The rare allele of DGKZ SNP rs10838599 is associated with variability in HDL-cholesterol levels among severely obese patients

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Abstract

Introduction: Diacylglycerol kinase-zeta, one of the ten isoforms of DGKs expressed in mammals is an important enzyme of lipid metabolism. It catalyzes the interconversion of diacylglycerol and phosphatidic acid, two major second messengers. Its gene DGKZ has been previously identified as being overexpressed and undermethylated in visceral adipose tissue of patients with (MetS+) versus without (MetS-) the metabolic syndrome (MetS).

Objective: The aim of this study was to investigate the associations between DGKZ gene polymorphisms (SNPs) and phenotypes related to MetS (BMI, waist girth, CRP, fasting glucose, lipid profile (triglycerides, total-cholesterol, LDL-cholesterol and HDL-cholesterol (HDL-C)), resting systolic and diastolic blood pressures).

Methods: The study sample included 1752 severely obese participants who underwent bariatric surgery. Associations between the five selected tSNPs of DGKZ and features of the MetS were tested. The effects of these SNPs on DGKZ methylation and expression levels were tested in subgroups of 32 and 14 obese subjects, respectively. Correlations between methylation and expression levels were also computed.

Results: Homozygotes for the rare allele of rs10838599 displayed higher plasma HDL-C concentrations compared to the other genotype groups (p=0.03). For gene methylation, only a trend with the cg05412031 CpG site (p=0.09) was found for the single significantly phenotype-associated SNP. There was no significant correlation between DGKZ methylation at cg05412031 and expression levels.

Conclusion: These results suggest that DGKZ SNP rs10838599 modulates plasma HDL-C levels thereby its gene contributes to the inter-individual variability observed in the cardiometabolic risk profile of patients with severe obesity.

Abbreviations: BMI: Body Mass Index; CRP: C-Reactive Protein; DAG: Diacylglycerol; DBP: Diastolic Blood Pressure; DGK: Diacylglycerol Kinase; HDL-C: High-Density Lipoprotein Cholesterol; HMZ: Homozygote; HTZ: Heterozygote; HWE: Hardy-Weinberg Equilibrium; LDL-C: Low-Density Lipoprotein Cholesterol; MetS: Metabolic Syndrome; PA: Phosphatidic Acid; SBP: Systolic Blood Pressure; SNP: Single Nucleotide Polymorphism; TG: Triglycerides; VAT: Visceral Adipose Tissue

Introduction

The metabolic syndrome (MetS) is a constellation of risk factors associated with cardiovascular diseases, and could explain the mortality related to obesity [1]. However, not all obese individuals develop MetS [2]. Consequently, the analysis of obesity etiology is critical to better understand and prevent its condition of epidemic proportions worldwide [3]. Differences in DNA sequence of obese individuals affected (MetS+) and unaffected (MetS-) by MetS can be examined. However, genetic factors are not the only contributor to the heterogeneous obesity phenotype. Epigenetic variations have also been associated with the development of metabolic disorders [4,5], including low HDL-cholesterol (HDL-C) levels, as observed among obese individuals [6]. Beside cholesterol transport, HDL-C particles also have antioxidant, anti-inflammatory and antithrombotic properties [7]. DGKZ gene is coding for the protein diacylglycerol kinase (DGK)-zeta, one of the ten DGK isoforms expressed in mammals [8]. It catalyzes the conversion of diacylglycerol (DAG) into phosphatidic acid (PA) and inversely [9], two essential lipid metabolic intermediates in the
constitution of membranes and signal transduction [10].

The DGKZ gene was identified by our team among a list of 488 additional loci as being differentially expressed in visceral adipose tissue (VAT) of MetS+ versus MetS- subjects [11]. Afterwards, DGKZ was shown to be differentially methylated in VAT of obese patients discordant for MetS [12]. We then hypothesized that DNA genetic/epigenetic variations in DGKZ are associated with MetS components and that CpG methylation levels are associated with the presence of obesity-related metabolic complications based on the role of methylation in the regulation of gene expression [13]. The aim of this study was therefore to determine the effects of DGKZ genetic and epigenetic variations on the metabolic complications of obesity.

