Are Common Polymorphisms of the Lipoprotein Lipase and Human Paraoxonase-1 Genes Associated with the Metabolic Syndrome in South African Asian Indians?

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Abstract

A cross-sectional study was performed to determine the possible contribution of the Human Paraoxonase-1 (PON1) and Lipoprotein Lipase (LPL) polymorphisms to the risk of the metabolic syndrome (MetS) in 817 participants of South African Asian Indian ancestry. Demographic and anthropometric data, including fasting blood for analysis of glycaemic and lipid parameters was collected. DNA was isolated from peripheral blood and allelic polymorphisms at positions Q192R, L55M in the PON1 gene and S447X and N291S in the LPL gene were studied using real-time PCR. Melting curve analysis was used to identify homozygotes and heterozygotes. The MetS was classified using the harmonised criteria.

The prevalence of the MetS was 47.99%, with the main drivers being the increased waist circumference (96.6%), raised blood pressure (76.8%) and raised triglyceride levels (72.4%). There was no significant difference in age prevalence in different ethnic groups with similar risk factor exposure, suggest a role for possible gene-gene and/or gene-environmental interactions in the pathogenesis of the MetS. Certain enzymes such as lipoprotein lipase (LPL) and Human Paraoxonase-1 (PON1) have been shown to play a pivotal role in lipoprotein metabolism. Polymorphisms in the genes that regulate these enzymes have been shown to alter their activity, manifesting clinically as insulin resistance, hyperlipidaemia and obesity [8] which are all components of the MetS.

Keywords: Lipoprotein lipase gene; PON1 gene; Metabolic syndrome; Asian Indians

Introduction

The metabolic syndrome (MetS) is characterised by cardiometabolic risk factor clustering, which interact synergistically to increase risk of cardiovascular (CV) disease [1]. It has been reported to afflict almost a quarter of the world's population [2]. The pathophysiology of the MetS is thought to develop as a result of the interplay between insulin resistance, visceral adiposity and a sedentary lifestyle, resulting in an increased risk for coronary artery disease (CAD).

Certain ethnic groups are more prone to CV risk factor clustering with an increased risk for coronary heart disease (CHD). A marked excess in risk for CHD has been consistently demonstrated in Asian Indian subjects [3-5]. Asian Indians in Durban are known to have a high propensity for adverse lipid profiles and type 2 diabetes mellitus (DM) [6,7]. Although thought to be due to environmental exposure, a study of the family history suggested a possible genetic component for the high risk factor profile in this community [6].

To what extent the risk factor clustering in the MetS has a genetic basis has not been fully investigated. Furthermore, varying prevalence in different ethnic groups [1] as well as differences in age prevalence in groups with similar risk factor exposure, suggest a role for possible gene-gene and/or gene-environmental interactions in the pathogenesis of the MetS. Certain enzymes such as lipoprotein lipase (LPL) and Human Paraoxonase-1 (PON1) have been shown to play a pivotal role in lipoprotein metabolism. Polymorphisms in the genes that regulate these enzymes have been shown to alter their activity, manifesting clinically as insulin resistance, hyperlipidaemia and obesity [8] which are all components of the MetS.

Recent research shows that single nucleotide polymorphisms in the coding and promoter region of the PON1 gene may affect the expression and catalytic activity of PON1. PON1 is exclusively associated with high density lipoprotein (HDL) and its antioxidant activity [9] of HDL; alteration in PON1 protein activity may therefore predispose to changes in plasma cholesterol and low density lipoprotein (LDL) levels as well as to DM [10], so increasing individual susceptibility to the MetS.

In this study, we determined the prevalence of the MetS in a random community sample, and evaluated gene polymorphisms related to lipid metabolism and lipid peroxidation in order to ascertain whether there was a genetic susceptibility to the MetS.
Methodology

Study design and time period

This project formed a sub-analysis of the Phoenix Lifestyle Project cohort which was an analytical, cross-sectional study where a random sample of participants from the Phoenix community was selected over a two-year period (January 2007 - December 2008). South African Asian Indians aged 15–64 years, residing in the Phoenix area (EThekwini Municipality, Durban, KwaZulu-Natal) formed the study group. Individuals within the target age group were randomly selected using the Kish [11] method of sampling. This method documents household members and selects one to be included in the study. The detailed methodology has been described previously [12]. Samples for genetic analysis were stored as aliquots in 1 ml cryotubes and frozen at -80°C until DNA isolation.

