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Impact of Promotor region Cdx2 (A/G) Variant of Vitamin-D Receptor Gene on Omentin-1, Leptin levels and Coronary Artery Risk in Pakistani Cohorts

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Abstract **Objectives:** Coronary artery disease remains a major contributor to global morbidity and mortality, primarily driven by atherosclerosis. Genetic variations and adipocytokines like omentin-1 and leptin play critical roles in inflammatory pathways and atherosclerotic processes. This study aims to evaluate the association of Cdx2 (A>G) variant, omentin-1 and leptin with CAD risk in a Pakistani population. **Methods:** This case-control study comprised 500 angiographically confirmed CAD patients and 500 age- and gender-matched healthy controls. Detailed anthropometric measurements, blood pressure and fasting blood samples were obtained from all contributors. Genotyping of the Cdx2 (A>G) variant was conducted using tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). Serum levels of omentin-1, leptin and vitamin-D were evaluated by using enzyme-linked immunosorbent assay (ELISA) kits. Statistical analyses was done by SPSS version 23. **Results:** The frequency of the AA genotype in the control group (49.2%) was significantly higher than in CAD patients (32.4%), indicating a protective effect ($p<0.001$). The AG genotype was associated with a 58% increased risk of CAD (OR = 1.58, 95% CI: 1.24-2.02). Serum omentin-1 levels were significantly lower in CAD patients (368±3.7 ng/mL vs. 615±6.5 ng/mL, $p<0.001$) compared to controls, whereas, leptin levels were significantly elevated in CAD patients (8.62±0.7 ng/mL vs. 4.02±0.5 ng/mL, $p<0.001$). Both omentin-1 and leptin levels were significantly associated with the AG and GG genotypes, suggesting a genetic influence on these adipocytokine. **Conclusion:** In conclusion Cdx2 (A>G) variant of promotor region of VDRG was found to be associated with greater risk of CAD and also influence on adipokines levels, particularly omentin-1 and leptin, may play a crucial role in CAD pathogenesis. These findings offer insights into the molecular mechanisms of CAD.

Key Words Coronary artery disease, atherosclerosis, vitamin d receptor, genetic variants, omentin-1, leptin, adipokines, genetic risk factors. Biomarkers in cardiovascular health

INTRODUCTION

Coronary artery disease (CAD) is a fatal condition driven by atherosclerosis in the endothelial lining of the principal coronary arteries [1]. Globally, CAD remains the leading cause of morbidity and mortality; however, South Asia, particularly Pakistan, bears a disproportionately high burden of the disease, which is exacerbated by younger age onset and unique environmental and genetic predispositions. Despite substantial advancements in CAD research globally, gaps persist in understanding region-specific risk factors and genetic determinants contributing to CAD progression in South Asian populations. Conventional risk factors for CAD include dyslipidaemia, hypertension, insulin resistance, obesity, stress, tobacco use and limited physical activity [2]. A significant contributing factor to the pathogenesis of CAD is vitamin D deficiency, which is a lipid-soluble vitamin

acquired from diet, supplements, or sunlight. It is essential for regulating the cardiovascular, immune and musculoskeletal systems [3].

Vitamin D, along with its receptor (VDR), functions as a transcriptional factor that controls the expression of numerous genes related to immune responses and cytokine production [4]. The VDR is encoded by the vitamin D receptor gene (VDRG), located on the long arm of chromosome 12 (12q13) [5]. The VDRG comprises eight coding exons (exons 2-9) and six non-coding exons (exons 1a, 1b, 1c, 1d, 1e and 1f) that undergo alternative splicing [6]. The Cdx2 (A>G) variant is a functional polymorphism located in exon 1e. This region has a binding site for the transcription-initiating protein Cdx2. The substitution of the nucleotide base adenine with guanine impairs the Cdx2 binding site, reducing the transcriptional activity of VDRG by 70% [7]. The A allele facilitates the binding of the Cdx2 transcription factor, enhancing VDRG transcriptional activity, whereas the G allele exerts the opposite effect [8]. Omentin-1, an anti-inflammatory adipocytokine, is primarily found in visceral adipose tissues (VAT) [9]. Omentin-1 lowers inflammation by blocking TNF-α-activated nuclear factor kappa B (NF-κB) and AMP-activated protein kinase (AMPK) [10]. Leptin, on the other hand, is a pro-inflammatory adipocytokine expressed in subcutaneous adipose tissues (SAT) and contributes to low-grade systemic inflammation by activating the JUN and COX pathways [11].

