Yadav *et al.*
Egyptian Journal of Medical Human Genetics (2023) 24:74
https://doi.org/10.1186/s43042-023-00440-y

Egyptian Journal of Medical Human Genetics

REVIEW

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Association of *ABCA1* gene with Coronary Artery Disease (CAD): an overview

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Abstract

Background This review is a summarized study on CAD, CVD, atherosclerosis, and its association with the *ABCA1* gene. Only 13 clinical as well as epidemiological and peer-reviewed research papers published in the associated field were chosen for the review from out of 55 articles.

Main body The research papers have been collected and studied from PubMed, Research Gate, and Google Scholar search engines. In the study, it has been found that GWAS, cell culture, and data-based studies were done to figure out the relationship of the *ABCA1* gene with heart diseases. Blood samples were collected and diagnosed both biochemically and genetically to find out the lipid level and its functioning in the efflux of cholesterol and its effect and association with the *ABCA1* gene, and with CAD researchers.

Conclusions Dysregulation of DNA methylation can be re-expressed epigenetically. These studies of the *ABCA1* gene and its polymorphic variants would help in future research studies and further can develop new drugs and methods the for treatment of heart disease and CAD.

Keywords Coronary artery disease, *ABCA1* gene, Nucleotide binding domain, Polymorphic variants

Background

Among various heart diseases, CAD is responsible for the mortality and morbidity of patients worldwide. CAD develops due to the deposition of cholesterol leading to plaque in the arterial inner walls. Being a multi-factorial disease its association with certain genes such as *ABCA1* and *ABCG1* gene has also been studied [18]. The *ABCA1* gene belongs to the ATP-binding membrane cassette genes (ABC) family, this uses ATP to transport any substrate from one organelle to another within a cell. These transporters have two conserved peptide motifs, Walker A and Walker B, on nucleotide-binding domains (NBD) and specific amino acids between motifs for identification of the family [17]. NBD follows the Hexa helical transmembrane in the structural halves repeats of the *ABCA1* gene. *ABCA1* contains two extracellular domains, one between transmembranes 1 & 2 and the other one between transmembranes 7 & 8, these domains have two disulfide bonds necessary for the formation of HDL and sticking of apoA-I to the *ABCA1* [9]. *ABCA1* gene proved as an essential factor in the reverse transportation of cholesterol and thus shows an anti-atherosclerotic effect, i.e., no development of plaque in the inner arterial walls. *ABCA1* gene is 249 bp long with 49 exons located on chromosome 9q31.1 and shows susceptibility toward coronary artery disease [3]. Due to its anti-inflammatory receptive behavior inflammatory expression of factors such as IL-6, IL-1β, and NEF-α were suppressed [12]. The relationship of the *ABCA1* gene SNPs with CAD has also been studied in previous research [4]. Clinical, and epidemiological studies were done on *the ABCA1* gene, its polymorphic variants, and their association with CAD and other heart diseases. Therefore, in this review article

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vivid worldwide research performed on the ABCA1 gene and inferences drawn from those were discussed and tabulated (Table 1). ABCA1 mechanism is described in the form of figure (Fig. 1).

Main body

Molecular studies on the ABCA1 gene

Fouladseresht et al. [6] conducted a study on the Iranian population. This haplotypic investigation has identified a link between SNPs and CAD. The study's findings suggested a substantial correlation between the ABCA1 gene's polymorphic variants rs2422493 and rs1800976, which had T and G allelic frequencies, and the sensitivity of ABCA1 expression to CAD. The presence of the G allele at the third position in the haplotype T-G-X-A was thought to be a substantial risk factor for coronary artery disease (CAD) among susceptible individuals for the haplotypes T-G-G-A and T-G-A-A, or variant rs2230806 of the ABCA1 gene. Although CAD patients will be benefited from the C–C-G-G haplotype.

