Review Article

CD36 gene variants and their clinical relevance: a narrative review

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Objective: This article aimed to describe *CD36* (SR-B2) gene variants and their clinical relevance by referring to existing related literature and electric database.

Background: Human CD36 is a transmembrane glycoprotein expressed on platelets, monocytes, macrophages, endothelial, skeletal and cardiac myocytes, and several other cell types. In parenchymal cells, CD36 also recycles between subcellular compartments and the plasma membrane, thereby regulating its presence and thus activity at the plasma membrane. As a highly polymorphic gene, a lot of nucleotide variants in or out of the coding regions may decrease CD36 expression level, change extracellular ligand-binding domain, or even cause protein deficiency, which may affect CD36 function and be associated with some diseases.

Methods: The medical literature of published investigational studies, systematic reviews, and database of National Center for Biotechnology Information (NCBI) regarding *CD36* gene variants and their clinical relevance were searched and analyzed.

Conclusions: More than 30 thousand nucleotide variants were found in the *CD36* gene, and at least 60 variants in the coding region can cause defective expression of CD36 antigen and lead to isoimmunization and further immune thrombocytopenia. Differential expression of CD36 glycoprotein, due to gene variants, on platelets, spleen monocytes and capillary endothelial cells also affects the severity of malaria development by varying the degree of adhesion to Plasmodium infected red blood cells. Furthermore, as a multifunctional receptor, CD36 mediates the cellular binding and recognition of various lipidic and proteinaceous ligands. Cellular responses to these ligands are involved in cell adhesion, angiogenesis, inflammatory response, oral fat perception and preferences, fatty acid processing and metabolism, and closely related to the occurrence and development of atherosclerosis and other cardiovascular diseases. Studies in different populations have found that multiple variants of *CD36* gene impact on fat intake and obesity, fatty acid processing and other metabolic syndromes.

Keywords: CD36; gene polymorphism; thrombocytopenia; malaria; metabolic syndrome

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Introduction

The cluster of differentiation 36 (CD36) was found over 40 years ago as glycoprotein IV (GPIV) by lectin affinity chromatography on human blood platelet membranes (1). It was later found to be identical to the antigen recognized by the monoclonal antibody OKM5, a marker for monocytes and macrophages (2). Subsequently, CD36 antigen was detected on many other tissues and cells including epithelial cells, vascular endothelium, adipocytes, skeletal and cardiac myocytes, microglia, pancreatic β-cells, dendritic cells, erythroid precursors, hepatocytes, specialized epithelia of the breast, kidney, gut and tongue, kidney glomeruli and tubules cells, retinal pericytes and pigment epithelium cells (3).

Biased expression of *CD36* gene in breast, adipose, heart, colon and white blood cells, which is higher than that in other 11 human tissues, was found in a transcription profiling by high throughput sequencing of Illumina Inc. (4).

The diverse expression pattern of CD36 is a reflection of its multiple cellular functions. Extensive research aiming at thoroughly understanding of CD36 protein has been carried out since its discovery. Initially, researchers focused on the characteristics of the CD36 gene and protein, its tissue and subcellular localization, and its function. Subsequently, other studies examined the role of CD36 in the pathogenesis of many diseases. Studies have reported that the CD36 protein serves as a receptor for thrombospondin in platelets and various cell lines. Since thrombospondins are widely distributed and involved in a variety of adhesive processes, CD36 protein may have important function as a cell adhesion molecule. The CD36 protein also binds to collagen and anionic phospholipids, and functions as a scavenger receptor that can absorb oxidized low-density lipoproteins (ox-LDL) and long chain fatty acids (LCFA), so it plays a role of fatty acid translocase (FAT) in the transport or serve as a regulator of fatty acid transport. Furthermore, CD36 directly mediates cytoadherence of *Plasmodium falciparum* parasitized erythrocytes (5). Mutations in the *CD36* gene can cause platelet glycoprotein deficiency, and may further lead to immune thrombocytopenia due to CD36 isoantibody (6). The various synonym of CD36, such as platelet GPIV, glycoprotein IIIb (GPIIIb), collagen type I receptor, thrombospondin receptor, PAS IV, FAT, scavenger receptor class B member 3 (SCARB3 or SR-B2), bleeding disorder platelet-type 10 (BDPLT10) and coronary heart disease type 7 (CHDS7), also show a variety of physiological or pathological functions of CD36. In this review, we focus on *CD36* gene variants and their clinical relevance especially on thrombocytopenia, malaria, lipid taste perception and obesity, and other metabolic syndromes including atherosclerosis and type 2 diabetes mellitus (T2DM). As a search literature strategy, the gene, Single Nucleotide Polymorphism database (dbSNP) and PubMed electronic database of National Center for Biotechnology Information (NCBI) was searched for publications on clinical relevance of CD36 without time limits using English language as a restriction. The Medical Subject Heading and key words used were: “CD36”, “gene”, “variant”, “polymorphism” and “thrombocytopenia”, “malaria”, “obesity”, “metabolic syndrome”, “atherosclerosis”, “Type 2 diabetes mellitus”, “Colorectal Cancer”, “Alzheimer’s disease”. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aob-21-49).

