^2_1	σ^2_2	σ^2_3	π_1	π_2	π_3				
1	0.000			0.999			1.000				3534.99		
2	-0.256	0.754		0.609	1.389		0.747	0.253			3470.74	64.25	
3	-0.576	0.091	2.466	0.296	0.884	0.824	0.237	0.735	0.028		3464.28	6.46	

II. Hospital-based															
Components	Component means				Component variances				Component proportions (%)				-2ln(l) + c	χ^2	P
	μ_1	μ_2	μ_3	μ_4	σ^2_1	σ^2_2	σ^2_3	σ^2_4	π_1	π_2	π_3	π_4			
1	0				0.999				1				3725.13		
2	-0.514	0.508			0.578	0.897			0.497	0.503			3708.05	17.08	0.001
3	-0.682	0.341	2.471		0.499	0.806	0.016		0.358	0.630	0.012		3697.61	10.44	0.015
4	-1.510	-0.275	1.043	2.359	0.258	0.529	0.218	0.104	0.048	0.732	0.186	0.034	3694.35	3.27	0.353

Table 4: Familial correlation coefficients in residual log TG/HDL values in the two populations, after adjusting with age and gender effects.

	Community-based		Hospital-based		P¶
	Numbers of Pair	Estimated coefficient	Numbers of Pair	Estimated coefficient	
Spouse	156	0.044†	530	0.142***	0.143
Parental-Offspring	894	0.215***	76	0.420***	0.046
Sibling	453	0.225***	52	0.276*	0.367

†: $P > 0.05$, *: $0.01 < P < 0.05$, ***: $P < 0.001$ to test if the estimated coefficients were different from zero ¶: the significant level of testing the hypothesis if two estimated correlation coefficients were the same

lower proportions of high mean components than the younger community-based families.

We found that all correlation coefficient values in hospital-based relative pairs were higher than those in community, and the parent-offspring coefficient in hospital was significantly higher than one in community (0.420 vs. 0.215, $P = 0.046$) (Table 4). The range of parent-offspring and sibling correlations were 0.22 to 0.42, highest in hospital-based families. Also, in the hospital families, the spouse correlation was 0.142, which implied possible assortive mating or common shared household factors in older hospital-based families. But in the community-based sample, the spouse correlation was only 0.044, without significant difference from zero. To explore the possible effects on examination dates, we re-arranged the dataset according to examination dates, and found all spouses in the hospital-based sample were recruited in the same day, and almost spouses (90%) in the community-based sample were recruited within two weeks. The spouse correlations in the remaining different exam date were similar as one in the same date (0.044), so the examination dates did not affect apparently spouse correlation values.

The heritability and common shared household estimates were presented in Table 5. After incorporating common household effects in the model, the heritability was still significant in younger community-based population (0.338 ± 0.114 , $P = 0.002$), but did not reach significant level in older hospital-based families (0.213 ± 0.164 , $P = 0.106$). The estimated common shared household effect was significant only in the hospital-based families (0.203 ± 0.042 , $P < 0.001$).

The estimated parameters and corresponding models by complex segregation analyses of TG/HDL-C in both populations were presented in Table 6. The results were consistent in both populations. Comparing with the general model, we found all p values were less than 0.05, and AIC values were lowest in the general models (1276.03 in

Table 5: Estimated heritability and common shared household effects of logarithm TG/HDL ratio in two study samples

	Community-based	Hospital-based
H ²	0.338	0.213
Standard error	0.114	0.164
P value	0.002	0.106
C ²	0.090	0.203
Standard error	0.065	0.042
P value	0.081	<0.001

Heritability estimates considering common household effects, Abbreviation: C², common household effects; H², heritability

community and 2645.11 in hospital). If excluding the general model, we found that in both populations the environmental plus familial correlation model had the lowest AIC values (1278.71 in community and 2651.51 in hospital). The major gene effects model had higher AIC values than the environmental model. So we concluded that the environmental model, compared with the major gene effects model, was the best-fit model in controlling TG/HDL-C. The estimated spouse correlation value was higher in hospital-based families than that in community (0.292 vs. 0.028), and the parent-offspring and sibling correlations were both high to 0.6.

