



## Association of *LDLR* Gene Polymorphism with the Risk of Cardiovascular Disease in End-Stage Kidney Disease Patients on Maintenance Hemodialysis

### Abstract

**Background:** The low-density lipoprotein receptor (*LDLR*) is essential for regulating intracellular cholesterol levels. Mutations in the *LDLR* gene can cause an increase in LDL cholesterol levels in the blood, elevating the vulnerability to cardiovascular disease (CVD). This study evaluated the correlation between the *LDLR* rs688 polymorphism and CVD risk in chronic kidney disease (CKD). **Materials and Methods:** Polymorphism in this case-control study was genotyped using the TaqMan real-time polymerase chain reaction in a cohort of 100 CKD patients (Group I) and 100 healthy controls (Group II). We examined the *LDLR* rs688 allele and genotype distribution in 50 CKD cases with CVD and 50 cases without CVD. **Results:** There was a significantly greater frequency of CT variant of LDL SNP rs688 in Group I than in Group II ( $p = 0.006$ ). CT and TT genotypes were significantly higher in CKD patients with CVD, with odds ratios (ORs) (95% CI) of 4.3 (1.6–11.8,  $p = 0.004$ ) and 7.6 (2.3–24.8,  $p = 0.001$ ), respectively. **Conclusion:** SNP rs688 C>T detection in the *LDLR* gene showed that CT and TT genotypes are associated with elevated CVD risk in CKD.

**Keywords:** *LDLR*, *Rs688*, Chronic kidney disease, Cardiovascular disease, SNP

### Introduction

Cardiovascular disease (CVD) is a primary contributor to mortality in people with chronic kidney disease (CKD). Patients diagnosed with CKD who simultaneously suffer from CVD have a much higher likelihood of death in comparison to the overall population. Indeed, their mortality risk is 20 times higher.<sup>1</sup> CKD affects around 10% of the population, totaling over 800 million individuals worldwide.<sup>2</sup>

The prevalence of CKD in Egypt has been calculated to be 483 individuals per million, as reported in the Egyptian Renal Registry.<sup>3</sup> The increasing occurrence and prevalence of advanced CKD can be linked to factors such as aging, escalating rates of type II diabetes and hypertension, a low rate of identification, and treatment inertia.<sup>4</sup> Dyslipidemia is one of numerous variables that contribute to atherosclerosis and CVD in the CKD population.<sup>5</sup>

Attachment and uptake of plasma LDL particles are carried out by *LDLR*, a cell surface glycoprotein essential for preserving cellular cholesterol homeostasis.<sup>6</sup> Increased

plasma LDL levels brought on by *LDLR* gene mutations can raise the risk of atherosclerosis and ischemic heart disease.

The genetic background is a significant component of CVD pathogenesis.<sup>7</sup>

The *LDLR* gene harbors many documented mutations that impact the promoter regions, splicing sites, and exons.<sup>8</sup> A few of these variations have been linked to high cholesterol in families. The 45 kb long *LDLR* gene, which codes for *LDLR* proteins, is located on chromosome 19 (19p13) and contains 18 exons.<sup>6</sup>

In *LDLR* exon 12, there is a single nucleotide polymorphism (SNP) rs688 (accession number NC\_000019.10:11116925: C: T) that has been associated with low-density lipoprotein cholesterol and the coronary artery disorder's development.<sup>9</sup> This SNP disrupts a splicing enhancer, which in turn causes alternative exon splicing that can alter the reading frame and the transcript of the gene.<sup>10</sup>

This study sought to determine whether CKD patients' susceptibility to CVD was correlated with the *LDLR* rs688 polymorphism.

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## Materials and Methods

The case-control study was performed between July and December of 2022. The research groups consisted of a total of 200 participants. They were categorized into two distinct groups. Group I involved 100 CKD cases; they were enlisted from the dialysis department of Theodor Bilharz Research Institute.

The Kidney Disease Improving Global Outcomes (KDIGO) criteria were utilized to classify the CKD stages.<sup>11</sup>

Subgroup (a) included 50 patients with CVD. Cardiovascular disease was characterized as the existence of congestive cardiac failure, hypertrophy of the left ventricle, coronary heart disease, or myocardial infarction. Clinical signs of CVD were validated using suitable radiographic, biochemical, echocardiographic, and vascular diagnostic criteria.