Material and methods

Subjects selection

Among patients undergoing bariatric surgery (biliopancreatic diversion with duodenal switch) at the Québec Heart and Lung Institute (IUCPQ) (Québec City, Québec, Canada), 1752 severely obese men (N=545) and women (N=1207) were consecutively recruited. There were three inclusion criteria: the participants should present a BMI higher or equivalent to 35, be French-Canadian and attend for a bariatric surgery at the IUCPQ. The surgical protocol is described elsewhere [14]. Body weight, height, waist girth, plasma lipid (triglycerides (TG), total-cholesterol (total-C), LDL-cholesterol (LDL-C) and HDL-C) and diastolic blood pressures were measured before the surgery using standardized procedures [15]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and C-reactive protein (CRP) plasma concentrations were measured with a high sensitivity-CRP immunoassay using a monoclonal antibody coated on polystyrene particles. The presence of MetS was determined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) criteria [16]. Tissue specimens were obtained from the Biobank of the IUCPQ according to institutionally-approved management modalities. All subjects included in the study provided a written informed consent previously approved by the local ethics committee.

Genotyping

DNA was extracted from blood buffy coat using the GenElute Blood Genomic DNA kit (Sigma, St Louis, MO). Four tagging single nucleotide polymorphisms (tSNPs) were selected for the analysis based on differential expression and methylation of the DGKZ gene established in a previous dataset [11,12]. These SNPs were genotyped using the QuantStudio™ 12K Flex OpenArray™ AccuFill™ system (Applied Biosystems), and analyzed with TaqMan Genotyper v1.3 (Life Technologies). The inclusion of the rs34470543 SNP in the current study is attributable to its close localization to the cg12856521 CpG site, previously found to be differentially methylated between MetS+ and MetS- subjects [17]. The tagger selection algorithm of the Haploview software (pairwise tagging, R² ≥ 0.80) was used for analysis of selected SNPs spanning promoter (2 kb), coding and intronic regions of the DGKZ gene in addition to the 3’ gene region (2 kb) [17]. This strategy allowed covering 100% of the genetic variability of the common polymorphisms (MAF ≥ 1%) at the DGKZ locus in the Caucasian population (CEU HapMap).

DNA methylation analysis

From the original sample, a subgroup of 32 obese individuals was used for DNA methylation analysis, including the 14 subjects (MetS+, N=7; MetS-, N=7) selected for gene expression profiling [11]. The 18 additional obese individuals (MetS+, N=9; MetS-, N=9) were selected to fulfill initial selection criteria [11] and to represent extremes of the MetS diagnosis criteria spectrum. Samples of 200 mg of VAT were used to achieve genomic DNA extraction using the DNeasy Blood and Tissue kit (QIAGEN, Mississauga, Ontario, Canada). Bisulfite conversion was conducted on 1 µg of DNA, and quantitative DNA methylation analysis was carried out at the McGill University and Génome Québec Innovation Centre (Montréal, Canada). Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA) covering more than 485000 methylation sites at single-nucleotide resolution were processed according to the manufacturer’s instructions. The GenomeStudio software version 2011.1 (Illumina Inc.) and the methylation module were used for visualisation and analysis of the methylation data. Methylation levels (beta values; β) were estimated as the ratio of signal intensity of the methylated alleles to the sum of methylated and unmethylated intensity signals of the alleles (β = C/(T+C)). We applied internal control probe pairs for data correction (background subtraction and normalization). The GenomeStudio Methylation Module was used to extract CpG sites located within the DGKZ locus and promoter region, thus leading to a total of 66 CpG sites analyzed. Based on the differentially methylated CpG site cg12856521 (chr11:46389249, genome build 37), DGKZ was identified as differentially methylated (Diffscore = -235.58).

Gene expression

The protocol leading to the selection of DGKZ for the current study and its expression data presented here were retrieved from a previous study aimed at the identification of differentially methylated genes between MetS+ and MetS- severely obese men [11]. Even if the DGKZ gene is not listed in the tables due to the large number of genes discovered, this investigation led to its determination as being overexpressed within VAT of MetS+ versus MetS- subjects (1.21-fold, p<0.004).