Discussion

This study clearly demonstrated that consistency of the mode of inheritance and genetic components of TG/HDL-C from two different populations in Taiwan. We found that the environmental model, compared with major gene effects model, was the more parsimonious one to explain the mode of inheritance of TG/HDL-C. There were relative importance of genetic heritability and shared household effects in both populations. In older hospital-based families, shared common household effects and high spouse correlation were found significantly, but in younger community-based families, genetic heritability seemed to play

Table 6: Logarithm triglyceride vs. HDL cholesterol ratio: Class D regressive models, conditional on proband phenotypes

I. Community-based:												
Model	Sporadic		Pure familial correlation, i.e. polygenic		Environmental + familial correlation		Pure major gene (Mendel)		Mendel + familial correlation		Unrestricted, general	
	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.
q_A	[1]		[1]		0.190	0.035	0.251	0.035	0.264	0.045	0.203	0.049
τ_{AA}	-		-		= q_A		[1]		[1]		0.266	0.144
τ_{AB}	-		-		= q_A		[0.5]		[0.5]		0.431	0.125
τ_{BB}	-		-		= q_A		[0]		[0]		0.044	0.073
μ_{AA}	0.864	0.024	0.903	0.043	2.450	0.170	2.363	0.162	2.316	0.196	2.514	0.227
μ_{AB}	= μ_{AA}		= μ_{AA}		1.281	0.082	1.149	0.074	0.971	0.165	1.326	0.130
μ_{BB}	= μ_{AA}		= μ_{AA}		0.555	0.057	0.560	0.035	0.651	0.095	0.554	0.075
σ^2	0.400	0.021	0.465	0.038	0.239	0.029	0.209	0.016	0.276	0.040	0.202	0.027
ρ_{MF}	[0]		0.041	0.071	0.028	0.125	-0.026	0.106	0.062	0.106	0.058	0.138
ρ_{MO}	[0]		0.401	0.067	0.555	0.114	[0]		0.284	0.077	0.286	0.318
ρ_{FO}	[0]		0.184	0.068	0.394	0.101	[0]		0.150	0.134	0.212	0.154
ρ_{SS}	[0]		0.513	0.067	0.643	0.084	[0]		0.332	0.085	0.457	0.257
#	2		6		9		6		9		12	
-2ln(L)	1372.22		1308.95		1260.71		1279.92		1266.27		1252.03	
χ^2	120.19		56.92		8.68		27.89		14.24			
Degree of freedom	10		6		3		6		3			
P value	0.000		0.000		0.034		0.000		0.003		Baseline	
AIC	1376.22		1320.95		1278.71		1291.92		1284.27		1276.03	
II. Hospital based,												
Model	Sporadic		Pure familial correlation, i.e. polygenic		Environmental + familial correlation		Pure major gene (Mendel)		Mendel + familial correlation		Unrestricted, general	
	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.	Parameter	S.E.
q_A	[1]		[1]		0.232	0.060	0.368	0.036	0.290	0.028	0.369	0.036
τ_{AA}	-		-		= q_A		[1]		[1]		0.598	0.277
τ_{AB}	-		-		= q_A		[0.5]		[0.5]		0.181	0.097
τ_{BB}	-		-		= q_A		[0]		[0]		0.756	0.099
μ_{AA}	0.801	0.019	0.801	0.020	1.997	0.125	1.751	0.077	1.953	0.098	1.727	0.062
μ_{AB}	= μ_{AA}		= μ_{AA}		1.215	0.134	0.396	0.016	0.289	0.040	0.396	0.014
μ_{BB}	= μ_{AA}		= μ_{AA}		0.443	0.076	0.945	0.029	1.036	0.032	0.944	0.020
σ^2	0.459	0.018	0.458	0.018	0.246	0.031	0.259	0.018	0.211	0.023	0.251	0.018
ρ_{MF}	[0]		0.160	0.043	0.292	0.081	0.247	0.001	[0]		0.247	0.001
ρ_{MO}	[0]		0.320	0.072	0.579	0.090	0.735	0.000	[0]		0.735	0.000
ρ_{FO}												
ρ_{SS}												
#	2		4		7		7		5		10	
-2ln(L)	2690.30		2662.03		2637.51		2637.78		2665.49		2625.11	
Degree of freedom	8		6		3		3		5			
P	0.000		0.000		0.000		0.006		0.005		Baseline	
AIC	2694.3		2670.03		2651.51		2651.78		2675.49		2645.11	

