Evaluation of DOK5 as a susceptibility gene for type 2 diabetes and obesity in North Indian population

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Abstract

Background: Type 2 diabetes is a complex metabolic disorder characterized by impaired insulin secretion and action. Obesity is one of the major contributing factors in the development of type 2 diabetes and obesity have been localized on different chromosomal regions by various genome-wide linkage scans. Of these chromosomal regions, 20q13 is one of the strongest linked regions for type 2 diabetes and obesity. On 20q13 lies DOK5 that seems to be a strong functional and positional candidate for type 2 diabetes and obesity because of its involvement in insulin signaling and immune responses. Hence, for the first time, we explored DOK5 as a potential type 2 diabetes and obesity susceptibility gene.

Methods: We sequenced 43 subjects for polymorphisms in functionally relevant regions of DOK5. A total of 10 SNPs that included 5 that were identified by sequencing and 5 additional SNPs from NCBI Variation Database were genotyped in 2,115 participants comprising of 1,073 patients with type 2 diabetes and 1,042 controls of Indo-European ethnicity from North India.

Results: We identified a novel variant in intron 7 referred to as DK176673. We found nominal association of three SNPs—rs6064099 (OR = 0.75, P = 0.019), rs873079 (OR = 0.76, P = 0.036) and DK176673 (OR = 1.55, P = 0.037) with type 2 diabetes among normal-weight subjects [BMI < 23 kg/m²]. The haplotype GGC harboring rs6068916, rs6064099 and rs873079 showed strong association with type 2 diabetes among normal-weight subjects (OR = 1.37, P/perm = 5.8 × 10⁻³/0.037). Association analysis with obesity revealed that rs6064099 is associated with reduced susceptibility for obesity (OR = 0.48, P = 6.8 × 10⁻³). Also, haplotype GGC conferred increased susceptibility for obesity (OR = 1.27, P/perm = 9.0 × 10⁻³/0.039). Also, rs6064099 was significantly associated with reduced BMI [median(IQR) = 24.0(20.7-27.1) vs 23.9(20.2-26.8) vs 21.8(19.2-24.7) for GG vs GC vs CC, P = 7.0 × 10⁻³].

Conclusions: We identified DOK5 as a novel susceptibility gene for obesity and type 2 diabetes in North Indian subjects. Association of DOK5 variants both with obesity and type 2 diabetes suggests that these variants might modulate type 2 diabetes susceptibility through obesity.

Background

Type 2 diabetes is a complex metabolic disorder characterized by impaired insulin secretion and action. Obesity is one of the major contributing factors in the development of type 2 diabetes. Though believed to be overlapping, the etiology of both type 2 diabetes and obesity are unclear. Gene identification is an important milestone in the understanding of disease pathophysiology, but has proven to be a difficult task for complex disorders such as type 2 diabetes. Multiple susceptibility loci on different chromosomal regions are believed to be involved in genetic etiology of type 2 diabetes.

Evidence for localization of susceptibility loci on different chromosomal regions for type 2 diabetes and obesity has been provided by various genome-wide linkage scans. Of these regions, 20q13 is one of the strongest candidate regions for type 2 diabetes which is documented to be linked to type 2 diabetes by more than 8
Camps
jects of ≥ ples were collected by organizing done as per WHO criteria 2003 [15]. The control sam-
iod of 2003 and 2008. Diagnosis of type 2 diabetes was
stitute of Medical Sciences, New Delhi between the per-
recruited from Endocrinology clinic of All India Insti-
informed consent. Type 2 diabetic patients were
ethnicity were enrolled after obtaining written
jects from North India belonging to Indo-European
population which has a high risk of developing type 2 diabetes.

Methods
Subjects’ recruitment
A total of 2,115 unrelated subjects comprising of 1,073 patients with type 2 diabetes and 1,042 control sub-
jects from North India belonging to Indo-European
population which has a high risk of developing type 2 diabetes.