Statistical analysis

At first, differences in metabolic biomarkers were tested between MetS+ and MetS- individuals of the study cohort. Gene expression level differences derived from microarray analysis between MetS+ and MetS- groups were tested using the unpaired Student’s t test. For the five selected DGKZ tSNPs, Hardy-Weinberg equilibrium (HWE) was verified. For SNPs with genotype frequency of rare homozygotes below 5% (2 SNPs: rs3809047 and rs3740976), homozygotes for the rare allele were merged to heterozygotes for statistical analysis. The five selected SNPs spanning promoter (2 kb), coding and intronic regions of the DGKZ gene were computed to assess the relationship between gene methylation, expression and MetS components were tested using the GLM procedure with adjustments for age, sex, BMI and medication to treat MetS features when appropriate. When a significant SNP effect was identified, all pairwise comparisons between genotype groups were tested using least squares means. Pearson correlation coefficients were computed to assess the relationship between gene methylation, expression and MetS components. P values were calculated for all associations and were considered statistically significant if the P value was less than 0.05. Phenotypic data are presented as mean ± SD. Statistical analyses were performed with SAS software version 9.3.

Results

Cohort description

The current study included 1752 subjects (545 men and 1207
women) who underwent bariatric surgery. From those, 1745 were classified as being MetS+ (n=1428) or MetS- (n=317 or 20.19%). Patients’ characteristics are presented in Table 1. Briefly, the MetS+ group was older and showed significantly higher waist girth, fasting glucose, TG, total-C/HDL-C ratio and blood pressure (SBP and DBP), as well as lower plasma total-C, LDL-C and HDL-C levels than the MetS- group.

Identification of DGKZ SNPs and selection of tSNPs

Among the 5 selected SNPs, 4 were located in introns whereas SNP rs34470543 was located in an exon (Table 2). These 5 SNPs were further genotyped in the entire cohort of 1752 participants. All SNPs were in HWE and genotype distribution is shown in Table 2.

Association of DGKZ SNPs

Associations between DGKZ SNPs and fasting plasma concentrations of glucose, TG, total-C, LDL-C, HDL-C, CRP and blood pressure (DBP and SBP) were tested taking into account the potential confounding effects of age, sex, and BMI. A significant association was found for rs10838599, homogygotes for the rare allele of rs10838599 displaying elevated HDL-C levels (p=0.03) compared to the two other genotype groups (Table 3). A trend toward higher DBP (p=0.08; 83.67 ± 10.91 vs. 83.43 ± 11.30 vs. 85.71 ± 11.97) was also observed. For rs3740976, a trend toward higher DBP (p=0.09; 84.32 ± 10.85 vs. 83.51 ± 11.30) was observed in rare allele carriers.

Gene methylation and expression analysis

To better understand the mechanism linking DGKZ genetic variations and cardiometabolic risk factors, we investigated the impact of these SNPs on gene methylation and expression levels in subgroups of 32 and 14 participants, respectively. Methylation levels were available for 66 CpG sites randomly distributed within the gene, their precise locations are presented in Table 4. The impact on methylation levels was tested only for SNP (rs10838599) found to be significantly associated with one cardiometabolic risk factor. For rs10838599, only a trend for genotype differences in methylation levels at the cg05142031 CpG site (p=0.09) was noted. No significant correlation was found between methylation levels at this CpG site and DGKZ expression levels.

Discussion

Our group previously observed that DGKZ was overexpressed [11] and undermethylated [12] in VAT of MetS+ vs MetS- severely obese subjects. DGKZ was thus revealed as a candidate gene having a potential effect on the development of obesity and MetS. Accordingly, it was appealing to test its associations with features of MetS. The ten diacylglycerol kinase isoforms expressed in mammals [8], including DGK-zeta, are important enzymes of lipid metabolism, because they are involved in the regulation of two major lipid messengers [18], controlling DAG and PA levels in cells [19]. The second messenger DAG regulates the activity of Rac1 and RhoA, two Rho GTPases [20] affecting the actin filaments of the cytoskeleton [21]. An increase in DAG, modulated by DGK, appears to reduce glycogen synthesis stimulated by insulin in liver, also decreasing the suppression of gluconeogenesis [21]. Therefore, the activity of DAG and PA may be altered by obesity and type 2 diabetes [22]. Specifically, the DGK-zeta isoform is expressed in diverse tissues, especially in brain [23]. At first, it is in the cell cytoplasm but can be translocated to various organelles.
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Table 3. Significant genotype differences identified between fasting glucose, lipid profile and blood pressure. Boldface values represent statistically significant results (P ≤ 0.05). a Values presented (means ± SD) are untransformed and unadjusted. b P values obtained are adjusted for the effect of age, sex, BMI and medication use except for BMI and waist girth which were adjusted for age and sex. Abbreviations: HMZ: Homozygote; WT: Wild-Type; HTZ: Heterozygote; N: Number; BMI: Body Mass Index; CRP: C-Reactive Protein; TG: Triglycerides; Total-C: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SD: Standard Deviation.