Promoter region polymorphisms largely influence the transcriptional operation of a gene by modifying the binding specificity for regulatory enhancers or suppressors, which affects gene expression and contributes to the genesis and progression of diseases. Due to the lack of TATA and CAAT transcription initiation sites, the VDRG experiences lower transcriptional activity, which successively affects the regulation of multiple protective mechanisms mediated by vitamin D [12]. This transcriptional dysregulation may play a role in modulating omentin-1 and leptin levels through VDR/NF-κB signalling, contributing to systemic inflammation and CAD. Despite the global focus on VDR polymorphisms, limited studies have explored their impact on CAD in South Asian populations, particularly the Pakistani cohort. This gap is significant given the unique genetic and environmental factors influencing CAD in this region.

Recent studies have provided conflicting evidence regarding the association of VDR polymorphisms with CAD. While some studies confirmed the role of the Cdx2 variant in altering inflammatory and lipid pathways, others questioned its significance, attributing observed effects to environmental interactions rather than genetic predisposition. These discrepancies underline the need for population-specific studies to untangle the complex interplay of genetics, epigenetics and environmental factors. Additionally, other genetic variants, such as the FokI, BsmI, ApaI and TaqI polymorphisms in the VDR gene, have also been linked to CAD, albeit with varying degrees of significance across populations. However, the functional implications of these polymorphisms remain underexplored in South Asian contexts, where their prevalence and impact might differ due to genetic heterogeneity.

This study aims to bridge critical knowledge gaps by exploring the association between VDR polymorphisms, circulating adipocytokines and CAD, focusing on the underrepresented Pakistani population. Furthermore, actionable goals include the identification of potential diagnostic biomarkers (omentin-1 and leptin) and genetic screening tools for early CAD detection. These findings could inform personalized treatment strategies and guide future research into therapeutic interventions targeting VDR-related pathways.

METHODS

Study Design and Setting

The case-control study was conducted in the Cardiac units of Civil Hospital Karachi (CHK), Pakistan, between June 2022 and June 2023.

Sample Size Calculation

The sample size for this case-control research was determined utilizing the OpenEpi formula. A total sample size of 1,000 participants (500 cases and 500 controls) was calculated to ensure adequate statistical power.

Participant Selection

The study included individuals diagnosed with CAD via coronary angiography. Coronary artery disease was defined as the presence of over 50% stenosis in one or more principal coronary arteries. Individuals presenting with symptoms indicative of cardiac issues, such as severe chest pain, dyspnea, or hypertension, but determined not to have CAD based on angiography, served as the control group.

Exclusion Criteria

Individuals with acute infectious diseases, cancer, congenital heart defects, pre-established valvular heart disease, liver disease, or pregnancy were excluded to reduce confounding effects. Additionally, participants taking medications that interfere with Vitamin D metabolism, such as Rifampicin, Barbiturates and Thiazide diuretics, were excluded.

The study was approved by the Ethical Review Committee of the Karachi Institute of Biotechnology and Genetic Engineering (KIBGE). Participants were provided with a comprehensive explanation of the study's rationale and methodology and written informed consent was obtained before data and blood sample collection.

Anthropometric and Blood Pressure Measurements

Height and Weight: Measured using a portable stadiometer (Seca 213, USA) and a digital weighing scale (Camry-China BR 9016). BMI was calculated by dividing weight (kg) by height squared (m^2).

Waist and Hip Circumference: Waist circumference (WC) was measured to a precision of 0.1 cm using a tape positioned above the umbilicus, while hip circumference (HC) was measured at the widest part of the hips.

Blood Pressure

Blood pressure was recorded using a YAMASU Model 600 sphygmomanometer while the participant was seated.

While these measurements were systematically conducted, the study lacks consideration of cultural or environmental factors that may influence anthropometric variables, such as seasonal variations or dietary habits. Future studies should incorporate these factors into their analysis.