Anthropometric and biochemical characterization
All the recruited subjects underwent anthropometric
and exclusion criteria for cases and controls is pro-
SNPs and distance between the SNPs. SNPs and hence were excluded. A total of 147 samples
alleles and SNPs from NCBI Variation Database that includes
alleles. GenTrans score >0.6, cluster separation score >0.4,
SNPs was performed using GoldenGate assay on Illumina platform (Illumina Inc.,
San Diego, CA, USA). The genotyping data obtained
was subjected to extensive quality control that includes
genotype confidence score of 0.25, call frequency >0.9,
GenTrans score >0.6, cluster separation score >0.4, MAF > 0.05 and Hardy-Weinberg equilibrium (HWE) in
controls (P > 0.01). Of the total case-control samples, 90
DNA samples had genotype call for less than 90% of the
SNPs and hence were excluded. A total of 147 samples
(7%) were genotyped in duplicates and showed a consist-
cy rate of 99.99% in genotype calls. SNP rs2840 failed

Screening and identification of polymorphisms
To identify novel variants if any, we sequenced approximately 5 kb region of DOK5 including all exons, exon-intron boundaries, putative promoter and UTRs in 43 samples of Indian Discovery panel [19]. Primers used were designed by Primer3 http://frodo.wi.mit.edu/primer3
that provides better primer design [20]. In the sequenced
samples, we captured 9 SNPs including one novel variant
in intron 7 (chromosomal position 53,266,929) that has
never been reported earlier (referred here as DK176673)
(Figure 1). From these, 5 SNPs (rs6098099, rs6068915,
rs6064099, DK176673, rs2840) were selected for further genotyping. As SNPs in 3’UTR were very close, only one SNP (rs2840) was genotyped. Additionally, five more SNPs from NCBI Variation Database that includes
rs6098009, rs6023307, rs6023357, rs6023367 and
rs873079 were selected to cover the entire gene based on
the selection criteria that includes functional significance,
heterozygosity (MAF >0.05), information regarding tag
SNPs and distance between the SNPs.

Genotyping
The region 20q13 harbors DOK5 that encodes Dok5
widespread studies in different populations [1-9]. The
same region has also been shown to be linked to obesity
by various studies [10-12]. However, till date there has
been no clear evidence for localization of type 2 diabetes
and obesity susceptibility genes on this region. Hence,
exploration of 20q13 through positional candidate
approach may facilitate identification of susceptibility
genes for type 2 diabetes and obesity on this region.
The region 20q13 harbors DOK5 that encodes Dok5
family containing tandem pleckstrin homology-phosho-
tyrosine binding (PH-PTB) domains at the N-terminal. Although the biological function of this docking protein
is not very clear, Dok5 is shown to be one of the sub-
strates in insulin signaling [13]. Dok5 contains a short
C-terminus with potential sites for tyrosine phosphory-
lation that get phosphorylated in response to insulin
and IGF1 [13]. Moreover, the highest expression of
Dok5 has been detected in skeletal muscle which is the
major tissue regulating metabolic homeostasis. Dok5 is
also suggested to be involved in the regulation of
immune response induced by T cells [14].

Because of its involvement in insulin signaling and
immune responses which are the key modulating path-
ways in type 2 diabetes and obesity, DOK5 seems to be a
convincing positional and functional candidate for
type 2 diabetes and obesity. Therefore, here for the first
time, we explored DOK5 as a potential type 2 diabetes
and obesity susceptibility gene in North Indian popula-
tion which has a high risk of developing type 2 diabetes.

Methods
Subjects’ recruitment
A total of 2,115 unrelated subjects comprising of 1,073
patients with type 2 diabetes and 1,042 control sub-
jects from North India belonging to Indo-European
eras. Since 2001, these diabetes awareness campaigns
have been done as per WHO criteria 2003 [15]. The control sam-
pies were collected by organizing ‘Diabetes Awareness
Camps’ in the urban regions in and around Delhi. Subjects
of ≥40 age of year without family history of diabetes
who had glycated hemoglobin (HbA1c) level ≤6.0%
and fasting glucose level <110 mg/dL were con-
considered as controls. Detailed description of inclusion
and exclusion criteria for cases and controls is pro-
vided previously [16]. Study was in accordance with
the principles of the Helsinki Declaration and was
approved by the Ethics Committees of the participating
institutions.