Abbreviation: #, number of parameters; SEM, standard error of mean; q_A , gene frequency; τ_{AA} , τ_{AB} , τ_{BB} , transmission probability; μ_{AA} , μ_{AB} , μ_{BB} , genotype means; σ^2 , variance; ρ_{MF} , ρ_{MO} , ρ_{FO} , ρ_{SS} , correlation coefficients among spouse, mother-offspring, father-offspring and sibling pairs; #, number of parameters; ln(L), logarithm of likelihood; AIC, Akaike information criteria; P, significance level compared with the unrestricted general model.

more significant roles in TG/HDL-C variations. Spouse correlations showed an environmental accent in pairs who spent probably longer time together.

There were rather healthy subjects in both samples. We have excluded cases with history of myocardial infarction and stroke, and extreme high levels of triglyceride in both samples. So, the results are particularly relevant for a population at low risk for atherosclerosis. Our findings were consistent with those of previous familial correlation and commingling studies which demonstrated that more than one component was needed to explain the distribution of HDL cholesterol levels [25]. The finding of multiple distributions is compatible with a major gene hypothesis; however, commingling may also arise through other causes. Thus, we must further apply complex segregation analysis to determine whether these major effects segregated in families according to Mendelian expectations.

In the complex segregation analyses results, we cannot define the major gene effects in controlling TG/HDL-C. The results were compatible with previous high risk population studies [18,19]. The reason is following. First, age-differential gene effect might be responsible for TG/HDL-C variance in different populations. Second, the trait can be influenced by various environmental and lifestyle risk factors. For examples, physical activity and exercise have proved to effect on triglyceride and HDL cholesterol levels, and not included in the analyses [26,27]. Third, there are gene-gene and gene environmental interaction that cannot be resolved by segregation analyses. Fortunately, even segregation analysis is assumed as one-locus model, the power of detecting major gene in multiple loci model is still significantly high [28,29]. Finally, the characteristics of study population in Taiwanese, a low risk of coronary heart disease, might have different patterns in risk factor profiles [30]. Although one gene locus was identified to control TG/HDL-C trait in a genome-wide scan in Framingham study [11], their population seem to be younger than our hospital-based families. Thus, lack of a major gene in the population, as was the case in this study, may not exclude the possibility that there are major genes that will influence TG/HDL-C levels in general population.

Especially, the age distribution differed much in these both study populations. Older hospital-based families had higher lipid levels and lesser standard deviation of lipid levels, such as cholesterol, triglyceride and lipoproteins, than younger community-based families. The commingling results also implied the same evidences with wider means and components estimations in the hospital-based sample than the community-based one. Further, we test if the distributions of logarithm TG/HDL-C levels of two samples were different. We found the sig-

nificance level of the Student *t* test statistics was 0.05, just rejecting the homogenous of two sample means. So we consider that there existed heterogeneity between two samples. The possible explanations of heterogeneity between two samples were following. The hospital-based participants were older than the community-based subjects and the lipid profiles were higher in hospital group. Poor lifestyle patterns, such as high fat diet and physical inactivity, might affect lipid levels greater in older than in younger persons. The genetic heritability was significant only in younger community-based families, but the shared household effects and spouse correlation were significant only in older hospital-based population. This finding implied that common household factors might play important roles in TG/HDL-C values in older age [31–34]. According, family-based intervention programs, such as dietary modification and exercise promotion, are important and suitable for dyslipidemia intervention [35,36].