Table 4. Association of phenotype-associated SNP rs10838599 with gene methylation levels.

SNP | cg138908017 Promoter | cg24878900 Promoter | cg18765542 Promoter | cg21029403 Promoter | cg26650731 Promoter | cg05414203 Promoter | cg25155153 Promoter | cg07276415 Promoter | cg05214900 Promoter | cg14503180 Promoter | cg10503202 Promoter
---|---|---|---|---|---|---|---|---|---|---|---
rs10838599 | 0.95 | 0.99 | 0.58 | 0.23 | 0.91 | 0.09 | 0.24 | 0.94 | 0.65 | 0.39 | 0.10
SNP | cg15825186 Exon 1 | cg24407308 Intron 1 | cg0848504089 Intron 1 | cg10050956 Intron 1 | cg09820018 Intron 1 | cg22948808 Intron 1 | cg22767438 Intron 1 | cg15925492 Intron 1 | cg20091215 Intron 1 | cg06061966 Intron 1 | cg07998213 Intron 1
rs10838599 | 0.27 | 0.36 | 0.38 | 0.44 | 0.94 | 0.87 | 0.48 | 0.93 | 0.34 | 0.70 | 0.86
SNP | cg05576959 Intron 1 | cg12347398 Intron 1 | cg20029947 Exon 1 | cg21663341 Intron 1 | cg03519157 Intron 1 | cg20666386 Intron 1 | cg07077241 Intron 1 | cg00503720 Intron 1 | cg15868421 Intron 1 | cg09039436 Intron 1 | cg03044514 Intron 1
rs10838599 | 0.55 | 0.66 | 0.40 | 0.51 | 0.68 | 0.63 | 0.34 | 0.67 | 0.93 | 0.99 | 0.73
SNP | cg20510601 Intron 1 | cg22675791 Intron 1 | cg18560067 Intron 1 | cg12087471 Intron 1 | cg07092212 Intron 1 | cg11320644 Intron 1 | cg17266233 Intron 1 | cg07121644 Intron 1 | cg21770622 Intron 1 | cg02685822 Intron 1 | cg18337963 Intron 1
rs10838599 | 0.87 | 0.44 | 0.92 | 0.20 | 0.28 | 0.45 | 0.47 | 0.74 | 0.52 | 0.68 | 0.54
SNP | cg02211741 Exon 1 | cg26473310 Intron 1 | cg14877903 Intron 1 | cg20240471 Intron 1 | cg26963644 Intron 1 | cg24731322 Intron 1 | cg12856521 Exon 3 | cg00107629 Intron 3 | cg24126592 Intron 4 | cg08769094 Exon 5 | cg16769381 Exon 5
rs10838599 | 0.27 | 0.59 | 0.53 | 0.67 | 0.84 | 0.48 | 0.68 | 0.91 | 0.32 | 0.73 | 0.12
SNP | cg276515070 Intron 9 | cg01529066 Exon 9 | cg6977596 Intron 16 | cg19272726 Exon 20 | cg05979087 Intron 20 | cg20154997 Exon 21 | cg12592499 Intron 27 | cg1436767 Exon 30 | cg07052627 Exon 31 | cg06626097 Exon 31 (3’-UTR) | cg11203377 Exon 31 (3’-UTR)
rs10838599 | 0.20 | 0.68 | 0.60 | 0.15 | 0.39 | 0.48 | 0.96 | 0.61 | 0.56 | 0.70 | 0.98

P-values for associations were obtained from a subset of 14 obese subjects (7 MetS+ and 7 MetS-). CpG sites positions according to genome build 37.