Samples from the Chinese armed police force were taken for six months in 2019 as part of [1], study of the Chinese population with 90 individuals with Premature Coronary Artery Disease (pCAD). The study examined the impact of methylation ABCA1 promoter on pCAD and its associations with lipid levels, inflammatory variables, and neutrophil extra traps (NETs) in patients with pCAd in China. The study concluded that the level of ABCA1 promoter methylation is positively correlated with the inflammatory cytokines (CRP, IL-1), and cfDNA/NETs. While the age and ABCA1 methylation status relationship were not significantly correlated in this study. Additionally, it has been noted that an individual's risk for pCAD can increase with a high rate of ABCA1 promoter methylation. This investigation might potentially produce a brand-new treatment for the regulation of DNA methylation for pCAD [1].

A study on 110 Iranian population was done, to check the severity development of CAD by studying the role of *ABCA1* DNA methylation. This research stated that DNA methylation frequency showed more significance in old-age CAD patients rather than in young CAD patients. It also found that *ABCA1* promoter methylation region and concentrations of plasma lipid have no significant association. Smoking affects the *ABCA1* methylation region too, in CAD patients was observed. This study limited itself in not assessing the gene expression levels and the cholesterol efflux activity assay was also not studied [8].

In case–control research that was just published in 2022 on a population of 260 people including both 120 cases and 20 more control people than the former.e.,140. The listing of CpG sites in base pairs to the transcriptional start site (TSS) and the positive distances downstream of TSS were both influenced by relative distance. 37 sites were downgraded compared to the control group for analysis, whereas 14 methylated sites of the case group were increased. According to the study's findings, the lipid metabolic genes APOC3, CETP, and APOC1 exhibited lower methylation levels (hypomethylated) in the case than the control ones. Two of the APOA5 lipid metabolic gene's four CpG sites were hypomethylated, while two were hypermethylated. While of the LIPC gene 3 sites were methylated out of four sites. ANGPTL4, APOB, and PCSK9 genes had shown no significant role in methylation. APOC3, LIPC, CETP, and APOC1 were discovered significant in each sex (male & female) whereas APOA5 and ANGPTL4 were notified only in males [11].

Mahmoodi et al. [14], studied a population of 220 including subjects and control. This study aimed to investigate the prevalence and effect of polymorphic C-565 T of the ABCA1 gene on lipid profiles in Iranian CAD patients. This study indicated that ABCA1 C-565 T polymorphism is a significant risk factor for the development and severity of CAD in the TT homozygotic Iranian population. No significant association between ABCA1 C-565 T polymorphism and plasma lipid levels was evaluated. Net flux of cholesterol toward the liver from the vessel wall would get affected by reduced activity of the T allele of ABCA1 C-565 T polymorphism. This study had not performed some of the experiments, firstly, assay assessment of cellular cholesterol efflux activity, secondly, other polymorphic variants of the ABCA1 gene in relationship with CAD, and thirdly, undetermined ABCA1 gene expression level.

A pilot study was done in Mumbai, India 2017 in which 150 CAD patients were selected as subjects. This study reported the presence of 3112 SNPs of HDL-associated genes in the untranslated region (UTR), intronic, and exonic regions. A significant allelic association of the *ABCA1* gene with other genes such as APOA1, GALNT2, COBLL1, SLC39A8, TRPS1, MADD, UBASH3B, MVK, SCARB1, VDR, LACTB, LILRA3, and HNF4A was observed between subjects and controls. HDL-C levels were significantly increased in controls than in the subjects. HDL-C levels showed a correlation with variants of MADD, PPP1R3B, and LILRA3 genes. This study was limited to a sample consuming lipid-modifying drug(s), a heterogeneous population, and a lack of sufficient data for calculating the potentiality of risk factors (for instance lifestyle) [20].