Initially, subjects were classified as overweight if BMI was ≥ 25 - 29.99 kg/m² and obese if BMI ≥ 30 kg/m² [13]. The revised cut point for Asian Indians [14] was also applied on all subjects, i.e. subjects with BMI <23 kg/m² were classified as normal, BMI ≥ 23.0 to 24.9 kg/m² as overweight and those with BMI ≥ 25.0 kg/m² as obese. Criteria for the diagnosis of abnormal lipid levels were based on those from the National Cholesterol Adult Panel (NCEP) guidelines [15]: total cholesterol >5.17 mmol/l, total serum triglyceride >1.69 mmol/l and HDL levels <1.04 mmol/l [men]; <1.29 mmol/l [women].

The American Diabetes Association (ADA) [16] criteria were used for classifying glycaemic categories based on fasting plasma glucose (FPG): diabetes was diagnosed if it was self-reported or if FPG was ≥ 7.0 mmol/l, or if the two-hour sample in the oral glucose tolerance test (OGTT) was ≥ 11.0. Impaired fasting glucose (IFG) was diagnosed if FPG was ≥ 5.6 - <7.0 mmol/l, or if the two-hour sample in the oral glucose tolerance test (OGTT) was ≥ 7.8–11.0 mmol/l. The diagnosis of the metabolic syndrome was made using the harmonised criteria [17].

Rationale for selection of polymorphisms

In view of the high propensity of Asian Indians for increased CV risk [18], we chose to examine the influence of the polymorphisms of the LPL and PON 1 genes on the predisposition to MetS in this sample. Following the functional approach, these polymorphisms were chosen based on their position in or near the coding and promoter regions, and if they interrupted the termination codon, leading to truncated peptides. The S447X (rs 328) and the N291S (rs 268) variants of the LPL genes were chosen because of their varying effects on LPL activity. Similarly, two common polymorphisms, L55M (rs854560) and Q192R (rs662), located at the coding region for the PON1 gene, were selected because of their association with increased oxidative stress and greater severity of risk factor clustering [19].

DNA isolation and genotyping

DNA was isolated from whole blood using the automated MagNA Pure Nucleic Acid Purification system (Roche Applied Science). Real-time polymerase chain reaction (PCR) was performed using the Light Cycler 480 System (Roche) by rapid cycling in a reaction volume of 10 μl with 0.5 μmol/L of primer, 0.2 μmol/L anchor and detection probes, genomic DNA and LightCycler 480 Genotyping Master Mix. The primer and probe sets (Roche Applied Science) for the selected polymorphisms are listed in Table 1. After pre-incubation at 95°C for two minutes, amplification was performed using 35 cycles of denaturation (95°C for 10 seconds), annealing (55°C for 10 seconds), and extension (72°C for 10 seconds). When target amplification was completed, a melting curve stage was recorded by cooling the reaction mixture to 45°C, and then slowly reheating it to 95°C. A final cooling stage cooled the reaction mixture to 40°C in 30 seconds. Melting Curve analysis was used to identify homozygotes and heterozygotes by virtue of their different melting points. At least two negative controls were run with each plate, by replacing the DNA template with PCR-grade water. This was done to detect carry-over contamination.

Statistical analysis

Descriptive data was expressed as mean and SD, and were compared using the Student's t-test. Categorical variables were compared using chi-squared testing. The Kruskal-Wallis test was used to determine the significance between non-parametric variables. Differences were considered statistically significant when p<0.05.
Results

A total of 871 subjects were genotyped for both LPL and PON1 polymorphisms. The risk factor profile in the sample is shown in Table 2. There was a high prevalence of raised BMI, with over two thirds of the sample classified as overweight or obese upon application of the WHO and Pan-Asian cut points. Over three quarters (77.5%) of subjects had increased waist circumference, and 22.7% were current smokers. Smoking was more prevalent in males, compared to females (50.1% vs. 13.7%).

Table 2: Cardiovascular abnormalities in the study sample.

Using the harmonised criteria for the definition of the MetS, the prevalence was 47.99% (Table 2). The cardiovascular risk factor profile of the sample is shown in Table 3. Subjects with the MetS were older, with a female preponderance. There was a high prevalence of generalised obesity (48% vs. 24%) in subjects with the MetS, and this increased to 84% when the Asian cut-points were applied. There were slightly fewer smokers in subjects with the MetS (20%).

