行政院國家科學委員會專題研究計畫成果報告
高三酸甘油酯／低高密度脂蛋白膽固醇之家族遺傳研究 (I)
Family genetic studies of hypertriglyceridemia and low HDL-cholesterol (I)

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一、中文摘要

背景及目的：三酸甘油酯／高密度脂蛋白膽固醇(TG／HDL-C)是胰島素抵抗性症候群的主要成份，同時也是動脈硬化重要的危險因子。而在台灣成人族群中 TG／HDL-C 的遺傳模式及其家族聚集的情形並沒有很多報告。本研究即是針對 TG／HDL-C 性狀探討家族相關性、混合分佈及遺傳模式。

材料與方法：從金山社區國中共收集 295 個家族成員參加此計畫。經調整年齡、性別、體質比及腰圍之後，經對數轉換的 TG／HDL-C 值取得其殘差後作進一步的遺傳分析。

結果：我們發現家族成員中，親子之間及手足之間存在很高的相關係數(分別是 0.21 及 0.23)。而混合分析顯示兩個常態分佈的模型是最佳的解釋模型，表示可能有基因的成份存在，其遺傳率的估計高達到 0.357 ± 0.052 (P<0.0001) 。利用迴歸模型的分離分析結果顯示 TG／HDL-C 的遺傳模式是多重基因背景，併有環境的因素，同時有很高的親子及手足相關係數。而主要基因模型並沒有辦法解釋其變異程度。

結論：在一般人口中的 TG／HDL-C 值的變動是由眾多因素決定，進一步的候選基因標識分析，特別是非參數性連鎖分析則其必要性。

關鍵詞：三酸甘油酯，高密度脂蛋白膽固醇，遺傳流行病學研究，遺傳模式

Abstract

Background & Objectives: Triglyceride/HDL cholesterol ratio (TG/HDL-C) is the major component of insulin resistance syndrome and considered as a risk factor for atherosclerosis. The mode of inheritance and associated family aggregation were still unknown in Taiwanese adult population. This study is aimed to investigate the familial correlation, commingling patterns and mode of inheritance of TG/HDL-C.

Materials & Methods: Total 295 families of adolescents systematically ascertained from the junior high school students in a rural community were recruited into this study. ~~Probands, s~~After adjustment for gender, age, body mass index, waist circumstance, residual values of logarithm transformed TG/HDL-C was subjected to subsequent analyses.

Results: Significant parent-offspring and siblings correlations were found (0.21 and 0.23 respectively). Commingling analyses indicated that a two-component distribution model was best model to account for log TG/HDL-C variation. The estimated heritability was up to 0.357 ± .052 (p <. 00001). Segregation analysis using regressive models revealed that the best-fit model of TG/HDL-C was a model of environmental effect plus familial correlation, in which a significant parent-offspring and siblings correlation existed. Models containing major gene effect were rejected.

Conclusion: These results suggest that variations of TG/HDL-C in the normal range, especially during adolescence, are likely to be influenced by multiple factors, including significant heritability components. Although one major gene effect could not be identified, further non-parametric linkage analysis with

known candidate genetic markers is still feasible to detect the genetic components controlling TG/HDL-C variations.

Keywords：triglyceride, HDL-cholesterol, familial correlation, mode of inheritance

二、緣由與目的

The ratio of triglyceride vs. high density lipoprotein cholesterol (TG/HDL-C) were important components in insulin resistance syndrome and considered as factors for cardiovascular diseases.(1-3), and suitable for an indicator for epidemiological and genetic studies.(4) They also can be considered as a single phenotype trait as cardiovascular risk.(5-7)