In past research carried out during 2016–2017, on 82 patients including control and subjects. This study includes an analysis of EAT (epicardial adipose tissue) and SAT (subcutaneous adipose tissue) collected from the ostium of the right coronary artery and the

Table 1 Enlisted research studies performed by various authors on coronary artery disease (CAD) and its association with the ABCA1 gene and also include tools and techniques performed by them

References	Polymorphic variants studied	Primers	Techniques involved	Statistical tools applied in the study	The outcome of the study
[6]	ABCA1/ rs2422493 & rs1800976, rs2230806, rs1883025	NA	Genotyping, Gene Amplification	Hardy–Weinberg equilibrium. Pearson χ2 testing. Binary logistic regression analysis	Polymorphic variants in haplotypes play a significant role in CAD
[1]	ABCA1	F: 5′-GGG TGG AGG GTA TAG TAG GT-3′ R: 5′-AAC AAA TTC CAC TAA TAC CCT TAA CT-3′ Seq: 5′-AAC AAA TTC CAC TAA TAC CCT TAA CT-3′	Genotyping, DNA sequencing	SPSS19.0 software, Kolmogorov–Smirnov test, t-test, Mann–Whitney test, Chi-square test, Pearson's and nonparametric Spearman's rank correlation test	ABCA1 is associated with inflammatory factors, CRP, IL-1β) and cfDNA/ NETs promote pCAD
[12]	ABCA1/ rs1800976, rs4149313, rs2230806	NA	Statistical study	Standard Deviation, Shapiro–Wilk test, one-way ANOVA analysis, χ^2 test, V.13.0 SPSS	the rs4149313 & rs2230806 variants cause lipid abnormality and may cause CAD, while rs1800976 can develop CAD
[8]	ABCA1	(Methylated F: AAT TTT ATT GGT GTT TTT GGT TGT C, methylated R: ATA TCT TAA AAT CCG CGA TCT ACG and (un-methylated F: AAT TTT ATT GGT GTT TTT GGT TGT T, un-methylated R: TAT CTT AAA ATC CAC AAT CTA CAT C)	Epigenetic study	Student t-test, Chi-square test or Fisher's exact tests, binary Logistic regression, SPSS 16 software	DNA methylation of ABCA1 is responsible for the development of CAD but not for the severity of CAD and has no significant association with plasma lipid concentrations
[11]	ABCA1, APOC3, CETP, APOC1, APOA5, LIPC	NA	Epigenetic study	SPSS package version 21.0, GraphPad Prism 5 Software. T-test analysis and standard deviation were performed	methylation levels of APOC3, CETP, and APOC1 gene promoters were found lower in CAD subjects while APOA5 and LIPC gene promoters were higher in CAD subjects, i.e., DNA methylated genes play a major role in CAD development
[7]	ABCA1/ rs111292742, rs9282541	NA	Epigenetic study	Ingenuity Variant Analysis	Variants of the ABCA1 gene are associated with the development of premature CAD
[14]	ABCA1 / C-565 T (rs2422493)	forward 5′-AAAGACTTCAAGGAC CCAGCTT-3′and reverse 5′-CCTCAC A TTCCGAAAGCATTA-3′	Epigenetic analysis	SPSS Software, Student's t-test, chi-square test, or Fisher's exact tests, Multiple binary logistic regression	C-565 T (rs2422493) variant of ABCA1 independently & significantly, increase the risk for CAD
[20]	ABCA1 / rs72735008, GALNT2 / rs11620, PPP1R3B/ rs330921, APOA2 / rs6413453, MADD/ rs8027027	NA	Genetic study	PLINK V.1.07 for minor allele frequencies Hardy–Weinberg equilibrium (HWE), linkage disequilibrium (LD), SPSS V.20 for normality of the phenotypical & genotypical comparative variables	low HDL-C patterns were observed in Indians and HDL-associated genetic loci to CAD

Table 1 (continued)

References	Polymorphic variants studied	Primers	Techniques involved	Statistical tools applied in the study	The outcome of the study
16	ABCA1	5′-AAC AAA TTC CAC TAA TAC CCT TAA CT-3′ 5′-biotin-GGG TGG AGG GTA TAG TAG GT-3′ Seq 5′-AAC AAA TTC CAC TAA TAC CCT TAA CT-3′	Epigenetic study	Shapiro–Wilk test, t-tests, Mann–Whitney's U-test. Wilcoxon's signed-rank test. Holm-Bonferroni, Fisher's exact test, Spearman correlation, Statistical analysis by SPSS 17.0 software & in R statistical computing environment	ABCA1 and ABCG1 DNA hypermethylated genes in EAT showed an association with CAD. Decreased ABCA1 mRNA expression in EAT results in multifocal atherosclerosis
	ABCG1 locus 1	5′-TGA GTT TAG GAG GTT AAG GAG AAA TT-3′ 5′-biotin-CAA ATA AAC CAA CAA CAA AAC AAT AC-3′ Seq 5′-TGA GTT TAG GAG GTT AAG GA-3′			
	ABCG1 locus 2	5′-GTA AGG TTT GGG GTT ATT TTA GTG G-3′ 5′-biotin-AAA ACA AAC CCT TAA ATC TCT TTA CAT-3′ Seq 5′-GAG ATT AGG GTT TTT TTT AGATA-3′			