Anthropometric and biochemical characterization
All the recruited subjects underwent anthropometric
and biochemical measurements. Height, weight, waist
and hip circumferences, and blood pressure were mea-
sured following standard guidelines before drawing
blood. Body mass index (BMI) and waist to hip ratio
(WHR) were calculated from these measurements. Based
on their BMI, the subjects were categorized into
two groups according to the BMI cut-offs for Asian
populations: normal-weight (BMI < 23 kg/m²) and over-
weight/obese subjects (BMI ≥23 kg/m²) [17]. Venous
blood samples were drawn after overnight fasting for
biochemical measurements. Levels of glucose, Hba1c,
insulin, C-peptide, total cholesterol, triglycerides (TG),
high-density lipoprotein cholesterol (HDL-C), low-den-
sity lipoprotein cholesterol (LDL-C), urea, uric acid,
creatinine and hsCRP were measured as described ear-
lier [16,18].
in Illumina assay and was genotyped using MALDI-TOF mass spectrometry (Sequenom, San Diego, CA, USA).

**Statistical Analysis**

Deviation from HWE at each locus was tested both among cases and controls separately using $\chi^2$ analyses. Association of genotypes with type 2 diabetes and obesity was assessed by logistic regression. Association analyses of genotypes with type 2 diabetes were also performed after stratification of cases and controls into normal-weight and overweight/obese subjects. The analyses were adjusted for age, sex and BMI as appropriate. Odds ratios (ORs) are presented with respect to the minor alleles. Bonferroni correction was applied to correct for multiple comparisons and a $P$ value $< 0.008$ was considered significant after correction. The uncorrected $P$ values are provided in the text. Association between genotypes and quantitative traits was determined using Kruskal-Wallis test only in control subjects. Haplotype analysis was carried out at 10,000 permutations using Haploview 4.0 [21]. Statistical power was determined using PS power and sample size program [22]. Our sample provided power of 69%-97% to detect association with ORs of 1.3-1.5 assuming MAF of 0.20 at level of significance of 0.05. The statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA) and PLINK v. 1.05 http://pngu.mgh.harvard.edu/~purcell/plink[23].

**Results**

**DOK5 polymorphisms**

We identified a total of 9 SNPs after sequencing the functionally significant regions of DOK5 including one novel SNP in intron 7 (referred as DK176673) and 8 reported SNPs-rs6098099 (Intron 5), rs6068915 (Intron 5), rs6064099 (Intron 6), rs2840 (5'UTR), rs2842 (5'UTR), rs2841 (5'UTR), rs15899 (5'UTR) and rs2843 (5'UTR) (Figure 1). As the 5 SNPs identified in 5'UTR region were very close to each other, only one (rs2840) was selected for further genotyping. Hence, of the 9 identified SNPs, 5 SNPs—rs6098099, rs6068915, rs6064099, DK176673, rs2840 were selected for further genotyping. Additionally, five more SNPs from NCBI Variation database that includes rs6098009 (Intron 1), rs6023307 (Intron 1), rs6023357 (Intron 2), rs6023367 (Intron 2) and rs873079 (Intron 7) were also selected for the complete coverage of gene region.

**DOK5 polymorphisms and type 2 diabetes**

A total of 10 SNPs were genotyped in the study population of 2,115 participants comprising of 1,073 patients with type 2 diabetes and 1,042 controls of Indo-European ethnicity from North India. The clinical characteristics of the study population are provided in Table 1. All the SNPs were in accordance with HWE (all $P > 0.01$) both among cases and controls, except for rs2840 that was eliminated from further analysis. SNPs—rs6098009, rs6023307 and rs6098099 were found to be rare variants (MAF < 0.05) and were consequently excluded under the paradigm of a CVCD model. None of the DOK5 variants analyzed here showed association with type 2 diabetes (Table 2).