Blood Sample Collection and Storage

Participants were instructed to fast for at least eight hours before morning blood collection. A standard venipuncture technique was used to collect 5 mL of blood, which was transferred into EDTA-containing vials (Becton Dickinson, Oxford, UK). Samples were transported in chilled containers to the laboratory, centrifuged at 3,000 RPM for 5 minutes using a 5810R AG® centrifuge (Hamburg, Germany) and stored in an ultra-freezer (Carlo ERBA, Germany) at -80°C before analysis. Compliance with fasting was ensured through pre-sampling interviews. Handling protocols were followed rigorously, although specific quality control steps to monitor participant compliance with fasting and sample handling could have been elaborated.

DNA Extraction and Genotyping

DNA Extraction: Genomic DNA was isolated using the salting-out method and its concentration and purity were assessed using a Nano-spectrophotometer (NanoPhotometer®, Germany). Integrity was confirmed via 0.8% agarose gel electrophoresis.

Amplification and Genotyping

Genomic DNA was amplified using T-ARMS-PCR with primers designed for the Cdx2 (A>G) variant. PCR products were visualized on agarose gel and allele-specific bands (110 bp for G allele and 235 bp for A allele) were recorded.

Quality Control for DNA Extraction

- Samples were processed in duplicates to ensure reproducibility
- Negative controls were included to monitor contamination

Biochemical Analysis

Circulating levels of Vitamin D, Omentin-1 and Leptin were measured using ELISA. The intra- and inter-assay coefficients of variation were as follows:

- **Vitamin D:** 12.1% (intra-assay) and 15.8% (inter-assay)
- **Omentin-1:** 4.1% (intra-assay) and 4.8% (inter-assay)
- **Leptin:** 6.91% (intra-assay) and 8.66% (inter-assay)

While the assays were performed in triplicate, additional details on quality control measures during ELISA procedures, such as standard curve verification and plate uniformity checks, could have strengthened the methodology.

Statistical Analyses

Data were analysed using SPSS version 23.0. Continuous variables were summarized as means±standard deviations and compared using the Student t-test for two groups or ANOVA for comparisons across multiple groups. Categorical variables were presented as frequencies and percentages, analysed using Pearson's chi-square test. To evaluate the association between the Cdx2 polymorphism and coronary artery disease (CAD), odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the MedCalc online calculator. Logistic regression analysis was performed to adjust for potential confounders, including age and gender. Subgroup analyses were performed to explore associations stratified by gender and age groups (e.g., <50 and ≥50 years) to assess potential interaction effects.

Primers Sequence for Cdx2 (A>G) variant

Genotype	Primers Sequence
G (Forward)	CGATAGAGAAAATAATAGAAAACATT
G (Reverse)	AACTCATTATAAGAAATAAGTTTTTAC
A (Forward)	AGCTGAGTTAACTAGGTCACAATTT
A (Reverse)	GGGTTAAGTTCAGAAAGATTCATTC

RESULTS

Participant Characteristics

Table 1 compares demographic, anthropometric, physical and biochemical characteristics of CAD patients (mean age 52.06±10.15) and controls. controls (mean age 49.95±10.17). Cases had higher systolic (147.67 vs. 132.13 mm Hg, $p<0.05$) and diastolic blood pressure (90.8 vs. 80.3 mm Hg, $p\leq0.05$) and a significantly higher body mass index ($p = 0.032$). CAD cases showed elevated levels of total cholesterol ($p = 0.033$), LDL-c ($p = 0.019$) and leptin (8.62 vs. 4.02 ng/mL, $p\leq0.05$) but lower HDL-c (35.06 vs. 43.3 mg/dL, $p\leq0.05$) and omentin-1 (368 vs. 615 ng/mL, $p\leq0.05$).

Genotype, Allele frequency and Genetic models

Table 2 indicates that the AG genotype of the Cdx2 (A>G variation was strongly correlated with an elevated risk of CAD (OR = 1.9, $p = 0.01$), but the GG genotype and G allele displayed no significant risk association ($p>0.05$). AG+GG carriers showed a higher risk of CAD in the dominant model (OR = 3.2, $p<0.001$), whereas in the over-dominant model, the AG genotype alone was similarly associated with heightened risk (OR = 2.5, $p<0.001$). Table 3 displays odds ratios and p-values regarding the risk association between Cdx2 genotypes (AA, AG, GG) and circulating omentin-1 and leptin concentrations in patients with CAD. The AG genotype exhibits an odds ratio of 2.4 ($p = 0.01$) for Omentin-1 and 1.98 ($p = 0.02$) for Leptin, signifying a notable relationship.