CD36 gene and protein

The *CD36* gene is located on chromosome 7q21.11 and spans about 77kb. At least 20 alternatively spliced transcript variants have been found for this gene, including 16 coding mRNA, 1 non-coding mRNA and 3 predicted mRNA obtained by automated computational analysis of CD36 mRNA and EST data. A total of 19 exons were found in the *CD36* gene, but there were up to 15 exons which could be spliced in a single mRNA variant and of which 12 exons are coding. In two major transcript variants (isoform 1 and 3), exon 1, 2 and 5'-end of exon 3 are non-coding. The coding region contains 1,419 nucleotides, ranging from 3'-end of exon 3 to exon 14, and encodes 472 amino acid (Aa) residues. The 3'-end of exon 14 in isoform 3 and exon 15 in isoform 1 are also non-coding regions (7).

The CD36 transmembrane protein contains both an N-terminal (Aa2–7) and a C-terminal (Aa462–472) cytoplasmic tail with Src-family tyrosine kinases necessary for signal transduction, two transmembranes (Aa8–29 and Aa440–461), and a big extracellular loop (Aa30–439) with hairpin-like membrane topology (8). The heavily glycosylated extracellular domain of CD36 includes three disulfide bridges in the carboxyl-terminal half that were shown to be important for CD36 membrane recruitment. The extracellular domain contains multiple binding sites for ligands and posttranslational modification sites including lipidation, acetylation, glycosylation and phosphorylation (*Table 1*). Besides the transmembrane form of CD36, soluble form sCD36 is also generated, which is formed by the abscission of extracellular domain of transmembrane CD36. Some data presented suggest a possible protective effect of a higher sCD36 concentration in relation to metabolic syndrome components (13).

So far, a total of 30,703 nucleotide variants of *CD36* gene, including 26,531 single nucleotide variants (SNVs) and 4,172 multiple nucleotide variants (MNVs) or deletion/insertion variants (DELINS), have been found and deposited in dbSNP database of NCBI website (14). Most of the gene variants are in the non-coding region and do not cause amino acids changes or functional changes, but a small number of nucleotide variants, including 590 missense mutations in the coding region or flanking splice sites, may affect function of the CD36 protein. In addition, some nucleotide variants in the non-coding region were

Table 1 Amino acid position of CD36 posttranslational modifications and ligand binding domains

Amino acid position	Modifications or binding ligands	Ref.
3, 7, 464, 466	Lipidation	(8)
8–29, 186–204, 440–461	Hydrophobic domain	(8)
52, 56, 169, 231, 394, 398, 403	Acetylation	(8)
79, 102, 134, 163, 205, 220, 231, 235, 247, 321, 417	N-linked glycosylation	(8,9)
92, 237	Phosphorylation	(8,9)
243–311, 272–333, 313–322	Disulfide bond	(8)
469, 472	Cross-link, ubiquitination	(8)
93–120	Thrombospondin	(8)
97–110, 139–184	Plasmodium falciparum	(5,8)
127–279	Fatty acids	(10)
139–183	Multiligand binding site	(9)
151–171, 155–183	Oxidized low-density lipoprotein	(10,11)
157–171	Oxidized phosphatidylcholine	(12)

also found to be associated with protein expression level and some clinical symptoms (15-17).

CD36 gene variants and thrombocytopenia

It has been shown that the Nak^a antigen is located on CD36 and that individuals who do not express CD36 on their platelets can probably be immunized with CD36 antigen, producing anti-Nak^a (anti-CD36) by transfusion or other immune pathways. The first described individual with deficiency of CD36 was a Japanese woman who was refractory to human leucocyte antigen (HLA)-matched platelet transfusions (6). Currently, CD36 deficiency is divided into two subgroups according to the phenotype. In type I deficiency, CD36 is not expressed in either platelets, monocytes or other tissue cells, whereas in type II deficiency, CD36 is expressed in monocytes but not in platelets. It can be inferred that anti-CD36 isoantibody is only produced in type I individuals, but not in type II individuals due to autoimmune tolerance. Production of anti-CD36 isoantibodies is an important risk factor for immune-mediated thrombocytopenia including fetal and neonatal alloimmune thrombocytopenia (FNAIT), platelet transfusion refractoriness (PTR), and posttransfusion purpura (PTP). Platelet CD36 deficiency varies widely between different ethnic groups, with a frequency of 2.6% in Arabians, 3% to 11% in Asians, 8% in sub-Saharan Africans, and less than 0.4% in Caucasians (18-20).

The *CD36* gene is highly polymorphic and more than 60 polymorphic sites have been found in exon or flanking intron regions, which can cause amino acids exchanges and is considered to be the molecular basis of CD36 deficiency (*Table 2*). A genome-wide association study of 374 Caucasian subjects showed strong associations of 23 single nucleotide polymorphisms (SNPs) in *CD36* gene with platelet surface CD36 expression (37). Some studies also showed CD36 expression on platelets is associated with -132A>G of 5'-untranslated region (UTR) or a silent allele linked to a (TG)n repeat polymorphism in intron 3 (15,16). Although the molecular basis of CD36 deficiency, especially type II deficiency, is still controversial, these gene mutations may be the potential molecular mechanism leading to CD36 deficiency and iso-immune response.