The estimates of component frequency in commingling analyses were different from the environmental factor allele frequencies. The possible explanation is due to different parameter assumptions in both analyses. We still can use the estimated parameters from commingling components as initial values for segregation analysis [37].

It remains a difficult task to dissect the genetic control of TG/HDL-C values despite of many candidate genes and genome-wide linkage analyses results [11,38–42]. The reasons were due to quantitative estimation of heritability values vary due to inter-generational difference or age effects, with relatively low genetic heritability in older adult families. Also, the population heterogeneity and phenocopy are also difficult problems to resolve. Anyway, in this study based on two different populations, we consider the results can extend to general adult Taiwanese population and provide clues for proposing prevention strategy for dyslipidemia.

The limitation of this study was two-folds. First, there were a disproportional low number of sibling pairs in hospital-based families. We can still find comparably significant sibling correlations in both samples, and it might be due to significant genetic components in TG/HDL-C. Second, complex mathematic algorithms in segregation analyses made researchers difficult to explain the results [42]. To incorporate genotype markers would make the results more convincing.

Conclusions

Consistency in mode of inheritance of TG/HDL-C by environmental factors and age-differential genetic heritability were clearly defined in two Taiwanese populations.

Methods

Subjects

There were two samples recruited into the study. One is from community-based subjects. It started in 1997 and was designed to recruit adolescent probands from students in the only junior high school in the community. At first, a total of 1063 students (response rate 94.6%) agreed to participate in a general health check-up after informed consent was obtained. They underwent examinations for anthropometric measures, blood pressure, and lipid profiles. The selected youths were stratified into two groups on the basis of seven measures, including total cholesterol, triglyceride, LDL cholesterol, body mass index, systolic pressure, diastolic pressure, and HDL cholesterol. Probands were then selected through stratified random sampling ($n = 368$). After obtaining informed consent from probands' family members, the same measures were performed for each family member. Only first-degree relatives were included for this genetic study. Total 988 subjects were included.

Another population was from persons who undertook health-screening examination in one tertiary hospital. We collected the subjects from the family pairs, such as spouse, parent-offspring, and sibling relatives when they came to hospital at the same time for health examination purpose. Every subject filled out one questionnaire and received physical examination when he/she admitted into the hospital. Detailed medical history, smoking and drinking history were taken. Also, family history of parental medical diseases was also collected. Physical examination and 12-lead electrocardiogram were performed concurrently. We also excluded significant cardiovascular morbidity, such as coronary heart disease and stroke history in our study population. The subjects treated with cholesterol-lowering agents were also excluded from our analyses. From Aug 1998 to Sep, 1999, total 4,331 subjects completed the health examination. Total 1,313 subjects were included into this family study due to concomitant family member involved in the health examination.

Laboratory tests

Blood sample was collected in each participant at the fasting status at least 12 hours. Serum total cholesterol levels were measured using the CHOD-PAP method (Boehringer Mannheim, Germany). HDL-C was measured following precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid and magnesium ions (Boehringer Mannheim, Germany) [43]. Triglyceride concentrations were measured by the GPO-DAOS method (Wako Co., Japan). All of the lipids mentioned above were measured using a Hitachi 7450 automated analyzer (Hitachi, Japan). LDL-C concentrations were calculated using the Friedewald formula [44]. All the measures of

both samples were carried out in the single hospital. The coefficient of variation was 5%.

Statistical Analyses

All lipid profiles were described by their mean, variance, skewness and kurtosis. Because of skewed distribution of shifting to right in the triglyceride and TG/HDL-C values, natural logarithm transformation was performed to get normalized distribution. Linear regression model was used to get the residual lipid values, after adjusting with age, gender, interaction of age and gender, body mass index effects, and the residual values plus sample means were used for further genetic analyses. Also, we excluded the cases of serum triglyceride higher than 400 mg/dL to exclude extreme outliers in our study population.