Table 1: Demographic, Anthropometric, Physical and Biochemical Characteristics of study population

Study Variables	Cases	Controls	p-value
Age (years)			
≤45	27	121	
≥45	473	379	
Mean±SD	52.06±10.15	49.95±10.17)	0.521
Gender			
Males	266	290	0.829
Females	234	210	0.651
Blood Pressure (mm Hg)			
Systolic	147.6±11.3	132.13±9.9	0.051*
Diastolic	90.8±13.5	80.35±7.1	0.001*
Body Mass Index (kg/m²)			
≤30	123 (24.6%)	155 (31.0%)	0.001*
≥30	377 (75.4%)	345 (69.0%)	0.032*
Waist-to-Hip Ratio			
≤0.85	148 (29.6%)	134 (26.8%)	0.109
≥0.85	352 (70.4%)	366 (73.2%)	0.002*
Smoking Status			
Non-smokers	150 (30%)	173 (34.6%)	0.322
Smokers	350 (70%)	327 (65.4%)	0.087
Biochemical Parameters			
Fasting Blood Sugar (mg/dL)	101.5±12.5	98.7±19.3	0.342
Total Cholesterol (mg/dL)	275.7±53.4	144.9±37.2	0.033*
HDL-Cholesterol (mg/dL)	35.1±9.1	48.3±3.1	0.022*
LDL-Cholesterol (mg/dL)	175.5±32.5	137.6±22.3	0.019*
Triglyceride (mg/dL)	168.2±12.4	151.3±15.6	0.082
Vitamin D (ng/mL)	24.4±8.8	26±13.8	0.602
Omentin-1 (ng/mL)	368±3.7	615±6.5	0.003*
Leptin (ng/mL)	8.62±0.7	4.02±0.5	0.005*

*p<0.05, significant

Table 2: Association of Cdx2 (A>G) Variant Genotypes, Allele Frequencies and Genetic Models with CAD

Parameters	CAD Cases	Control	χ^2	p-value	OR	95% CI	p-value
Genotype/Allele							
AA	166 (33.2%)	246 (49.2%)	26.68	< 0.001	1 (Ref)	-	-
AG	314 (62.8%)	170 (34.0%)	14.31	< 0.001	1.9	1.01-3.14	0.01*
GG	20 (4.0%)	84 (16.6%)	15.25	< 0.001	1.08	1.03-1.22	0.08
Allele Frequency							
A	323	331	-	-	1 (Ref)	-	-
G	177	169	-	-	1.012	1.01-1.44	0.21
Genetic Models							
Dominant							
AA	166 (33.2%)	246 (49.2%)	20.13	< 0.001	1 (Ref)		
AG + GG	334 (66.8%)	254 (50.8%)	21.09	< 0.001	3.2	0.40-0.84	0.02*
Recessive							
AA + AG	480 (96%)	416 (83.2%)	12.91	< 0.001	1 (Ref)		
GG	20 (4.0%)	84 (16.6%)	13.01	< 0.001	1	0.43-1.98	1.01
Over-Dominant							
AA + GG	186 (37.2%)	330 (65%)	30.11	< 0.001	1 (Ref)		
AG	314 (62.8%)	170 (34.0%)	31.67	< 0.001	2.5	0.01-0.09	0.03*

Table 3: Risk Association of Genotype-Specific Odds Ratios for Omentin-1 and Leptin Levels

Genotype	Odds Ratio for Omentin-1 (95% CI)	p (Omentin-1)	Odds Ratio for Leptin (95% CI)	p (Leptin)
AA	1 (Ref)	-	1 (Ref)	-
AG	2.4 (0.81-2.99)	0.01*	1.98 (1.39-2.56)	0.02*
GG	1.00 (0.53-1.34)	0.95	1.70 (1.40-2.09)	0.05*

This study hypothesizes the role of the Cdx2 variant in modulating leptin and omentin-1 release, as shown in Figure 1.

The ARMS-PCR amplification results for the Cdx2 variant are shown in Figure 2, depicting bands corresponding to different genotypes.