CD36 gene variants and malaria

A critical step in infection by *Plasmodium falciparum*, the microorganism that causes the most severe form of malaria, is the adhesion of infected red blood cells (iRBCs) to capillary endothelium. The human protein CD36 is a major receptor for *Plasmodium falciparum*-iRBCs and may contribute to the development of malaria by sequestering iRBCs and inhibiting the immune response to the parasite. However, it cannot be simply concluded that CD36 is only

Table 2 Mutations in exon and flanking intron of *CD36* gene causing amino acid changes

Exon-intron	Nucleotide change	Amino acid change	dbSNP ID	Ref.
E1	del exon 1	No expression of CD36 protein	–	(21)
E2	del exon 2	No expression of CD36 protein	–	(22)
E3	c.14G>T	p.Arg5Leu	rs13306227	(16)
E3	del exon 3	No expression of CD36 protein	–	(21)
I3-E4	c.121-126delgCAAGTT	del Aa41-42 or splicing variation	rs1165943635	(23)
E4	c.220C>T	p.Gln74*	rs545489204	(23)
E4	c.268C>T	p.Pro90Ser	rs75326924	(24)
E4	c.275C>G	p.Thr92Arg	rs150037612	(18)
E5	c.287G>C	p.Arg96Pro	rs70961715	(16)
E5	c.319_324delGCTGAG	del Aa107-108	–	(25)
E5	c.329_332delAC	Frameshift at Aa110	rs572295823	(25)
E5	c.367G>A	p.Glu123Lys	rs183461468	(26)
E5	c.371C>T	p.Pro124Leu	rs776927712	(27)
E5	c.380C>T	p.Ser127Leu	rs201765331	(17)
E5	c.410T>C	p.Val137Ala	rs2272350	(28)
E5	c.416A>G	p.Ile139Val	rs770021143	(18)
I5	c.429+4insg	Exon 6 skipping	rs777551390	(23)
I5	c.430-1G>C	Exon 6 skipping	rs199530093	(29)
E6	c.446_449dupATCA	Frameshift at Aa151	rs780114238	(18)
E6	c.491A>G	p.Lys164Arg	rs201801344	(18)
E6	c.503C>T	p.Ser168Glu	–	(18)
E6	c.520A>G	p.Thr174Ala	rs756525492	(26)
E6	c.538T>C	p.Trp180Arg	rs201759307	(16)
E6	c.539delG	Frameshift at Aa180	–	(18)
E6	c.550G>A	p.Asp184Asn	rs138897347	(18)
E6	c.551A>T	p.Asp184Val	rs770839462	(18)
E6	c.560insT	Frameshift at Aa187	rs770779882	(30)
E7	c.619_624delACTGCA/insAAAAC	Frameshift at Aa207	–	(31)
E7	c.638_639delAA	Frameshift at Aa213	rs780525946	(18)
E7	c.649G>A	p.Gly217Arg	rs200067322	(18)
E7	c.658_667del10bp	Frameshift at Aa220	rs778808650	(18)
E7	c.660_664delCATAA	Frameshift at Aa220	rs768699378	(18)
E7	c.660_665delCATAAG	del Aa221-222	–	(18)
E7	c.691_696delAAAGGT	del Aa231-232	rs776495734	(31)
E7	c.696insAAT	p.232insAsn	rs745642173	(26)

Table 2 (*continued*)

Table 2 (*continued*)

Exon-intron	Nucleotide change	Amino acid change	dbSNP ID	Ref.
E9	c.760T>C	p.Phe254Leu	rs142186404	(32)
E9	c.806C>A	p.Ser269Tyr	rs201376087	(18)
E9	c.812T>C	p.Ile271Thr	rs370072057	(26)
E10	c.845_849delACGTT	Frameshift at Aa282	–	(31)
E10	c.944_949insA	Frameshift at Aa317	rs70961716	(33)
E10	c.957_958insA	Frameshift at Aa320	rs749271701	(18)
E10	c.975T>G (1264T>G in ref.)	p.Tyr325*	rs3211938	(34)
I10	c.1006+2T>G	Exon 10 skipping	rs555480623	(29)
E11	c.1047_1051dupAAGT	Frameshift at Aa351	–	(18)
E11	c.1079T>G	p.Leu360*	rs56381858	(31)
E12	c.1133G>T	p.Gly378Val	rs146027667	(18)
E12	c.1144C>T	p.Gln382*	rs201657731	(18)
E12	c.1150G>C (1439G>G in ref.)	p.Ala383Pro	rs201346212	(34)
E12	c.1155delA (1444delA in ref.)	Frameshift at Aa385	rs886043043	(34)
E12	c.1156C>T	p.Arg386Trp	rs148910227	(35)
E12	c.1157G>A	p.Arg386Gln	rs187500047	(16)
E12	c.1163A>T	p.Gln388Leu	rs201355711	(16)
E12	c.1172_1183del12bp	Deletion Aa391-394	rs763471880	(16)
E12	c.1179_1183insCAGC	Frameshift at Aa393	–	(18)
E12	c.1189G>T	p.Glu397*	–	(18)
I12	c.1200_5inv49bp	Exon 13 skipping	rs767892046	(23)
I12-E13	c.1200_1202deltattacagAG	Exon 13 skipping	rs1261358979	(31)
E13	c.1204_1246dupl43bp	Frameshift at Aa416	rs7749967939	(28)
E13	c.1209ins16bp	Frameshift at Aa404	–	(18)
E13	c.1218_1224delGAGGAAC	Frameshift at Aa406	rs760817974	(31)
E13	c.1226A>G	p.Tyr409Cys	rs1489861412	(27)
E13	c.1228_1239del12bp	del Aa410-413	rs1085307060	(36)
E13	c.1236delT	Frameshift at Aa412	rs1451278617	(16)
E13	c.1237A>C	p.Ile413Leu	rs121918035	(31)
E14	c.1343_1344insTCTT	Frameshift at Aa446	rs201958707	(16)
E14	c.1345_1348delCTCA	Frameshift at Aa449	rs1261881244	(18)
E14	c.1409C>T	p.Thr470Ile	rs200771788	(16)