[24]. Such translocation may be attributable to its unique myristoylated alanine-rich C-kinase substrate (MARCKS) phosphorylation domain [19,23]. The overexpression of DGKZ has been associated with decreased cell cycle progression [19], as DAG is important for this process as well as for cell differentiation [25]. Moreover, a previous study reported a relationship between DGK-delta and insulin resistance [26], but has not been reported for other isoforms. Insulin resistance may be an important event in the development of MetS, inducing hyperglycemia and dyslipidemia, although not all MetS+ patients are insulin resistant [27,28]. In addition, DAG is increased in humans with MetS and with reduced HDL-C levels [29]. DAG is also part of the pathway leading to the translocation of GLUT4 to the cell membrane [30].

Among the 5 tSNPs selected, only one was significantly associated with obesity-related metabolic complications in the present study. More specifically, rare allele homozygotes of rs10838599 had significantly higher plasma HDL-C levels compared to heterozygotes and homozygotes for the wild-type allele. To our knowledge, this study is the first to report an association of DGKZ gene variations and cardiometabolic risk factors in severely obese patients. Rs10838599 wild-type allele was associated with decreased plasma HDL-C levels, a lipid disturbance associated with an alteration of free fatty acid metabolism [16,31]. Low plasma HDL-C level is a criterion of MetS—a lipid disturbance associated with an alteration of free fatty acid metabolism [16,31]. Low plasma HDL-C level is a criterion of MetS—a lipid disturbance associated with an alteration of free fatty acid metabolism [16,31]. Low plasma HDL-C level is a criterion of MetS—a lipid disturbance associated with an alteration of free fatty acid metabolism [16,31].
functionality [40]. PA is in low abundance in HDL-C particles known for their heterogeneous composition and structure [41].

No significant association was found between the phenotype-associated SNP rs10838599 and methylation levels. There was also no correlation between gene methylation and expression levels. These results suggest that DNA sequence and methylation variations are not significant contributors to DGKZ expression levels, at least in severely obese patients. As DAG is a major regulator of many important biological processes, its abundance in cells might be tightly controlled, which is a key role for DGK [9]. Expression of the gene coding for DGK isoforms such as DGKZ, may be closely regulated accordingly by epigenetic mechanisms, influenced by environmental factors such as diet [42]. Through excessive intake in food, an accumulation of TG can lead to fat storage in ectopic sites, which is associated with dyslipidemia and other obesity-related metabolic complications such as hypertension, glucose intolerance [43], and insulin resistance [44]. The lipid profile measured in plasma has been shown to be an indicator of both genetic and environmental backgrounds [29]. Moreover, the expression of DGKZ has been described to be stimulated in hypothalamus by a high-fat diet [45]. Thus, this suggests that an excess of fat intake may influence the expression level of DGK genes. Besides, DAG might also be playing a role in hypertension pathophysiology [46], but the current study only revealed a trend between two of DGKZ SNPs, rs10838599 and rs3740976, and higher DBP for rare allele carriers. Nevertheless, altered lipid metabolism and hypertension are associated [47].

Some limitations need to be taken into account when interpreting the results presented in this study. First, a relatively small number of obese participants were available to measure gene methylation and expression levels in VAT. The limitation to 32 subjects used for methylation analysis is due to the highly stringent selection criteria. For expression analysis, the number of individuals included in the subgroup was limited to 14 because this part of methodology was retrieved from a previous study [11]. However, identifying the potential mechanism relating phenotype-associated SNPs to MetS was, however, a secondary objective. Also, the effects of DGKZ SNPs may have been altered by the systemic inflammation generated by obesity [48], so more studies with different study cohorts are needed.

Conclusion

With this study, we found that DGKZ rs10838599 is associated with plasma HDL-C thereby suggesting that it may contribute to the interindividual variability observed in the cardiometabolic risk profile of patients with severe obesity. However, methylation levels of CpG sites were not associated to this gene variation.

Authors’ contributions

SBégin wrote the article; SBégin and FG completed the statistical analyses; MCV, AT, YD and LP established study design; FSH, SL and PM recruited patients, collected clinical data and samples; SBégin and MCV have principal liability for final content. All authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

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