Subgroup (b) included 50 CKD patients without CVD on regular hemodialysis treatment for more than 6 months and, confirmed by electrocardiogram (ECG) and echocardiography. All patients underwent a comprehensive evaluation, including a thorough medical history assessment, laboratory tests, and a physical checkup.

Group II consisted of 100 healthy individuals. They were randomly selected, primarily from Theodor Bilharz Hospital personnel and blood donors who had undergone health checks. All individuals exhibited a normal ECG and showed no clinical indications of CVD. There was no history of kidney disease in the control group.

Before enrolling, we measured serum creatinine levels for all participants in Group II. Individuals with a first-degree relative who had a family history of renal or cardiovascular illness were excluded from the research. The study obtained approval from the Institutional Review Board of Theodor Bilharz Research Institute (FWA 00010609) with a protocol serial number PT (710). All participants provided informed consent, adhering to the ethical guidelines of our hospital's ethics committee, the 1975 Helsinki Declaration, and its subsequent revisions.

### Sample size estimation

As per the prior study via Buraczynska *et al.*,<sup>12</sup> the frequencies of the rs688 genotypes CC among CKD CVD+ were 23% and 45% in normal control. At a power of 80% and a significance level of 5%, a minimum sample size of 160 individuals is required to detect the difference between groups, i.e., 80 participants in each group. To compensate for possible dropouts, 15% was added, and the total sample size was 184 participants (92 participants in each group). G\*Power (Germany; version 3.1.9.2) was employed to determine the sample size.

### Laboratory investigations

Four milliliters of venous blood were collected in a plain sterile vacutainer from all subjects used to determine serum creatinine, serum triglycerides, total cholesterol,

HDL-C, and LDL-C. In addition, 2 mL of venous blood was collected in an EDTA vacutainer to determine *LDLR* rs688.

In the clinical chemistry department of TBRI Hospital, regular laboratory tests were analyzed using a (Beckman Coulter)<sup>1</sup> AU 480 chemistry analyzer.

### Analysis of SNPs

#### Serum preparation and DNA extraction

The ThermoFisher Sci GeneJET Whole Blood Genomic DNA Purification Mini Kit<sup>2</sup> (Catalog number: K0781, supplied by Clinilab, Egypt) was used to extract DNA as directed by the kit instructions. Qubit fluorometric quantification assays were employed to measure the DNA concentration and its purity in the samples.

#### Genotyping assay

Amplification and real-time PCR with sequence-specific primers were utilized to detect *LDLR* rs688 in all the investigated subjects. (Applied Biosystems<sup>3</sup>) StepOne PCR equipment was utilized to assess the real-time PCR allelic discrimination tests generated from TaqMan<sup>®</sup> SNP Genotyping assays (Catalog number: 4371353, supplied by Clinilab, Egypt).<sup>13</sup>

The 40-fold SNP Genotyping Assay was diluted with 1×TE buffer to yield a 20× working stock. The mixture was then vortexed, centrifuged, and separated into aliquots holding 20 µl in microcentrifuge tubes. After that, it was kept for regular use at -20°C. As advised by Applied Biosystems, one negative control (NTC) was added to each plate, and the total volume of each component required for each experiment was computed. A 20 µl reaction mix was prepared for each well, comprising 10 µl of the TaqMan Universal PCR Master Mix (2×), 1.0 µl of the SNP Genotyping Assay's 20× working stock, 4.0 µl of DNase-free water, and 5 µl of the extracted DNA. The cycling conditions were the AmpliTaq Gold enzyme activation for 10 minutes at 95°C, denature for 15 seconds at 95°C, and anneal/extend for 1 minute at 60°C.

#### Allelic discrimination plate read and analysis

An endpoint plate read was carried out after PCR amplification utilizing an Applied Biosystem Real-Time PCR. Plotting fluorescence (Rn) values depending on the signals from each well were conducted by the Sequence Detection System (SDS) software using the fluorescence measurements taken during the plate read. The displayed fluorescence signals indicated the presence of specific alleles in each sample. Subsequently, an allelic discrimination plate read document was generated and

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configured in the SDS program to discern the alleles present.