Figure 3 shows distribution of Cdx2(A>G) variant with omentin-1 and leptin in CAD patients a statistically significant difference in Omentin-1 and Leptin levels across the AA, AG and GG genotypes. The AA genotype is significantly correlated with the highest Omentin-1 concentration whereas the AG genotype exhibits the highest Leptin concentration.

DISCUSSION

Vitamin-D is a multifunctional hormone, which is essential for calcium and bone metabolism, as well as playing crucial role in immunoregulation, inflammation, anticoagulation and

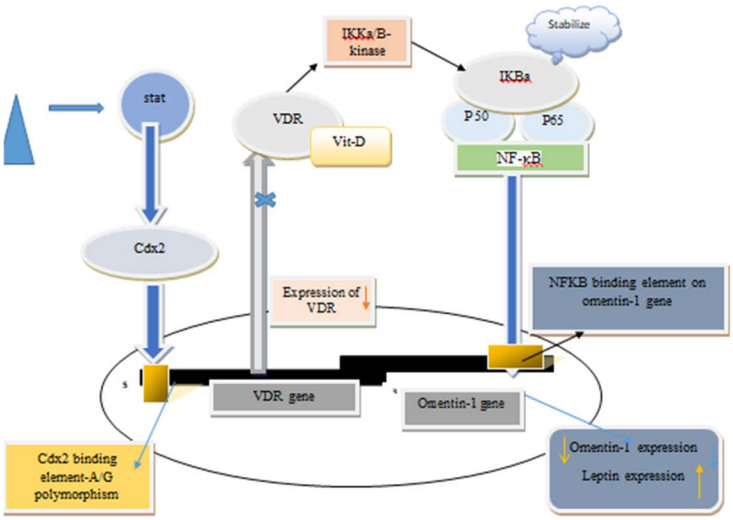

Figure 1: Proposed mechanism of the cdx2 variant of vdrg in regulating the release of leptin and omentin-1

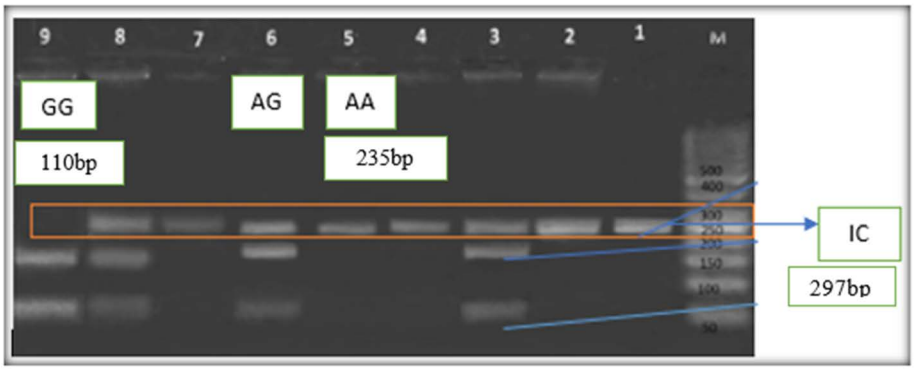

Figure 2: Arms-PCR products of Cdx2 variant of VDRG, M = 100 bp ladder, AA = Wild homozygous, GG = Mutant homozygous, IC = Internal control

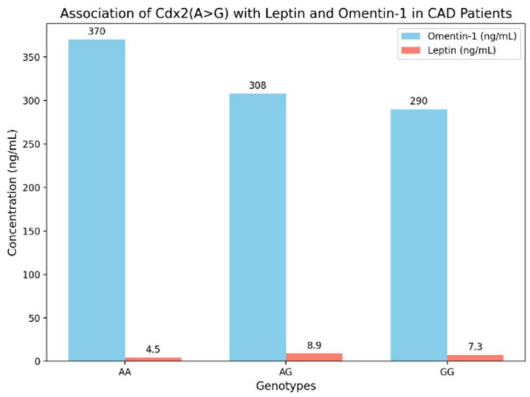

Figure 3: Distribution of omentin-1 and leptin in genotypes of Cdx2 variant of VDRG

antioxidation [13]. Vitamin-D needs VDR, a ligand-dependent nuclear transcription factor, to perform its metabolic functions [14].