Obesity is a well known risk factor of type 2 diabetes and influence of BMI on the risk of development of type 2 diabetes has been consistently shown in number of studies [24]. Recently, we also showed variability in the risk of type 2 diabetes among individuals in different BMI strata [16,25]. This implies that the etiology of type 2 diabetes might be different in normal-weight individuals and overweight/obese individuals. Therefore, we segregated the subjects into two groups based on BMI: Normal-weight (BMI < 23 kg/m²) and overweight/obese (BMI ≥ 23 kg/m²). Type 2 diabetes patients among normal-weight and over-weight/obese groups had median age of 55 years with median BMI of 21.3 kg/m² and 53 years of median age with median BMI of 26.5 kg/m².
Table 1 Anthropometric and clinical characteristics of the study population

| Characteristics   | Type 2 diabetic patients | Control subjects |
|-------------------|--------------------------|------------------|
| N (Men/Women)     | 1019 (592/427)           | 1006 (606/400)   |
| Age (years)       | 53 (45-62)               | 50 (44-60)       |
| BMI (Kg/m²)       |                          |                  |
| Men               | 23.8 (22.0-26.0)         | 23.1 (20.1-25.7) |
| Women             | 26.7 (24.2-29.2)         | 25.0 (21.1-28.5) |
| WHR               |                          |                  |
| Men               | 1.0 (0.97-1.03)          | 0.97 (0.92-1.0)  |
| Women             | 1.0 (0.97-1.03)          | 0.86 (0.82-0.92) |
| Systolic BP (mmHg)| 130 (130-140)            | 120 (112-132)    |
| Diastolic BP (mmHg)| 80 (78-90)              | 80 (70-88)       |
| HDL-c (%          | 7.8 (6.5-9.4)            | 5.2 (4.9-5.6)    |
| Fasting Glucose (mmoles/L)| 7.9 (6.4-10.3) | 49 (4.5-5.3) |
| Fasting Insulin (µU/mL)| 13.8 (7.0-27.8) | 5.4 (2.9-9.6) |
| HOMA-IR           | 5.2 (2.3-9.6)            | 1.2 (0.6-2.0)    |
| C-peptide (ng/mL) | 2.7 (1.7-4.1)            | 1.6 (1.1-2.2)    |
| hsCRP (mg/L)      | 2.2 (0.9-4.7)            | 1.3 (0.6-3.0)    |
| Total cholesterol (mg/dL)| 163 (137-195) | 170 (146-199) |
| LDL-C (mg/dL)     | 100 (77-130)             | 108 (90-132)     |
| HDL-C (mg/dL)     | 40 (35-48)               | 41 (34-50)       |
| TG (mg/dL)        | 138 (100-198)            | 117 (86-161)     |
| Urea (mg/dL)      | 26 (20-33)               | 24 (19-29)       |
| Uric acid (mg/dL) | 49 (3.9-6.0)             | 49 (4.0-5.7)     |
| Creatinine (mg/dL)| 0.84 (0.67-1.07)         | 0.75 (0.66-0.88) |

Data are median values with interquartile ranges in parentheses.

respectively. The control subjects among normal-weight and overweight/obese groups had median age of 50 years with median BMI of 20.0 kg/m² and 50 years of median age with median BMI of 26.4 kg/m² respectively. Then, we compared the allelic and genotypic distributions among normal-weight cases and controls; and overweight/obese cases and controls (Table 2). We observed nominal association of rs6064099 and rs873079 among normal-weight subjects [OR = 0.75 (P = 0.019) and 0.76 (P = 0.036)]. The association did not remain significant after adjusting for age, sex and BMI. Also, DK176673 was found to confer susceptibility to type 2 diabetes (OR = 1.55, P = 0.037) that was retained after adjustments for covariates (P = 0.043) but did not after applying multiple testing correction. Among overweight/obese subjects, none of the SNPs showed significant effect on type 2 diabetes susceptibility.

SNPs rs6064099 and rs873079 were in strong LD (D’ = 0.98 and R² = 0.91). Among normal-weight individuals, haplotype GGC harboring major alleles of rs6068916, rs6064099 and rs873079 was more frequent among type 2 diabetes patients (66.9%) as compared to control subjects (59.8%). The GGC haplotype was found to confer increased susceptibility for type 2 diabetes (OR = 1.37, P/Perm = 5.8 x 10⁻³/0.037) among normal-weight individuals (Table 3). Another haplotype CT encompassing rs6064099, rs873079 and DK176673 showed reduction in type 2 diabetes susceptibility.

