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Research paper

Familial aggregation and linkage analysis with covariates for metabolic syndrome risk factors

Parisa Naseri[a,1], Soheila Khodakarim[b,1], Kamran Guity[c], Maryam S. Daneshpour[c,*]

[a] Department of Biostatistics, School of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Epidemiology, School of Public Health, School of Paramedical Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Cellular and Molecular Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: Mechanisms of metabolic syndrome (MetS) causation are complex, genetic and environmental factors are important factors for the pathogenesis of MetS In this study, we aimed to evaluate familial and genetic influences on metabolic syndrome risk factor and also assess association between FTO (rs1558902 and rs7202116) and *CETP*(rs1864163) genes' single nucleotide polymorphisms (SNP) with low HDL_C in the Tehran Lipid and Glucose Study (TLGS).

Materials and methods: The design was a cross-sectional study of 1776 members of 227 randomly-ascertained families. Selected families contained at least one affected metabolic syndrome and at least two members of the family had suffered a loss of HDL_C according to ATP III criteria.

In this study, after confirming the familial aggregation with intra-trait correlation coefficients (ICC) of Metabolic syndrome (MetS) and the quantitative lipid traits, the genetic linkage analysis of HDL_C was performed using conditional logistic method with adjusted sex and age.

Results: The results of the aggregation analysis revealed a higher correlation between siblings than between parent-offspring pairs representing the role of genetic factors in MetS. In addition, the conditional logistic model with covariates showed that the linkage results between HDL_C and three marker, rs1558902, rs7202116 and rs1864163 were significant.

Conclusions: In summary, a high risk of MetS was found in siblings confirming the genetic influences of metabolic syndrome risk factor. Moreover, the power to detect linkage increases in the one parameter conditional logistic model regarding the use of age and sex as covariates.

1. Introduction

Metabolic syndrome (MetS), a complex disorder with high socio-economic costs, is considered a worldwide epidemic. MetS factors (hyperglycemia, hypertension, dyslipidemia, and abdominal obesity) increase the risk of cardiovascular diseases (CVD), diabetes mellitus type 2 (DMT2), and cancer.

The prevalence of MetS is increasing worldwide. 23% of the population have this syndrome in Western countries (Keller and Lemberg, 2003). According to the International Diabetes Federation criteria, one in four adults in the world suffers from MetS. In subjects with MetS, the risk of death, stroke and heart attacks is two to three times more compared to individuals without this syndrome. Also, the prevalence of this disorder is increasing in children and young adults globally (Dalvand et al., 2017).

The prevalence of the MetS varies among different ethnic groups (Meigs et al., 2003; Delavari et al., 2009; Azizi et al., 2003a), it is 24% and 42% in males and females from the Tehranian population, respectively (Azizi et al., 2003b). Although the underlying pathway is not fully clear; however, genetic and environmental factors are the most serious factors for the pathogenesis of MetS.

Because the family displays an interaction role between genetic and

Abbreviations: MetS, metabolic syndrome; CVD, cardiovascular diseases; ICC, intraclass correlation coefficient; TLGS, Tehran Lipid and Glucose Study; IBD, identity-by-descent; SNP, single nucleotide polymorphisms; ARP, Affected Relative pair; PON1, paraoxonase 1; LCAT, lecithincholesterol acyltransferase; CETP, cholesterylester transfer protein; PLTP, phospholipid transfer protein

* Corresponding author at: Cellular and Molecular Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, PO Box 19195-4763, Iran.
E-mail address: daneshpour@sbmu.ac.ir (M.S. Daneshpour).

[1] The second first author: Parisa Naseri and Soheila Khodakarim *contributed equally* to this manuscript. Parisa Naseri and Soheila Khodakarim are the first author and the second first author, respectively.

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environmental factors, so it is one of the main factors for metabolic risk factors in children.

Familial aggregation is the clustering of certain traits, behaviors or disorders within a given family. The genetic or environmental similarities may cause family aggregation. Studies estimate the increased risk of disease in relatives of affected probands, or the risk for an individual given his or her family history. The degree of familial aggregation was evaluated by using an intraclass correlation coefficient (ICC).

Different genetic studies conducted on MetS traits, significant familial correlation coefficients in sibling up to 0.4 was reported (Trégouët et al., 1999). The heritability of MetS components in twins data was very high, up to 70% (Poulsen et al., 2001). Du to, family studies are well suited to investigate the genetic structure underlying the MetS and because of different distribution of familial aggregation status in different population, the first aim of this study was to evaluate familial aggregation of MetS, in Tehranian population.

On the other hand, genome wide association and linkage studies have attempted to answer the question of which pathways have affected on individuals for various phenotypes of the metabolic diseases and risk factors to type 2 diabetes and cardiovascular disease. Model-free linkage analyses are increasingly used to assess these genetic factors implicated in complex traits since they do not require any specification of the underlying genetic model and tend to be more powerful and simple than based models. A model free linkage analysis is conditional-logistic likelihood–ratio was developed by Olson (1999). This model was parameterized in terms of the logarithms of allele-sharing specific relative risks. Because of the parameterization, the model can be easily expanded to include the effects of covariates and model more than one disease locus.