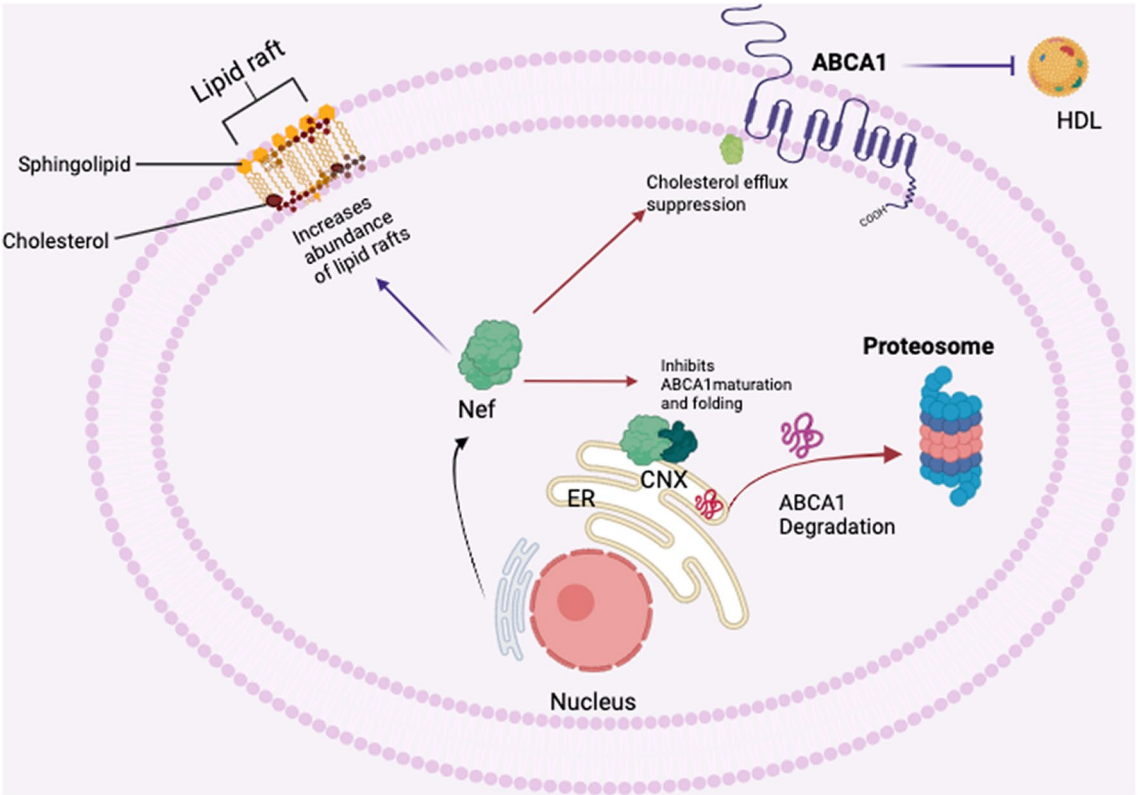

Fig. 1 An illustration showing how the ABCA1 gene's ability to produce HDL is inhibited. The ABCA1 gene, which encodes the cellular cholesterol transporter, is shown in this figure to be downregulated by Nef. Nef also alters the function of ABCA1 protein upgradation by blocking its interaction with the chaperone Calnexin (CNX), which results in the gene's degradation in the proteasome and prevents the production of HDL [10]

incision of the chest area samples, respectively. ABCA1 DNA hypermethylation is associated with CAD in EAT. Downregulation of the ABCA1 gene was observed for CAD with concomitant carotid artery disease or peripheral artery disease in EAT. Whereas the association of hypertriglyceridemia and obesity with DNA methylation levels at the ABCG1 cg27243685 locus in SAT. No significant association of mRNA levels with CAD and no correlation between DNA methylation and mRNA levels was observed. In macrophages, upregulation of ABCA1 mRNA levels and decreased levels of protein were reported. Gender differences in studied individuals show no association with changes in DNA methylation [16].