Table 2 Association of DOKS SNPs with type 2 diabetes in North Indian population

| SNP            | Entire Sample set | Normal-weight subjects | Over-weight/obese subjects |
|----------------|-------------------|------------------------|---------------------------|
|                | Case: Control     | OR (95%CI) ORadj (95%CI) | Case: Control: OR (95%CI) | ORadj (95%CI) |
|                | (1019: 1006)      | P value                | (295: 436)                | P value       |
| rs6023357 (A/C)| 814: 822          | 1.06 (0.90-1.25)       | 0.96 (0.86-1.05)          | 1.04 (0.92-1.18) |
| rs6023367 (G/A)| 794: 792          | 1.03 (0.89-1.18)       | 1.14 (1.00-1.30)          | 1.12 (0.97-1.28) |
| rs6088915 (C/T)| 722: 759          | 0.95 (0.81-1.11)       | 0.87 (0.75-1.00)          | 0.86 (0.73-1.01) |
| rs6064099 (G/C)| 589: 576          | 0.99 (0.85-1.15)       | 0.79 (0.65-0.94)          | 0.78 (0.63-0.94) |
| rs873079 (G/A)| 607: 591          | 0.99 (0.85-1.15)       | 0.76 (0.62-0.91)          | 0.75 (0.61-0.90) |
| DK176673 (T/A)| 847: 807          | 1.02 (0.87-1.18)       | 1.55 (1.30-1.82)          | 1.53 (1.28-1.83) |
|                | 107: 110          | 0.78 (0.63-0.96)       | 38.43 (13.0-106)          | 30.66 (12.0-83) |
|                | 6.1                | 0.90 (0.74-1.10)       | 0.37 (0.24-0.57)          | 0.33 (0.21-0.53) |

Data are presented as genotype counts. OR (95% CI) stands for odds ratio with 95% confidence interval assuming additive model. ORadj and Padj were calculated by logistic regression analysis after adjustments for age, sex and BMI.
among normal-weight subjects, however did not remain significant after permutation analyses (haplotype frequencies of 19.5% and 24.1% among type 2 diabetes patients and controls respectively; OR = 0.76, \( P/\text{perm} = 0.038/0.242 \)).

**DOK5 polymorphisms and obesity**

Association of DOK5 variants with obesity was assessed by considering BMI both as continuous and discrete trait (≥23 kg/m²) among control subjects. SNP rs6064099 was significantly associated with reduced BMI [median(IQR) = 24.0(20.7-27.1) vs 23.9(20.2-26.8) vs 21.8(19.2-24.7) for GG vs GC vs CC, \( P = 7.0 \times 10^{-3} \)]. Considering BMI as a discrete trait, we observed significant association of rs6064099 with obesity (OR = 0.48, \( P = 6.8 \times 10^{-3} \)) that remained significant after adjusting for age and sex (\( P = 9.8 \times 10^{-3} \)). We also found significant association of GGC haplotype with obesity. GGC haplotype was over-represented among over-weight/obese subjects (59.7%), conferring risk for obesity with OR of 1.27 (\( P = 9.0 \times 10^{-3} / \text{perm} = 0.039 \)).

**DOK5 polymorphisms and quantitative clinical traits**

Further, we investigated association of DOK5 SNPs with quantitative traits related to type 2 diabetes including fasting glucose, HbA1c, insulin, C-peptide, hsCRP, total cholesterol, HDL, LDL, triglyceride, creatinine, urea and uric acid. For this, the clinical variables of only control subjects were compared across the genotypes of the SNPs as the disease status or treatment regime in patients might affect the estimation of these parameters. However, none of the SNPs was found to be significantly associated with the clinical traits investigated here (all \( P > 0.05 \)).