Table 3: Characteristics of subjects with MS versus those without.

The proportion of the contribution for the individual components of the MetS are shown in Table 4: the main drivers for MetS were the...
increased waist circumference (96.6%), raised blood pressure (76.8%) and raised triglyceride levels (72.4%).

Table 4: Proportion of contribution of individual components to MS diagnosis.

The genotype and allele frequencies are shown in Table 5. No variants were detected for the N291S polymorphism. There was a higher prevalence of the homozygous genotype of the S447X polymorphism, found in 76.7% of subjects with only 1.7% presenting with the homozygous mutant genotype, and a dominance of the S447X allele. This was similar for the L55M polymorphism. In contrast, there was a higher prevalence (59.8%) for the heterozygous variant of the Q192R polymorphism, with no homozygous mutants (Table 6a).

Table 5: Frequency of gene polymorphisms.

Table 6a: Genotype frequencies in the subjects with and without MS.

Table 6c: Gene-gene and gene environmental interactions and the MS.
In addition, individual genotypes of the three polymorphisms were combined into twenty one pairs in order for search for a gene-gene association which predisposed to MetS (Table 6c). Subjects who had both the SX genotype (S447X polymorphism) and the LM genotype (L55M polymorphism) were more likely to have the MetS than those without (p=0.016; OR 2.19; 95% CI: 1.17, 4.06). A search for environmental-genotype interactions (Table 6c) revealed that MetS was less likely in smokers with the SS genotype of the S447X polymorphism (p=0.049; OR 95% CI=0.85 (0.73, 0.99). There was no predisposition to MetS in smokers for the all the polymorphisms studied.

### Discussion

This is the first community-based study to document the prevalence of the MetS in South African Asian Indians and shows that one in two subjects in the district of Phoenix have the MetS. Our study shows that the high prevalence of the MetS in this sample was not associated with the genotype or the allele of the selected gene polymorphisms.

Our findings are in keeping with several other studies showing that the MetS is highly prevalent amongst Asian Indians in India [3,20], as well as across the diaspora [4,21]. The accractive effects of urbanisation and westernisation have been well documented to result in an increased susceptibility to risk factor clustering (dyslipidaemia, hyperinsulinaemia, and hyperglycaemia) [22], body anthropometry (“thin-fat” phenotype) [21], perinatal conditioning [23] and a pro-coagulant state [24], all of which result in an increased predisposition to CVD in Asian Indians. In addition, Yusuf et al. [18] proposed a genetic contribution to the increased risk of CVD in Asian Indians.

Several pathogenetic mechanisms have been proposed to explain how risk factors cluster to form the MetS. These suggest that lifestyle patterns (dietary habits, physical inactivity, adiposity and harmful behavioural traits) exert their effects on endothelial function, resulting in inflammation and oxidative stress, thrombosis or arrhythmia [25] leading to insulin resistance, risk factor clustering and the development of the MetS [26].

We selected the S447X polymorphism on exon 9 because the LPL gene is considered a strong candidate gene for atherogenic lipid profiles and for the development of CAD. There have been inconsistent observations made with regards to the allelic frequencies of the S447X polymorphism of the LPL gene. The frequencies for the S447X range from 4.4% in London [27] to 14% in the Mediterranean population [28]. The HuGe meta-analysis [29] reported a frequency of 9.9% for the 447X allele, with this mutation being more common in East Asians (12.2%) than Caucasians (10.3%), and is in keeping with our study findings (13%). The S447X polymorphism is characterized by a C-G transversion, where the 447X allele encodes a prematurely truncated LPL protein, serine. This converts the 447 codon prematurely to a termination codon [8], and has been linked to increased lipolytic activity, which leads to increased clearance of triglyceride-rich lipoproteins and protection against the MetS [30-32]. There were very few participants in our study with the mutant genotype, and we were not able to confirm this protective effect; in keeping with other Asian studies [33].

Similar to the findings of Bhanushali & Das [34] in South Indians, the N291S polymorphism was not detected in our study, although this variant has been reported to be associated with dyslipidemia, DM and coronary artery disease in a meta-analysis [35].