### Statistical methods

We used SPSS statistical software (version 26). The normality of the data was evaluated using the Kolmogorov–Smirnov test. The mean and standard deviation (SD) were computed to synthesize the numerical data. At the same time, the qualitative data were represented by using frequencies and percentages. The correlation among qualitative data was evaluated using the chi-square test. The Mann–Whitney test was utilized to evaluate the numerical data of the two groups. When comparing more than two groups, the Kruskal–Wallis test was applied; for pairwise comparisons, a post-hoc test was utilized. The odds ratio (OR) and its correlated 95% confidence intervals (CI) were calculated using logistic regression to evaluate the degree of risk. By employing stepwise logistic regression, the multivariate analysis incorporated all pertinent variables that influence the risk of CVD. A p-value, or probability, less than or equal to 0.05 was considered to indicate statistical significance.

### Results

Genotyping of the *LDLR* rs688 in the studied groups revealed a significantly higher CT variant in CKD patients than among the controls ( $p = 0.006$ ) [Table 1].

CKD patients with CVD showed a significant increase in the average cholesterol, triglyceride, LDL ( $p$ -value  $< 0.001$ ), and years of dialysis ( $p$ -value = 0.027); however, a significantly lower HDL in CKD patients with CVD ( $p$ -value  $< 0.001$ ) was observed. Gender, creatinine level, and eGFR

**Table 1: Genotypes and allele distribution of the rs688 polymorphism in CKD patients and controls**

	N	CKD (n = 100)	Control (n = 100)	OR	95% CI	p-value
CC	82	33 (33%)	49 (49%)	1		
CT	83	43 (43%)	40 (40%)	3.2	1.4–7.5	0.006
TT	35	24 (24%)	11(11%)	2.0	0.9–4.7	0.096

CKD cases with CVD were significantly older than CKD cases without CVD ( $55.4 \pm 10.8$  years versus  $49.7 \pm 12.1$  years;  $p = 0.008$ ). There was a significantly greater percentage of hypertension among CKD cases with CVD ( $p$ -value = 0.026). CKD: Chronic kidney disease; OR: Odds ratio; CI: Confidence interval, CC: Cytosine/cytosine genotype, TT: Thymine/thymine genotype, CT: Cytosine/thymine genotype.

demonstrated no significant differences between CVD patients and patients without CVD ( $p$ -value = 0.398, 0.828, and 0.051, respectively) [Table 2]. There was a significant relationship between the CT and TT genotypes and the presence of CVD in CKD patients, with OR (95% CI) 4.3 (1.6–11.8), ( $p = 0.004$ ), and 7.6 (2.3–24.8), ( $p = 0.001$ ), consecutively [Table 3].

A multivariate logistic regression analysis was conducted to determine the relationship between the rs688 T variation and the risk of CVD in cases with CKD. The independent factors affecting the increased risk of developing CVD were hypertension and the T allele in both CT and TT [Table 4].

The results revealed a significant difference between gene allele and cholesterol with an overall  $p$ -value of  $< 0.001$ . Upon pairwise comparisons, a significantly lower cholesterol level was observed in individuals with the CC genotype compared to those with CT and TT genotypes (adjusted  $p$ -values = 0.015 and  $< 0.001$ , respectively).

**Table 2: Sociodemographic and clinical profile of CKD patients**

Characteristics	Total (n = 100)	CKD with CVD (n = 50)	CKD without CVD (n = 50)	p-value
Age (years)	52.3 $\pm$ 11.7	55.4 $\pm$ 10.8	49.7 $\pm$ 12.1	0.008
Gender (%)				
Female	34 (34%)	19 (38%)	15 (30%)	
Male	66 (66%)	31 (62%)	35 (70%)	0.398
Hypertension (%)				
No	28 (28%)	9 (18%)	19 (38%)	
Yes	72 (72%)	41 (82%)	31 (62%)	0.026
Systolic blood pressure (mmHg)	137.8 $\pm$ 15.6	142 $\pm$ 17	133 $\pm$ 13	$< 0.001$
Diastolic blood pressure (mmHg)	85.6 $\pm$ 12.6	90 $\pm$ 13	81 $\pm$ 11	$< 0.001$
Cholesterol (mg/dL)	232.4 $\pm$ 48.4	271 $\pm$ 34	194 $\pm$ 24	$< 0.001$
Triglyceride (mg/dL)	229.1 $\pm$ 75.2	270 $\pm$ 72	188 $\pm$ 53	$< 0.001$
HDL (mg/dL)	35.9 $\pm$ 5.6	32 $\pm$ 4	40 $\pm$ 5	$< 0.001$
LDL (mg/dL)	150.7 $\pm$ 43.7	184.9 $\pm$ 31.4	116.5 $\pm$ 22	$< 0.001$
Creatinine (mg/dL)	7.2 $\pm$ 1.1	7.3 $\pm$ 1.2	7.1 $\pm$ 1	0.828
eGFR (ml/min/1.73m <sup>2</sup> )	7.7 $\pm$ 1.9	7.4 $\pm$ 1.7	8.1 $\pm$ 2.1	0.051
Years on dialysis	7.4 $\pm$ 3.9	8.1 $\pm$ 3.6	6.8 $\pm$ 4.1	0.027

CKD: Chronic kidney disease; CVD: Cardiovascular disease; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; eGFR: Estimated glomerular filtration rate.