Table 3 The conflicting results on the association between *CD36* variants and severe malaria

Nucleotide change	dbSNP ID	population	Variation effect	Ref.
539delAC (now c.329_332delAC)	rs572295823	Thai	Harmful to host (cerebral malaria)	(39)
1264T>G (now c.975T>G)	rs3211938	Gambians and Kenyans	Harmful to host (severe malaria)	(34)
1439G>C+1444delA (now c.1150G>C+c.1155delA)	rs201346212 rs886043043	Gambians and Kenyans	Harmful to host (severe malaria)	(34)
1264T>G (now c.975T>G)	rs3211938	Tanzanian children	Beneficial to host (protects against malarial anemia)	(40)
188T>G in exon 10 (now c.975T>G)	rs3211938	African children	Beneficial to host (protects against severe malaria)	(41)
188T>G in exon 10 (now c.975T>G)	rs3211938	India	Beneficial to host (protects against severe malaria)	(42)
in3(TG) repeat	rs3138813	Thai adult	Beneficial to host (reducing the risk of cerebral malaria)	(17)
1264T>G (now c.975T>G); 1439G>C (now c.1150G>C); 1444delA (now c.1155delA)	rs3211938; rs201346212; rs886043043	African	No effect to host	(43)

beneficial to malaria and harmful to the host.

In *Plasmodium falciparum* malaria, the consequences of erythrocyte adhesion to CD36 depend on the tissue type expressing CD36. Adhesion of iRBCs to CD36 present on monocytes in the spleen enhances phagocytosis and host clearance of the parasite, that is beneficial to the host. Adhesion of iRBCs to CD36 expressed on platelets or endothelium may result in platelet mediated clumping or sequestration, either of which could produce blockage of blood flow to critical organs including brain and reduce the possibility of cerebral malaria. This is also beneficial to the host. Adhesion of iRBCs to CD36 on endothelial cells of skin, fat, or muscle is less harmful to the host while still allowing the parasite to undergo growth and replication (38). Numerous studies have explored the relation between malaria severity and mutations of the *CD36* gene. Results have been conflicting, with most studies suggesting a benefit to host associated with CD36 mutations, some showing a disadvantage to host, and some studies showing no effect to host (*Table 3*).

In the studies of CD36 mutations harmful to the host, Aitman *et al*. (34) first found that two mutation alleles, 1264T>G (now c.975T>G) and 1439G>C+1444delA (now c.1150G>C+c.1155delA), had higher frequency in cerebral malaria group than anemia malaria group and control malaria group in Gambians and Kenyans. The authors speculated that the gene variants leaded to the CD36 deficiency and then reduced parasite sequestration in organs outside the brain. Another study showed that 539delAC (now c.329-332delAC) allele in exon 5 was detected in three cerebral malaria patients (3/107), but not in mild malaria patients (0/203). It suggested that the 539delAC allele might be a high-risk variant for cerebral malaria in Thais (39).

However, more studies support that *CD36* gene mutations were beneficial to the host. Chilongola *et al.* (40) also examined the 1264T>G mutation known to decrease CD36 expression in Tanzanian children, but they came to the opposite conclusion. They found that strong CD36 expression by the host might worsen anemia as a result of increased splenic clearance, platelet-mediated clumping, or erythrocyte sequestration, whereas CD36 deficiency derived from 1264T>G mutation protects against malarial anemia. Pain *et al.* (41) identified a non-sense mutation, 188T>G (now also c.975T>G) in exon 10, and looked at the influence of this mutation on the outcome of malaria infection in 693 African children with severe malaria and a similar number of ethnically matched controls. The result showed that heterozygosity for this mutation is associated with protection from severe malaria. Das *et al.* (42) also investigated the possible association of 188T>G polymorphism in exon 10 with severe clinical manifestations of malaria in 95 adult patients with severe malaria (severe group) and 95 ethnically matched controls (mild group) in India. The frequency of the wild-type (188T) allele of the *CD36* gene was 0.91 in the severe group and 0.78 in the mild group of patients, while mutant (188G) allele frequency was 0.09 in the

severe group and 0.22 in the mild group. The study shows that the presence of 188T>G mutant allele renders protection against severe malaria. Omi *et al.* (17) performed systematic variation screening, including all 16 exons with neighboring introns and two promoter regions of the *CD36* gene, and examined the possible association between CD36 polymorphisms and the severity of malaria in 475 adult Thai patients with *Plasmodium falciparum* malaria. Although 1264T>G mutation was not detected, nine CD36 polymorphisms with a high-frequency (>15%) minor allele, including -14T>C, 59T>A, -53G>T, 158C>A, IVS3-6T>C, IVS7+103C>T, IVS8-156A>G, IVS11-150A>C and IVS14-419del9bp, were identified in Thai. Of these, the frequencies of the -14T>C allele in the upstream promoter region and the -53G>T allele in the downstream promoter region were significantly decreased in patients with cerebral malaria compared to those with mild malaria. The analysis of linkage disequilibrium between the nine common polymorphisms revealed that there are two blocks with strong linkage disequilibrium in the *CD36* gene and that the 514T>C and 553G>T polymorphisms are within the upstream block of 35 kb from the upstream promoter to exon 8. Further association testing after the second variation screening in the upstream block indicated that the 12TG repeats in intron 3 [in3$(TG)_{12}$] allele is most strongly associated with the reduction in the risk of cerebral malaria. The study found that in3$(TG)_{12}$ is involved in the nonproduction of the variant CD36 transcript that lacks exons 4 and 5. Since exon 5 of the gene is known to encode the ligand-binding domain for *Plasmodium falciparum*-iRBCs, in3$(TG)_{12}$ itself or a primary variant on the haplotype with in3$(TG)_{12}$ may be responsible for protection from cerebral malaria in Thailand (17).