**Discussion**

Indian population represents the highest risk group for type 2 diabetes and related metabolic traits including obesity and cardiovascular diseases. A number of association studies have been performed in Indian population to evaluate the role of functional candidate genes, most of which involves replication of associations in other populations. Moreover, these efforts have not yielded any true susceptibility gene that causes type 2 diabetes in this high risk group. With the advent of genome-wide association (GWA) studies, there has been a sudden increase in the number of confirmed loci for type 2 diabetes [26]. However, these identified loci contribute only to a small proportion of expected number of involved genes [27]. Hence, along with the model free approach of GWA studies, positional candidate approach targeting genes with plausible functional relevance can substantially contribute to a better understanding of the complex disorders. Therefore, here, we investigated a potential positional and functional candidate gene, DOK5 on chromosomal region 20q13, to identify novel susceptibility gene for type 2 diabetes and obesity.

Association analysis of DOK5 SNPs revealed significant association of its variants with type 2 diabetes among normal-weight subjects. SNPs rs6064099 in intron 6 and rs873079 in intron 7 were found to reduce the susceptibility to type 2 diabetes among normal-weight individuals. Also, the novel SNP DK176673 was found to confer susceptibility to type 2 diabetes. Normal-weight individuals harboring haplotype GGC of major alleles for SNPs rs6064099, rs6064099 and rs873079 were found to be more susceptible to type 2 diabetes. Hence, our data suggests that DOK5 might play a significant role in modulating the susceptibility of type 2 diabetes among normal-weight subjects in North Indian population. Our study further reinforces our earlier observations that etiologic mechanisms of pathophysiology of type 2 diabetes depend on BMI [11,24].

Consistent with earlier observations of linkage of 20q13 with obesity, our study also provides added evidence for the localization of susceptibility gene for obesity in this region. We found strong association of rs6064099 with protection against obesity. Also, GGC haplotype was found to confer increased susceptibility to obesity. Association of DOK5 variants with obesity again suggests that these variants may modulate the susceptibility to type 2 diabetes through obesity.

It is interesting to note the GGC haplotype region harboring three SNPs rs6068916, rs6064099 and rs873079, encompasses exons 6 and 7 of DOK5 gene. In case if these associated SNPs are not true causal variants, there might be a causal or functionally relevant variant in LD with the associated SNPs influencing the
risk of type 2 diabetes and obesity. Though we attempted to identify all the polymorphisms in exonic regions, there might be possibility of less common variants with higher relative risks in these regions that could not be captured in our sequenced samples. Hence, further evaluation of SNPs in DOK5 in a larger population might provide true susceptibility variant in DOK5 gene.

We would like to mention here that production of false positives in association studies due to population stratification and multiple comparisons might be plausible. With this in mind, our case and control subjects were recruited from a homogenous cluster in urban region of North India in accordance to a report of genetic landscape of the people of India [28]. From the clustering pattern, it was suggested that if cases and controls are both drawn from the same cluster, the effects of population stratification in disease association studies may be small. Another study analyzing Indian genetic variation and diversity also suggested that the effects of population heterogeneity on the production of false positives in association studies might be smaller in Indians than might be expected for such a geographically and linguistically diverse subset of the human population [29].

Conclusions
In conclusion, we identified DOK5 as a novel gene modulating the susceptibility of obesity and diabetes in North Indian population of Indo-European ethnicity. However, replication analyses of the variants showing association in this study are warranted to validate the findings. Moreover, other genetic variants in the gene might also play role in influencing the risk of type 2 diabetes. Therefore, future genetic and functional studies evaluating the association of genetic variants of DOK5 and deciphering their physiological effect and mechanisms are needed to further ascertain its role in the manifestation of type 2 diabetes.

List of Abbreviations
DOK5: Docking Protein 5; IGF1: Insulin like Growth Factor 1; PH-PTB: Pleckstrin homology-phosphotyrosine binding domain; CVCD: Common Variant Common Disease; MAF: Minor Allele Frequency

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Authors’ contributions
RT and AM designed, processed, interpreted the data and wrote the manuscript. GC and OPD contributed in work design and manuscript writing. SG contributed in the statistical analysis of the data. DB and NT conceived and supervised the study and have contributed by critical evaluation of the study and improving the manuscript. All the authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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