**Table 3: Relation between CVD risk in CKD patients and rs688 polymorphism**

	N	CKD cases		OR	95% CI	p-value
		CKD with CVD (n = 50)	CKD without CVD (n = 50)			
CC	33	8 (16%)	25 (50%)	1		
CT	43	25 (50%)	18 (36%)	4.3	1.6–11.8	0.004
TT	24	17 (34%)	7 (14%)	7.6	2.3–24.8	0.001

CKD: Chronic kidney disease; OR: Odds ratio; CI: Confidence interval, CC: Cytosine/cytosine genotype, TT: Thymine/thymine genotype, CT: Cytosine/thymine genotype.

**Table 4: Multivariate analysis of factors impacting CVD risk in CKD patients**

	P-value	OR	95% CI	
			Lower	Upper
Hypertension (yes vs > no)	0.002	6.2	1.9	19.6
<i>LDLR</i> SNP rs688				
CT vs ≥ CC	<0.001	9.8	2.9	33.2
TT vs ≥ CC	<0.001	8.7	2.6	29.8

*LDLR*: Low density lipoprotein receptor; CKD: Chronic kidney disease; CVD: Cardiovascular disease; OR: Odds ratio; CI: Confidence interval; SNP: Single nucleotide polymorphism, CC: Cytosine/cytosine genotype, TT: Thymine/thymine genotype, CT: Cytosine/thymine genotype.

A significant difference was observed between gene alleles and triglyceride levels, with an overall p-value < 0.001. Subsequent pairwise comparisons revealed a significantly higher triglyceride level in individuals with the TT genotype than those with CC and CT genotypes (adjusted p-values < 0.001 and 0.041, respectively).

Furthermore, a significant difference was identified between gene alleles and HDL levels, yielding an overall p-value of 0.001. Further pairwise comparison revealed a significantly lower level of HDL in individuals with the TT genotype compared to those with the CC genotype (adjusted p-value < 0.001).

Moreover, a significant difference was observed between gene alleles and LDL levels, with an overall p-value of 0.002. Upon pairwise comparisons, a significantly lower LDL level was noted in individuals with the CC genotype compared to those with CT and TT genotypes (adjusted p-values = 0.022 and 0.003, respectively).

There was a significantly higher proportion of hypertension in individuals with TT and CC genotypes compared to those with the CT genotype [Table 5].

## Discussion

CVD is one of the most common consequences of CKD,<sup>14</sup> which suggests the existence of multiple risk factors related to kidney disease.<sup>15,16</sup> These risk factors include chronic inflammation and elevated oxidative stress.<sup>7</sup>

Elevated serum cholesterol, LDL concentration, and dyslipidemia are among the various factors that contribute

**Table 5: Correlation between rs688 polymorphism in both CKD subgroups and the laboratory data**

Characteristics	CC (n = 33)	CT (n = 43)	TT (n = 24)	p-value
Age	51.2 ± 12.8	51.2 ± 11.8	57 ± 9.5	0.068
Years of dialysis	7.4 ± 4.5	7.3 ± 3.7	7.7 ± 3.4	0.705
Systolic blood pressure	138.8 ± 14.0	138.5 ± 18.2	135.2 ± 12.9	0.773
Diastolic blood pressure	85.3 ± 11.7	84.3 ± 14.5	88.5 ± 10.1	0.413
eGFR	8.3 ± 1.9	7.4 ± 1.6	7.4 ± 2.1	0.063
Gender				
Female	8 (24.2%)	16 (37.2%)	10 (41.7%)	0.329
Male	25 (75.8%)	27 (62.8%)	14 (58.3%)	
Hypertension				
No	4 (12.1%)	21 (48.8%)	3 (12.5%)	<b>&lt;0.001</b>
Yes	29 (87.9%)	22 (51.2%)	21 (87.5%)	
Cholesterol	207.2 ± 46.2	238.1 ± 42.1	256.8 ± 47.8	<b>&lt;0.001</b>
Triglyceride	196.6 ± 68.3	228.4 ± 68.7	274.8 ± 74.6	<b>&lt;0.001</b>
HDL	38.5 ± 5.2	35.4 ± 5.4	32.9 ± 5.1	<b>&lt;0.001</b>
LDL	129.3 ± 39.6	156.9 ± 39.4	168.8 ± 46.1	<b>0.002</b>
Creatinine	6.9 ± 1.2	7.3 ± 1.1	7.2 ± 1.2	0.497