In view of the conflicting results of the above study on the association between the 1264T>G polymorphism and severe malaria, Fry *et al.* (43) employed a largest sample size (4,692 cases and 6,230 controls) from four African population to analyze the association between 1264T>G mutation and malaria. They found that the nonsense allele carrying 1264G was not associated with severe malaria. They further screened 70 variants within and around *CD36* gene, including 1439G>C and 1444delA in previously studies, for association study. No mutation was associated with either a higher or lower risk of severe disease.

Although it is still a question whether CD36 and malaria are friend or foe, current research data indicate that the interaction between *Plasmodium falciparum* and CD36 may be a co-adaptation, which is beneficial to both parasite and host (44).

CD36 gene variants, lipid taste perception and obesity

The epidemic of obesity is posing a serious world-wide threat to human health and world widely that can no longer be ignored. The factors of genetics, environment and dietary habits are involved in development of obesity. Dietary fat is consumed in high amounts by obese subjects because of its olfactory, visual and textural cues. Growing evidence suggests that oral fat sensing plays a significant role in development of obesity. The CD36 glycoprotein expressed on taste bud cells of lingual surface has been shown to be implicated in this mechanism (45). The fatty acids and triacylglycerol in food provide sensory signals that allow the fat to be perceived. As a fatty acid translocase, CD36 receives the sensory signals and determines the individual's preference degree for dietary lipids. It has been proposed that gene variants and functionality alteration of CD36 might influence the individual's sensitivity, preference and intake of fat (46).

There is a controversy on how genetic variations in CD36 influence obesity. Ma *et al.* (47) first investigated associations between common polymorphisms at the *CD36* gene, plasma free fatty acid (FFA) levels and risk for cardiovascular disease (CAD) in Caucasians. Two linkage disequilibrium blocks represented by a haplotype tagged by five polymorphisms (-33137A>G or rs1984112, -31118G>A or rs1761667, 25444G>A or rs1527483, 27645del>ins16bp or rs3840546 and 30294G>C or rs1049673) were detected through the screening of 21 polymorphisms evenly spanned the *CD36* gene. When the five tag polymorphisms were considered together, men carrying the AGGIG haplotype had 31% higher plasma fatty acid and 20% higher triglycerides than non-carriers. The same haplotype was associated with increased risk of CAD in type 2 diabetic individuals from the US and Italy. Bokor *et al.* (48) also assessed the relationship between 10 SNPs of *CD36* gene and obesity in European adolescents, in which 4 SNPs (rs3211867, rs3211883, rs3211908 and rs1527483) were associated with increased risk of obesity, higher body mass index (BMI) and percentage of body fat (BF%). Further analyses identified a haplotype carrying the minor allele of 4 SNPs (haplotype AAAA) as being associated with obesity and excess adiposity. But this finding was inconsistent with study done by Choquet *et al.* (49) who found no effect of those four variants on obesity risk in young populations of European ancestry using big data analysis of case-control (n=3,509), population-based (n=4,667), and meta-analysis

study designs (n=9,973).

Based on the correlation data between CD36 polymorphisms and obesity, it was speculated that CD36 may play an important role in oral fat perception and individual preferences for fatty foods. The rs1761667, a common variant which lies between two alternative promoters of *CD36* gene and associates with reduced CD36 expression on human platelets (37) and mice circumvallate taste papillae (50), is the most studied polymorphism for the association of CD36 variants with fat taste, oro-gustatory thresholds, fat intake and obesity. A study in obese Tunisian women showed that the participants with A-allele of rs1761667 polymorphism exhibited decreased oral sensitivity (high oro-gustatory thresholds) to oleic acid (51). Another study in young Algerian teenagers also showed that the A-allele frequency was higher in obese teenagers than that in lean children, and the obese teenagers exhibited higher lingual detection threshold for oleic acid than lean participants (52). The results suggested that individuals with AA genotype of rs1761667 have reduced sensitivity to fat content, which could lead to increase fat intake and obesity. The role of CD36 polymorphism in taste perception may be more impactful in children due to the lack of cultural influence compared to adults, and taste acuity may decline with age. The positive correlation between fat detection thresholds, BMI, BF% and A-allele of rs1761667 was also confirmed in Japanese (53), Morocans (54) and Poles (55). However, an opposite result was observed in Mexican children. The authors found that G-allele, rather than A-allele, of rs1761667 in *CD36* gene was associated with overweight and obesity in Mexican children, and this polymorphism did not appear to modulate the preferences and satisfaction scores to fat (56). A recent study also found that 2 variants (rs1054516 and rs3173798) were associated with higher saturated fatty acids intake, and 1 variant (rs1054516) was associated with higher serum triglycerides among overweight/obese individuals (57), and an earlier study also showed the link between 9 mutations of the *CD36* gene and a defect in the accumulation of LCFAs in the human heart (30).

Although some polymorphisms of CD36 have been shown to be related to lipid taste perception and obesity, those studies still lack of repetition and in some cases the results were controversial. Further research is necessary to clarify the truly effective polymorphisms of *CD36* gene and its interaction with environmental factors including lipid diet and physical exercise.