Epidemiological studies

An epidemiological study was done on 112,776 men and 145,476 women for 3 years (2014–2016) by diagnosing serum and plasma for assessment of total cholesterol, triglycerides, LDL-C (direct & sdLDLC), HDL-C, apoA-I, apoB, glucose, insulin, adiponectin, hs-CRP, fibrinogen, myeloperoxidase (MPO), SGOT & SGPT levels of liver. HDL-C and TG plasma-associated variants- *ABCA1* rs111292742, *ABCA1* rs9282541, *LCAT* rs4986970, and *LPL* rs268 were studied. It concluded that the defect in HDL-deficient male patients was due to malfunctioning of the *ABCA1* gene products, resulting in the inefficiency to efflux cholesterol onto HDL. Premature ASCVD had shown an association with HDL loss due to mutations or variants at the locus of *ABCA1* or *APOA1* in data-based sequencing [7].

Another study on a population of Nanchong, China had been done to analyze the polymorphic activity of the *ABCA1* gene in 442 CAD patients and 217 normal subjects. This study had also shown the outcome of CAD risk factors, and CAD's development with polymorphic genes. This study inference that rs1800976, the polymorphic form of *ABCA1*gene and its C allele, shows an association with hs-CRP and CysC plasma levels and with high CAD risk, whereas rs4149313 and rs2230806 variants show no significant association with CAD severity. The rs1800976 variant shows association with CAD but doesn't play any role in the expression of *ABCA1* gene regulation rather it shows association with the expression of the same gene, as it resides in *ABCA1*gene promoter region and affects the plasma levels of hs-CRP and CysC. [12].

In a CAPIRE study, 525 patients of age 45–75 who had a normal fraction of left ventricular ejection and with no coronary syndrome history were accepted for the study. It was concluded in the study that HDL functions instead of HDL levels had shown a significant association with coronary artery disease. SR-BI-mediated cholesterol efflux showed an association with decreased CAD like HDL while *ABCA1*-mediated cholesterol efflux had shown no improvement beyond the traditional risk factor in patients and neither helped in the prediction of cardiovascular events. This study suggested that HDL functions as a predictor of cardiovascular disease but shows no relation to improved atherosclerotic plaque characteristics [13].

A total of 860 patients were included in an observational study from January 2015 to February 2018 to examine the effectiveness of novel cardiovascular imaging methods. According to the study, ApoE-HDL-C and ApoC-III in HDL determine how serious a CVD is. Males were more at risk for CVD than females. Sex differences in the correlations between ApoE and ApoC-III can be studied in future too [19].

A study on the anti-atherosclerosis properties of apolipoprotein A1(apoA1). This study includes a half rise in the production of cholesterol involving *ABCA1*, the resultant rise of 30% in HDL-C level leads to a decrease in the risk of coronary artery disease by 35–50%. *ABCA1* gene promoter can be regulated by using many drugs such as myocardin, and rutaecarpine while for gene expression, microRNA and long noncoding RNA genome-wide techniques were incorporated after transcription for its regulation. Downregulated microRNA-17-5p (miR-17-5p) restricts lipid aggregation thereby upregulating the *ABCA1* gene. miR-17-5p allows *ABCA1* binding to the 3-untranslated region of miRNA. Further, enhanced RCT and cholesterol metabolism levels in patients with CVD can be identified by miR- 144 along with antisense oligodeoxynucleotides. It was studied that miR-33 can accelerate atherogenesis due to the inhibition of the *ABCA1* gene. The chemical compound N-benzothiazolyl-2-benzenesulfonamide acts as an up-regulator of the *ABCA1* gene and promotes cholesterol efflux by enhancing *ABCA1* mRNA [22].