Analysis of the two PON1 polymorphisms (Q192R and L55M) in our study showed that the QR genotype was present in 59.8% and the MM genotype was present in 3.3% of the study population. The distribution of the 192R allele was 29%, and the 55 M allele was 21%, in keeping with the ranges reported by Ginsberg et al. [26]. Although impairment of the anti-oxidative activity of HDL [36] contributes to the development of insulin resistance and adiposity, we were not able to show any predisposition for these alleles to the development of the MetS.

PON1 genotypes were equally distributed between subjects with and without MetS, in keeping with data reported by Senti et al. [19]. In terms of the association with MetS components, we found that two genotypes (QQ and QR) of the Q192R polymorphism were significantly associated with increased triglyceride levels (Table 6b), in keeping with a recent study by Bounafaa et al. [37]. In contrast to our findings, the QQ genotype has been reported to provide the highest protection against lipid oxidation when compared to other PON1 polymorphisms, while carriers of the 192R allele is known to reduce protection against lipid peroxidation [9]. This would result in lower anti-aerotogenic properties, with subjects manifesting with higher triglyceride and lower HDL levels as an adverse phenotype. This finding therefore warrants further investigation into the underlying mechanism of increased risk, as the mechanism by which PON1 polymorphisms influences serum triglyceride level remains unclear, and may well reflect the varying metabolic capacity of PON1 in different populations. This further underscores the importance of population-based studies as associations found in one population may not necessarily be extrapolated to others [28].

Our findings are in contrast to other studies which found that the LPL [30] and PON1 gene polymorphisms [38] predisposed to the MetS in certain ethnic groups. A few studies focused on the etiological role of polymorphisms on the MetS, and have demonstrated individual component genetic correlates amongst Asian Indians. For example, in a study of 492 young male patients presenting with myocardial infarction, the leptin receptor (LEPR) gene Q223R TT genotype was associated with low HDL-C levels [30]. In that study, when the NCEP ATP III criteria were applied, a significant relationship was found with the LPL–93 T/G polymorphism (OR 2.72). Other genes have been shown to predispose to the MetS in Asian Indians like the hepatic glucokinase promoter gene, fatty acid binding protein 2 (FABP2) gene, and apolipoprotein C-III gene (APOC3) [39] and APOA1 [40].

Our study supports the view that there is no strong evidence for a common genetic basis for MetS in Asian Indians [10,20]. We found associations between the PON1 gene-gene interactions and an increased predisposition to the MetS. Previous studies in this community have documented high risk factor prevalence and have suggested a genetic component based on the family history [6] to explain the high prevalence for DM in this population group. It appears that the main driver for risk factor development in Asian Indians and predisposition to the MetS is largely environmental. Our study also shows a smaller number of smokers with the MetS, and a significant protective interaction between smokers with the SS genotype and the MetS. We suggest that this data be interpreted with caution, as smoking is known to decrease HDL and raise triglyceride levels, hence increasing the number of MetS components, and the propensity for MetS. In addition, our data on smokers was not validated with cotinine levels.

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Conclusion

The main driver for the MetS in our subjects appears to be obesity. Using the Asian cut-points, we have shown that the increased waist circumference in our sample is in fact, a measure of generalized obesity, rather than isolated abdominal obesity, which has been well-documented in this high-risk group in the INTERHEART study [18]. The absence of significant associations suggests that the MetS in this population may not be directly associated with the polymorphisms studied. The PON1 gene may increase the risk of MetS through gene–gene interactions, or predispose to risk factors such as hypertriglyceridemia. Aggressive population-wide interventional strategies should be urgently employed to reduce the impending epidemic of CV disease in this community by addressing lifestyle behavior patterns resulting in obesity and its associated risk components that contribute to the MetS.

Strengths and Limitations of the Study

MetS is known to be a multifactorial disease, without a single pathophysiological pathway. In this context, this means that some polymorphisms may be strongly associated with the disease in one population, but weak in others due to the presence of genetic factors. This therefore underscores the importance of population-based studies like these.

In terms of the weaknesses of the study, the present project looked at four polymorphisms from two genes. Given the complexity of lipid and insulin regulation, as well as the multifactorial pathophysiology that is characteristic of the MetS, it is reasonable that many genes may be responsible for these functions. Future studies in this population should look at genome-wide association scans [41], which may yield more information about the genetic pathways contributing to the common pathogenesis of the metabolic syndrome.

The challenges of deeming causality based on genetic association were also highlighted in this study, as shown by the lack of direct significant relationships between the SNPs studied and the MetS, which have been reported in other population groups.

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