Some studies have proven that several variants of the *FTO* and *CETP* genes are significantly associated with HDL_C that is one of the components of MetS (Kristiansson et al., 2012; Global Lipids Genetics C et al., 2013; Willer et al., 2008). In this Study, in addition to evaluate familial aggregation of MetS, the association of FTO (rs1558902 and rs7202116) and *CETP* (rs1864163) genes' SNP with HDL_C in Tehranian population with one parameter logistic model after adjusting for confounding factors such as age, sex has been analyzed.

2. Materials and methods

2.1. Study population

This family-based study was conducted on families participating in TLGS. According to ATPIII, at least one member had metabolic syndrome and two members had low HDL-C levels. The design of TLGS includes two major components; a cross-sectional prevalence study of CVD and associated risk factors; and a prospective 20-year follow up in several phases. The details of TLGS presented elsewhere (Azizi et al., 2009). The families under examination were recruited from the 5th phase of TLGS. They were 227 multinuclear families with 1776 subjects.

Participants provided informed consent and the study was approved by the institutional ethics committees of the Research Institute for Endocrine Sciences affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. The details of the disease definition and genotyping are presented elsewhere (Sedaghatikhayat et al., 2015). According to conducted studies, three polymorphisms (rs1558902, rs7202116 and rs1864163) were selected to investigate the association with low HDL-C.

2.2. Statistical analysis

The kolmogorov-smirnov goodness-of-fit test was used to assess normal distribution of continuous data. All continuous data are expressed as means ± SD. Natural logarithm transformation was performed to normalize the distribution of TG. The exploratory factor analysis was used to reduce the dimension of MetS and quantitative lipid traits. The principal component method with a varimax rotation was employed and the final factors were determined by Eigenvalues greater than 1.0. Adjusted factor loading and explained variance of various quantitative traits were obtained. All statistical analyses were performed on SPSS software (version 21; SPSS, Chicago, IL, USA). Probability values < 0.05 were considered statistically significant.

2.2.1. Familial aggregation

Familial intra-trait correlation coefficients of Mets and quantitative lipid traits between spouse, parent–offspring, sibling and grandparent-grandchild were estimated by using the FCOR program in SAGE v4.6 (S.A.G.E., Statistical Analysis for Genetic Epidemiology, 1997). FCOR uses the equation below to calculate the correlation between the pairs:

$$r_{xy} = \frac{\sum_{i=1}^{N} w_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{N} w_i (x_i - \bar{x})^2 \sum_{i=1}^{N} w_i (y_i - \bar{y})^2}}$$

where $\bar{x} = \sum_i w_i x_i / \sum_i w_i$ and $\bar{y} = \sum_i w_i y_i / \sum_i w_i$ is for arbitrary non-negative weights $\{w_i\}$.

2.2.2. Linkage analysis using conditional logistic model

In the Olson's general conditional-logistic model (Olson, 1999), the likelihood ratio (LR) for a relative pair of type r is:

$$LR = \frac{\sum_{i=0,1,2} \lambda_i \hat{f}_{ri}}{\sum_{i=0,1,2} \lambda_i f_{ri}}$$

where λ_i is the relative risk of disease for individuals sharing i alleles IBD with an affected relative; f_{ri} is the prior probability that a pair will share i alleles IBD; and $\hat{f}_{ri}$ is the estimated probability that a pair will share i alleles IBD conditional on available marker data. The model is parameterized in terms of the logarithms of relative risk, so:

$$\lambda_i = \exp\left(\beta_i + \sum_{j=1}^{k} \delta_{ij} x_j\right)$$

where δ_{ij} is the parameter associated with the covariate x_j, with $\beta_0 = \delta_{0j} = 0$.

We used a one-parameter model so that only one additional parameter was estimated for each included covariate (Song et al., 2011). The conditional logistic regression was used for genetic linkage on the basis of Affected Relative pair (ARP) relationships. This non parametric model allowed incorporation of covariates. Covariate-based affected relative pair linkage analysis using single-point identity-by-descent (IBD) probabilities and a general conditional logistic model was performed as implemented in GENIBD and LODPAL of S.A.G.E v4.6 (Statistical Analysis for Genetic Epidemiology). In LODPAL, all affected relative pairs are treated as independent observations, and covariate value is calculated for each affected relative pair as the sum of the covariate values of the two affected relatives in the pair (Olson, 1999; Goddard et al., 2001; Koivu et al., 2004; Doan et al., 2005). Sex and age were considered as covariates in this study.

3. Results

3.1. Descriptive population

The present study included a total of 1776 subjects from 227 families. The characteristics of the study population are shown in Table 1. The mean age of the male subjects was slightly higher than the females. Most characteristics differed significantly between men and women. Compared with men, women on average had a higher HDL-C and lower