CD36 gene variants and other metabolic syndromes

As a multifunctional receptor, CD36 not only plays an important role in thrombocytopenia, malaria, lipid taste perception and obesity, but also is associated with other metabolic syndromes such as hypercholesterolemia, peripheral vascular atherosclerosis, arterial hypertension, cardiomyopathy and other CAD, diabetes, Alzheimer's disease and colorectal cancer (*Table 4*).

Atherosclerosis

Macrophage CD36 participates in atherosclerotic arterial lesion formation through its interaction with oxLDL, which triggers signaling cascades for inflammatory responses. CD36 functions in oxLDL uptake and foam cell formation, which is the initial critical stage of atherosclerosis. In addition, oxLDL via CD36 inhibits macrophage migration, which may be a macrophage-trapping mechanism in atherosclerotic lesions. Platelet CD36 also promotes atherosclerotic inflammatory processes and is involved in thrombus formation after atherosclerotic plaque rupture. Both persistent up-regulation of CD36 and deficiency of CD36 increase the risk for atherosclerosis. Abnormally up-regulated CD36 promotes inflammation, foam cell formation, endothelial apoptosis, macrophage trapping and thrombosis. However, CD36 deficiency also causes dyslipidemia, subclinical inflammation and metabolic disorders, which are established risk factors for atherosclerosis. Morii *et al.* (70) examined the association of CD36 SNPs with certain metabolic characteristics in a young male Japanese population. The G allele in a SNP located at +30,215 (rs7755) on the 3'-UTR was significantly correlated with the plasma LDL-cholesterol concentrations. In contrast, for the SNPs at positions +9,794 (rs3173798) and +10,214 (rs3212165), neither significant correlation nor association was found between genotypes and clinical characteristics. Boghdady *et al.* (58) studied the relationship between rs1761667 polymorphism and the risk of coronary atherosclerosis in Egyptian population. The frequency of the AG genotype was significantly higher in the CAD group than in the control group. The expression level of CD36 in the CAD group was significantly higher than that in the control group. The AG genotype of rs1761667 was associated with an increased risk of CAD. Momeni-Moghaddam *et al.* (59) also found that rs1761667 was

Table 4 The correlation between *CD36* variants and some metabolic syndromes

dbSNP ID	Variants	Allele or genotype	Related to metabolic syndromes	Population	Ref.
rs1761667	5'-UTR-31118G>A	AG	CAD pathogenesis, BMI, T2DM and metabolic syndrome	Egyptian	(58)
		A	Increased risk of CAD with hypertension	Iranian	(59)
		A or G	No correlation between genotype and macroangiopathy in patients with T2DM	Chinese	(60)
		A or G	No correlation between genotype and T2DM combined with carotid atherosclerosis	Chinese	(61)
rs1527479	5'-UTR-3489T>C	TT	T2MD and insulin resistance	Netherlands	(62)
		T or C	No correlation between genotype and T2DM	Chinese	(63)
rs1010122521	c.52A>C	CC	Increase the risk of colorectal cancer	Japanese	(64,65)
rs3138813	In3(TG) repeat	(TG)11/12	High BMI and cardiovascular risk for men	Korean	(66)
rs3173798	IVS3-6 T>C	C	High prevalence of obesity and diabetes	Pole	(67)
		TC + CC	More likely to have an atherogenic lipid profile in male	Chinese	(68)
rs3211892	IVS4-10 G>A	A	Lower risk of hypercholesterolemia	Pole	(13)
			Older age of myocardial infarction	Pole	(67)
			Higher risk of Alzheimer's disease	Czech	(69)
rs1049673	3'-UTR+2887 C>G	G	More likely to have an atherogenic lipid profile in male	Chinese	(68)
rs7755	3'-UTR+30215G>A	G	Plasma low-density lipoprotein-cholesterol concentration	Japanese	(70)
		A	More likely to have an atherogenic lipid profile in male	Chinese	(68)

CAD, cardiovascular disease; BMI, body mass index; T2DM, type 2 diabetes mellitus.

associated with hypertension and coronary artery disease in a southeastern Iranian population.

Type 2 diabetes mellitus (T2DM)

Corpeleijn *et al.* (62) found that T2DM was more prevalent in the TT genotype than in the CC genotype in the upstream promoter region (rs1527479, -3489C>T) of the *CD36* gene. It showed a direct association of the TT genotype with the presence of T2DM in subjects from a Caucasian population at risk for the metabolic syndrome. This is most evident in women and in obese subjects. But Zeng *et al.* (63) showed that no significant differences were found in alleles and genotype frequencies of *CD36* gene rs1527479 polymorphism between diabetic patients and non-diabetic controls in Chinese Han population. No correlation was also found between the polymorphisms of rs17154181 and rs1761667 sites and macroangiopathy in patients with T2DM in Chinese population (60). Yang *et al.* (61) also showed that the rs1761667 and rs10499859 polymorphisms of *CD36* gene may not be correlated with the occurrence of T2DM combined with carotid atherosclerosis in Chinese Han population.

Colorectal cancer

Kuriki *et al.* (64) suggest that interactions between moderate-high meat consumption and the *CD36* gene 52A>C polymorphism may increase the risk of colorectal cancer. They also found a significant interaction between alcohol consumption and the *CD36* gene 52A>C polymorphism related to the metabolism of long-chain

fatty acids and oxidized LDL in the etiology of colorectal cancer (65). In addition, CD36 was also found to have potential contributions to key cellular events in oncogenesis or metastasis development of pancreatic cancer and other malignancies, although the relationship between *CD36* gene variants and these diseases has not been reported (71).