Many factors have reported to be associated with concentration of HDL-C and triglyceride levels, such as age, gender, lifestyle activities, and obesity. But the proportions of variance of TG/HDL-C explained by known factors were small. Genetic factors play a significant role in determining serum HDL-C and triglyceride levels. Reports on HDL-C or TG/HDL-C showed different patterns about inheritance modes, due to different ascertainment strategies and population characteristics.(8-14) Genetic heritability estimates of HDL and TG were reported to around 0.40~0.65 in twin studies, but the results of the mode of inheritance were controversial. In review of literature, most of studies on mode of inheritance of HDL cholesterol is major gene effects. Amos et al. result showed major gene effect existed in a multiple generation pedigree family(8). Also, Borecki et al demonstrated (15) HDL-C is affected by major gene effect. In the Jerusalem families, the major recessive gene frequency was 0.06(16). In Utah families, Williams et al. (1993) demonstrated major gene effect also, and Coresh et al. (17) proved one autosomal dominant gene, with frequency of 0.25, and explain 34% variation of HDL3-C, but only 9% HDL-C variation. Mahaney et al. also demonstrated in Mexican American, HDL is controlled by a major dominant recessive gene in the San Antonia Family Heart Study(13). But Cupples et al. can not demonstrate the major gene effect in Berkeley data (11). Moll et al. also cannot define the major gene effect in high risk probands of coronary heart disease (18). Prenger et al. (14) reported families based on probands receiving cardiac catheterization also no major gene effect in HDL concentration. This study, based on healthy adult subjects who undertook health examination, was designed to collect family pairs in hospital-based population to estimate the roles of genetic components and the mode of inheritance of TG/HDL-C.

三、結果與討論

Descriptive analysis: There were 156 spouse, 894 parental-offspring, and 453 sibling pairs in the study population. There existed significantly different mean values among three generations, even adjusting for age, gender, body mass index and waist circumstance. After adjusting above important factors, the residual logarithm transformed triglyceride and TG/HDL-C values were used for further genetic analyses.

Commingling analysis: The two component distribution models are the best-fit model to explain the distribution of TG/HDL-C. The component means, variances, and proportions for the 2-component distribution model were (-0.256, 0.754), (0.609, 1.389), and (74.7%, 25.3%), respectively. The χ^2 for comparing the 3-component with 2-component distribution was 6.46 (degree of freedom [df] =3, p=0.091), while that for comparing the 2-component with 1-component distribution was 64.25 (df=3, p=0.001). The data supported genetic proportion controlling high TG/HDL-C concentration.

Familial correlation coefficients and estimated heritability: We found that there were very low spouse correlations (0.044), and high parent-offspring and sibling correlations (0.21 and 0.23, respectively. Because there were higher correlation in parent-offspring and sibling pairs in TG/HDL-C traits, major gene hypothesis; however, commingling and familial correlation may also arise through other causes. Thus, segregation analysis was used to determine whether these major effects segregated in families according to Mendelian expectations. The estimated

heritability by SOLAR software was up to 0.357 ± .052 (p <. 00001), with proportion of variance explained by final covariates was 19.44%.

Segregation analysis: We compared several models, including the sporadic, pure polygenes, pure major genes, mixed environmental, mixed major gene effects, dominant and recessive major gene effect models, with the general model. The χ^2 values were less than 0.05 in several models, including the sporadic, mixed major gene, dominant and recessive models. If we choose the best model by AIC criteria, the environmental plus polygenes model is the best model than other model (AIC=1278.71). So we concluded that there exists polygenes components and environmental factors effect controlling TG/HDL-C concentrations.

四、計畫成果自評

This study clearly demonstrated that there were familial association and commingling components in TG/HDL-C concentrations among adult volunteers receiving health examination. Moreover, we found that significant heritability values in TG/HDL-C. There were rather healthy adult in this study population. We have excluded significant cardiovascular events and extreme high levels of triglyceride. So, the results are particularly relevant for a population at low risk for atherosclerosis. Our results 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 TG/HDL-C. In this study, we can not clearly demonstrate the major gene effect in TG/HDL-C trait. One reason is that more complex mechanism involved in the controlling TG/HDL-C level. More environmental factors should be taken into consideration. Another possible reason for our failure to detect a major gene effect is the characteristics of study population. Although one gene locus was identified to control TG/HDL-C trait in a genome-wide scan in Framingham study, their population seem to be younger than our study population. Thus, lack of a major gene in adolescence, 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 adulthood. Genes involved in apolipoprotein and reverse cholesterol transport metabolism are important candidate genes to control TG/HDL-C concentrations. Also, lipase and enzymes involved in bile acid synthetic pathways and insulin metabolism should be taken into consideration. Further investigation by candidate gene and genome-wide scan should be investigated.

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附件：封面格式

行政院國家科學委員會補助專題研究計畫成果報告

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※ 高三酸甘油酯／低高密度脂蛋白 ※

※ 膽 固 醇 之 家 族 遺 傳 研 究 **(I)** ※

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共同主持人：許 秀 卿

計畫參與人員：李 源 德

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執行單位：臺大醫院

中　華　民　國　91 年　5 月　23 日