The anti-inflammatory function of ABCA1 was investigated in the treatment and prevention of coronary heart disorders. Inflammation occurs during atherogenesis when cholesterol builds up in macrophage foam cells. This inflammatory reaction reduced macrophage ABCA1, which reduced cholesterol export and increased inflammation. The anti-inflammatory properties of HDL decrease the signaling of toll-like receptors. Migration of monocytes happens as a result of inflammation brought on by lipid buildup in the arteries, which causes macrophage lipid accumulation to increase. It can be said that the activator of ABCA1 efficiently reduces atherosclerosis/CAD [15].

Criteria for inclusion of subjects in the studies reviewed

The following inclusion criteria were accepted in the reviewed studies-

A blockage in the left bundle branch, an inversion in the T-wave of more than three millimeters in three or more leads, an elevation or depression of 0.5 mm or more in the ST-segment, an elevated level of troponin-T, a cardiac marker, and an elevated level of creatine-kinase muscle/brain in serum were used to identify and select CAD patients for research [6]. Subjects having stenosis of more than 50% were included. The trials also included individuals with low-risk factors and no CAD, individuals with multiple risk factors and no CAD, those with low-risk factors and CAD diffusion extended to > 5 of the 16 segments, and individuals with multiple risk factors and CAD diffusion extending to > 5 segments [13].

Exclusion criteria for subject selection in past studies

Exclusion criteria for the selection of CAD subjects used in various pieces of research are followed as-

Autoimmune disease patients or previous malignant neoplasms were not included in the study [6]. Cardiogenic attack, heart failure, liver and kidney malfunction, malignant tumor, and patients on treatment with drugs for lowering lipid level, coronary angiography, or tomography, and had stenosis results less than < 50%, were excluded [1]. Subjects were excluded based on the intake of drugs that may affect their metabolism [12]. Subjects with a family history of CAD, solid tumor patients, and febrile disease were also excluded [8]. Lower stenosis report of the patients was also an important exclusion criterion [11]. Type 1 and type 2 diabetic patients were also excluded from the research [13].

Conclusions

In this review study, we explored CAD and its relationship to the ABCA1 gene, which encodes a large membrane protein that performs reverse cholesterol transportation (RCT) activity in humans to transfer lipids to HDL and is also linked to apoA-1 [21]. The SNP rs2230806 of ABCA1's K allele showed a strong connection with a lower incidence of CAD in the Asian population [5]. Dysregulation of DNA methylation can lead to cardiac conditions including CAD and CVD and can be epigenetically re-expressed. It can happen owing to mutation or in the absence of a methyl donor due to a shortage of nutrients in the body [2].

ABCA1 SNPs like rs1883025 have been linked to CHD via epigenetic alterations, according to Churilin et al. [4].

This review will assist new researchers in identifying diverse gene variants and their associations with coronary artery disease (CAD) and lipid levels in the body, as well as in the development of new hypotheses for a variety of heart disorders and the study of epigenetics.

Abbreviations

CAD	Coronary artery disease
CHD	Coronary heart disease
CVD	Coronary vascular disease
CAC	Coronary artery calcium
EAT	Epicardial adipose tissue
SAT	Subcutaneous adipose tissue
NBD	Nucleotide binding domain
MPO	Myeloperoxidase
CCTA	Coronary computed tomography and angiography
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

Acknowledgments
Not Applicable.

Author contributions
All authors contributed to this work. SS & TY conceived and designed the study strategy and quality assessment; TY independently completed the processes of the article search, article assessment, data extraction, and wrote the manuscript. AY edited the article. AJ completed the second time article analysis. All authors reviewed and approved the final manuscript.

Funding
No funding agency has contributed to this article.

Availability of data and materials
The present review article data are from publicly accessible sites and the data that supports the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent participation
Not applicable.

Consent for publication
Not applicable.

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

Received: 18 December 2022 Accepted: 21 September 2023
Published online: 11 November 2023

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