Single nucleotide polymorphisms (SNPs) in various regions of the VDRG can influence the expression of VDR [15]. Among these, FokI, BsmI, TaqI and ApaI variants have been extensively studied across different populations [16-18]. The current study specifically focuses on the Cdx2 (A>G) variant located in the promoter region of the VDRG.

In this investigation, the heterozygous AG genotype was more common in CAD patients (62%) than in controls (34%). Both the dominant (OR = 3.2, 95% CI = 0.402-0.842, p = 0.002) and over-dominant (OR = 2.3, 95% CI = 0.009-0.013, p = 0.003) genotype models showed a significant relationship with CAD. The allele frequency difference (A vs. G) between patients and controls was not significant in this study (OR = 1, 95% CI = 1.009-1.441, p = 0.89). Rehman M et al., investigated Cdx2 (A>G) polymorphism in various cancer patients in Pakistani population and observed that AG and GG genotypes were found to be more prevalent in the cancer patients as compared to controls ($p<0.05$). However, the

frequencies of "A" and "G" alleles were not significantly different between two groups, consistent with our findings [18].

Iqbal *et al.* [19] on the other hand, found a substantial difference in allele frequency, which was probably caused by variances in sample size and connected the "G" allele to breast cancer risk and decreased VDRG transcription. Qadir *et al.* [20] found that patients with rheumatoid arthritis have the heterozygous AG genotype of the Cdx2(A>G) polymorphism, although the data had non-significant values, this genotype still represents the majority among the patients with rheumatoid arthritis [20]. However, González *et al.* [21] found no link between Cdx2 (A>G) polymorphism and coronary heart disease in the Caucasian population of Spain.

Our findings suggest that omentin-1 is negatively associated with coronary artery disease. Bai *et al.* [22] identified low circulating levels of omentin-1 as an independent risk factor of coronary heart disease in postmenopausal women. CERİK *et al.* [23] concluded that reduces levels of omentin-1might be an independent predictor of heart failure in patients with ischemic heart disease. The current study found that heterozygous AG genotype of the Cdx2(A>G) variant was significantly associated with lower omentin-1 levels (OR = 2, 95%, CI = 0.81-0.99, p = 0.001), indicating increased CAD susceptibility. Additionally, CAD patients with the AG genotype had significantly lower omentin-1 levels (p = 0.001) and higher leptin levels (p = 0.001), suggesting a significant role of the AG genotype in CAD development.

Compared to other cardiovascular risk factors, leptin has been demonstrated to raise the risk of coronary events [24]. According to the current study, CAD patients had noticeably greater serum leptin levels than controls. Higher leptin levels were linked to the AG heterozygous genotype of the Cdx2(A>G) variation in VDRG, however there was no statistically significant association with an increased risk of CAD (p = 0.43).

Limitations

While our findings are insightful, there are several limitations that need to be addressed. This study was conducted at a single site and as such, the results may be influenced by regional biases, potentially limiting the generalizability of the findings. To increase the external validity of these results, multi-site studies or recruitment from diverse ethnic populations should be considered in future investigations. This approach would help determine whether the association between the Cdx2 (A>G) variant and CAD is consistent across different regions and ethnic backgrounds. Another important consideration is the sample size. The small sample size in this study may limit the statistical power to detect subtle genetic associations. Larger-scale studies with more robust sample sizes are warranted to confirm the associations observed in our study and further investigate the potential clinical applications of these genetic markers.

CONCLUSIONS

This study demonstrates the significant association between the Cdx2 (A>G) polymorphism and increased CAD susceptibility, particularly in individuals with the AG genotype. The findings highlight the practical significance of genetic screening for early identification of high-risk individuals, enabling personalized treatment strategies. Future research should aim to replicate these findings in multi-centre, diverse populations and explore the functional role of the Cdx2 variant in VDR expression and CAD mechanisms. Furthermore, biomarker assessment like omentin-1 may enhance risk stratification. These results suggest policy implications such as incorporating genetic testing into routine cardiovascular risk evaluations, promoting targeted preventive measures and advancing precision medicine approaches for CAD prevention.

Acknowledgment

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Ethical Statement

The study got approval from the Ethical Review Committee of Karachi Institute of Biotechnology and Genetic Engineering (KIBGE).

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