Commingle analysis, familial correlation coefficients and heritability analyses

Commingle analysis of various lipid profiles was performed using the ADMIX program [45] to test whether the data were best described by one, two, or more component distributions. The parameters for each component's mean, variance, and proportion were estimated by the maximum likelihood method. Hypothesis testing for nested models was carried out with the likelihood ratio test. The correlations of various lipid profiles between spouse, parent-offspring, and siblings were estimated by using the FCOR program in SAGE [46]. We tested if the correlation coefficients were different from zero and tested if the two family coefficients between two samples by the methods of Snedecor and Cochran [47]. To estimating the shared environmental effects by inclusion of household effects, we used the variance component models to evaluate the heritability and common shared environmental factors, implemented in SOLAR software [48].

Complex Segregation Analysis

Segregation analyses of HDL-C and TG/HDL-C were conducted using regressive models as implemented in the REGC program in SAGE [46]. These models assume that variation of HDL-C and TG/HDL-C concentration among family members is the result of a major gene effect, with the residual variation reflecting both familial correlations and individual variation. The presence of a major gene is assessed by allowing two factors or alleles (A and B) at a single locus, resulting in three 'ousiotypes' (AA, AB, BB) in individuals. The means of HDL-C and TG/HDL-C for each ousiotype is denoted μ_{AA} , μ_{AB} , μ_{BB} , with one common variance of σ^2 . The frequencies of allele A and B are denoted q_A and $(1 - q_A)$, respectively. The distribution of types in the population is assumed to be in Hardy-Weinberg equilibrium. Individuals of each type are assumed to transmit allele A to their offspring with transmission probabilities τ_{AA} , τ_{AB} and τ_{BB} , respectively. Residual familial resemblance not explained by this major locus is

modeled by familial correlations. The correlation between spouses, parent and offspring, mother and offspring, father and offspring, and between siblings, are denoted ρ_{MF} , ρ_{PO} , ρ_{MO} , ρ_{FO} , and ρ_{SS} , respectively. For this study, we adopted class D regressive models, in which residual sib-sib correlations are equal among all sibs of common parentage and can be due to any cause. In the hospital-based family population, there were more numbers of spouse than parental-offspring pairs, so initially we tested if familial correlation numbers can be reduced from four (ρ_{MF} , ρ_{PO} , ρ_{MO} , and ρ_{SS}) to two (ρ_{MF} , $\rho_{PO} = \rho_{MO} = \rho_{FO} = \rho_{SS}$). If ρ_{PO} is held equal to ρ_{SS} , these models have been shown to be mathematically and numerically equivalent to the conventional mixed model of inheritance in nuclear families [49]. In community-based families, we still adopt 4-parameter familial correlation model. The analyses started with fitting a general model, in which all parameters were allowed to be estimated. Then we compared the general model with various submodels in which certain parameters were restricted to specific values. Under a Mendelian model, the transmission probabilities, i.e., τ_{AA} , τ_{AB} and τ_{BB} , were held equal to Mendelian expectations of 1, 0.5, and 0. A nontransmitted environmental effect model predicts that the probability that an individual has one outisotype or another is independent of both the person's generation and the outisotypes of his/her parents. For the environmental model in this study, each of the transmission probabilities is taken to be equal to the factor frequency, i.e., $\tau_{AA} = \tau_{AB} = \tau_{BB} = q_A$. Both the Mendelian and environmental models can allow for residual familial correlations. A pure polygenic model assumes no major gene effect, so gene frequency and transmission probabilities are all fixed to one. The fit of hierarchical models is compared with the likelihood ratio test, calculated as -2 of the difference between the \ln likelihood of the models being compared. The likelihood ratio value follows a chi-square distribution, with degrees of freedom equal to the difference between the models in the number of parameters estimated. Among nonhierarchical models, the most parsimonious model is that with the lowest values of Akaike's information criterion ($AIC = -2 \ln \text{likelihood} + 2 [\text{number of estimated parameters}]$) [50].

Authors' contributions

KLC carried out the data collection, statistical analyses, participated in the study design and processing data. YTL participated in the design of the study and supervised the ideas developing in hypothesis generation. TCS & CYJ performed the data collection and participated in the field work. HCH performed the laboratory measurement in lipid levels and in charge of quality control. All authors read and approved the final manuscript.

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