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; eGFR: Estimated glomerular filtration rate. Bold indicates significant values, CC: cytosine/cytosine genotype, TT: thymine/thymine genotype, CT: Cytosine/thymine genotype.

to atherosclerosis and CVD in individuals with CKD. In hemodialysis patients, CVD may be partially attributed to acquired LDL receptor deficiency. Extensive research has demonstrated that genetic variables, such as genetic predisposition has a significant role in the development of CVD.<sup>17</sup>

In the current study, genotyping of rs688 in the *LDLR* gene revealed a significantly higher frequency of rs688 genetic CT variant in CKD cases than in the controls.

We compared the distribution of rs688 genetic polymorphism in the *LDLR* gene between CKD patients with CVD and CKD cases without CVD. The CT and TT genotypes were significantly greater in the CKD patients with CVD, respectively suggesting that rs688 genetic polymorphism may exert its influence in a dominating manner. Moreover, the rs688 a functional SNP in the *LDLR* gene that affects the efficiency of exon splicing, and raises the proportion of *LDLR* transcripts lacking exon 12 or exons 11 and 12.<sup>18</sup> Exon-12-deficient *LDLR* and exon-11- and 12-deficient *LDLR*, results in alterations in the *LDLR* gene's reading frame and the appearance of premature stop codons in exons 13 and 14.<sup>10</sup>

Therefore, it is anticipated that the translation of these *LDLR* isoforms would generate proteins that include the LDL-binding domain encoded by exons 1–7 but do not have the transmembrane domain represented via exons 16–17.<sup>18</sup> Consequently, this will lead to elevated levels of both whole and LDL cholesterol.<sup>19</sup>

Our study's findings are consistent with a Polish study that included 500 people regarded as healthy controls and 800 patients with CKD. According to their findings, the CVD subgroup had considerably higher frequencies of the T allele and TT genotype, with OR (95% CI) 3.4 (2.71–4.26,  $p < 0.0001$ ) and 13.2 (7.87–22.09,  $p < 0.0001$ ), respectively.<sup>12</sup>

The *LDLR* rs688 TT genotype exhibited a robust association with an increased risk of CVD in Indian patients (OR = 3.0; 95% CI = 1.43 × 6.2;  $p = 0.003$ ). Similarly, the *LDLR* rs688 T allele demonstrated a significant association with a higher likelihood of CVD (OR = 0.74; 95% CI = 1.57–0.97;  $p = 0.03$ ) compared to the C allele. This study involved a cohort of 400 individuals from India. These results align with the outcomes of our investigation.<sup>10</sup>

A recent study has shown a correlation between *LDLR* gene variations and cardiovascular disease. This association was particularly pronounced among the rs688 TT genotype male carriers. The odds ratio for hyperlipidemia was significant in those with the TT genotype (OR = 0.5, CI: 0.29–0.907) but not in those with the CT or CC genotypes.<sup>5</sup>

There may be a connection between *LDLR* polymorphism and cardiovascular disease through mechanisms other than the lipoprotein metabolism cascade. The rs688 polymorphism in the *LDLR* gene appears to be one of the possible risk factors in the development of cardiovascular disease in people with CKD, even though a single polymorphism has little effect on prevalent illnesses.

The present investigation exhibits certain limitations. Originally, this study was conducted at a single center. In addition, specific comorbidities observed in CKD patients may be a confounding variable.

The detection of SNP rs688 C>T in *LDLR* genes demonstrated a significant correlation between the CT and TT genotypes and the occurrence of cardiovascular disease in CKD cases. The potential utilization of this SNP as a predisposing genetic marker for CVD in CKD cases is suggested.

### Conflicts of interest

There are no conflicts of interest.

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