Alzheimer's disease

The relationship between a polymorphism of *CD36* gene and Alzheimer's disease was also reported in Czech population. The presence of A allele on rs3211892 has a significant increase in the risk of Alzheimer's disease. The most likely mechanisms involve changes in cholesterol regulation, formation of reactive oxygen species and/or induction of pathological inflammatory cascades (69).

Conclusions

CD36 gene variants are associated with alloimmune thrombocytopenia, malaria severity, lipid taste perception obesity, and other metabolic syndromes. Some of these correlations are due to gene mutations leading to CD36 protein not expressed. Some are due to CD36 protein expression down-regulation in specific cells, and some are due to the conformation change or inactivation of the ligand binding domain in the protein extracellular domain. There is significant evidence that CD36 on various cells and tissues is involved in the development of different disorders. However, it seems that anti-CD36 induced thrombocytopenia is the only undoubtful relation between complete CD36 absence and disease. But even within thrombocytopenia the impact of single SNV on type I deficiency is under discussion. Concerning disorders other than immune thrombocytopenia data are much more conflicting not only with regard to single variations but also with respect to general inhibitory or inducing effects. Some correlations between *CD36* gene variation and clinical symptoms may be only a superficial phenomenon lacking underlying mechanism. Current evidence on CD36 and health-related outcomes is limited and more functional genomics studies are needed to confirm its role and mechanism. Research on the relationship between *CD36* gene variants and diseases will help us to further clarify the *CD36* gene ontology, the protein function, and pathophysiological basis of related diseases. CD36 is also increasingly becoming a potential biomarker and target for drug development and treatment of specific diseases (72-74).

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Footnote

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References

1. Clemetson KJ, Pfueller SL, Luscher EF, et al. Isolation of the membrane glycoproteins of human blood platelets

by lectin affinity chromatography. Biochim Biophys Acta 1977;464:493-508.
2. Knowles DM 2nd, Tolidjian B, Marboe C, et al. Monoclonal anti-human monocyte antibodies OKM1 and OKM5 possess distinctive tissue distributions including differential reactivity with vascular endothelium. J Immunol 1984;132:2170-3.
3. Febbraio M, Hajjar DP, Silverstein RL. CD36: a class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. J Clin Invest 2001;108:785-91.
4. Available online: https://www.ncbi.nlm.nih.gov/bioproject/PRJEB2445/
5. Baruch DI, Ma XC, Pasloske B, et al. CD36 peptides that block cytoadherence define the CD36 binding region for Plasmodium falciparum-infected erythrocytes. Blood 1999;94:2121-7.
6. Ikeda H, Mitani T, Ohnuma M, et al. A new platelet-specific antigen, Naka, involved in the refractoriness of HLA-matched platelet transfusion. Vox Sang 1989;57:213-7.
7. Available online: https://www.ncbi.nlm.nih.gov/gene/948
8. Pepino MY, Kuda O, Samovski D, et al. Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism. Annu Rev Nutr 2014;34:281-303.
9. Glatz JFC, Luiken JJFP. Dynamic role of the transmembrane glycoprotein CD36 (SR-B2) in cellular fatty acid uptake and utilization. J Lipid Res 2018;59:1084-93.
10. Zhao L, Varghese Z, Moorhead JF, et al. CD36 and lipid metabolism in the evolution of atherosclerosis. Br Med Bull 2018;126:101-12.
11. Puente Navazo MD, Daviet L, Ninio E, et al. Identification on human CD36 of a domain (155-183) implicated in binding oxidized low-density lipoproteins (Ox-LDL). Arterioscler Thromb Vasc Biol 1996;16:1033-9.
12. Tian K, Xu Y, Sahebkar A, et al. CD36 in atherosclerosis: pathophysiological mechanisms and therapeutic implications. Curr Atheroscler Rep 2020;22:59.
13. Rać ME, Safranow K, Garanty-Bogacka B, et al. CD36 gene polymorphism and plasma sCD36 as the risk factor in higher cholesterolemia. Arch Pediatr 2018;25:177-81.
14. Available online: https://www.ncbi.nlm.nih.gov/snp/?term=CD36
15. Kashiwagi H, Tomiyama Y, Kosugi S, et al. Family studies of type II CD36 deficient subjects: linkage of a CD36 allele to a platelet-specific mRNA expression defect(s) causing type II CD36 deficiency. Thromb Haemost 1995;74:758-63.
16. Xu X, Liu Y, Hong X, et al. Variants of CD36 gene and their association with CD36 protein expression in platelets. Blood Transfus 2014;12:557-64.
17. Omi K, Ohashi J, Patarapotikul J, et al. CD36 polymorphism is associated with protection from cerebral malaria. Am J Hum Genet 2003;72:364-74.
18. Flesch BK, Scherer V, Opitz A, et al. Platelet CD36 deficiency is present in 2.6% of Arabian individuals and can cause NAIT and platelet refractoriness. Transfusion 2021;61:1932-42.
19. Curtis BR, Aster RH. Incidence of the Nak(a)-negative platelet phenotype in African Americans is similar to that of Asians. Transfusion 1996;36:331-4.
20. Wu G, Zhou Y, Li L, et al. Platelet immunology in china: research and clinical applications. Transfus Med Rev 2017;31:118-25.
21. Sato O, Kuriki C, Fukui Y, et al. Dual promoter structure of mouse and human fatty acid translocase/CD36 genes and unique transcriptional activation by peroxisome proliferator-activated receptor alpha and gamma ligands. J Biol Chem 2002;277:15703-11.
22. Yanai H, Chiba H, Morimoto M, et al. Human CD36 deficiency is associated with elevation in low-density lipoprotein-cholesterol. Am J Med Genet 2000;93:299-304.
23. Xu X, Ye X, Xia W, et al. Studies on CD36 deficiency in South China: Two cases demonstrating the clinical impact of anti-CD36 antibodies. Thromb Haemost 2013;110:1199-206.
24. Kashiwagi H, Honda S, Tomiyama Y, et al. A novel polymorphism in glycoprotein IV (replacement of proline-90 by serine) predominates in subjects with platelet GPIV deficiency. Thromb Haemost 1993;69:481-4.
25. Kashiwagi H, Tomiyama Y, Kosugi S, et al. Identification of molecular defects in a subject with type I CD36 deficiency. Blood 1994;83:3545-52.
26. Gelhaus A, Scheding A, Browne E, et al. Variability of the CD36 gene in West Africa. Hum Mutat 2001;18:444-50.
27. Li R, Qiao Z, Ling B, et al. Incidence and molecular basis of CD36 deficiency in Shanghai population. Transfusion 2015;55:666-73.
28. Imai M, Tanaka T, Kintaka T, et al. Genomic heterogeneity of type II CD36 deficiency. Clin Chim Acta 2002;321:97-106.
29. Li LL, Chen JR, Jiang LH, et al. Two novel mutations at the CD36 gene splicing sites and their molecular basis for the CD36 deficiency. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2020;28:2056-65.

30. Tanaka T, Nakata T, Oka T, et al. Defect in human myocardial long-chain fatty acid uptake is caused by FAT/CD36 mutations. J Lipid Res 2001;42:751-9.
31. Rać ME, Safranow K, Poncyljusz W. Molecular basis of human CD36 gene mutations. Mol Med 2007;13:288-96.
32. Hanawa H, Watanabe K, Nakamura T, et al. Identification of cryptic splice site, exon skipping, and novel point mutations in type I CD36 deficiency. J Med Genet 2002;39:286-91.
33. Kashiwagi H, Tomiyama Y, Nozaki S, et al. A single nucleotide insertion in codon 317 of the CD36 gene leads to CD36 deficiency. Arterioscler Thromb Vasc Biol 1996;16:1026-32.
34. Aitman TJ, Cooper LD, Norsworthy PJ, et al. Malaria susceptibility and CD36 mutation. Nature 2000;405:1015-6.
35. Okajima S, Cho K, Chiba H, et al. Two sibling cases of hydrops fetalis due to alloimmune anti-CD36 (Nak a) antibody. Thromb Haemost 2006;95:267-71.
36. Kashiwagi H, Tomiyama Y, Nozaki S, et al. Analyses of genetic abnormalities in type I CD36 deficiency in Japan: identification and cell biological characterization of two novel mutations that cause CD36 deficiency in man. Hum Genet 2001;108:459-66.
37. Ghosh A, Murugesan G, Chen K, et al. Platelet CD36 surface expression levels affect functional responses to oxidized LDL and are associated with inheritance of specific genetic polymorphisms. Blood 2011;117:6355-66.
38. Cserti-Gazdewich CM, Mayr WR, Dzik WH. Plasmodium falciparum malaria and the immunogenetics of ABO, HLA, and CD36 (platelet glycoprotein IV). Vox Sang 2011;100:99-111.
39. Omi K, Ohashi J, Naka I, et al. Polymorphisms of CD36 in Thai malaria patients. Southeast Asian J Trop Med Public Health 2002;33 Suppl 3:1-4.
40. Chilongola J, Balthazary S, Mpina M, et al. CD36 deficiency protects against malarial anaemia in children by reducing Plasmodium falciparum-infected red blood cell adherence to vascular endothelium. Trop Med Int Health 2009;14:810-6.
41. Pain A, Urban BC, Kai O, et al. A non-sense mutation in Cd36 gene is associated with protection from severe malaria. Lancet 2001;357:1502-3.
42. Das A, Das TK, Sahu U, et al. CD36 T188G gene polymorphism and severe falciparum malaria in India. Trans R Soc Trop Med Hyg 2009;103:687-90.
43. Fry AE, Ghansa A, Small KS, et al. Positive selection of a CD36 nonsense variant in sub-Saharan Africa, but no association with severe malaria phenotypes. Hum Mol Genet 2009;18:2683-92.
44. Serghides L, Smith TG, Patel SN, et al. CD36 and malaria: friends or foes? Trends Parasitol 2003;19:461-9.
45. Laugerette F, Passilly-Degrace P, Patris B, et al. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. J Clin Invest 2005;115:3177-84.
46. Chamoun E, Mutch DM, Allen-Vercoe E, et al. A review of the associations between single nucleotide polymorphisms in taste receptors, eating behaviors, and health. Crit Rev Food Sci Nutr 2018;58:194-207.
47. Ma X, Bacci S, Mlynarski W, et al. A common haplotype at the CD36 locus is associated with high free fatty acid levels and increased cardiovascular risk in Caucasians. Hum Mol Genet 2004;13:2197-205.
48. Bokor S, Legry V, Meirhaeghe A, et al. Single-nucleotide polymorphism of CD36 locus and obesity in European adolescents. Obesity (Silver Spring) 2010;18:1398-403.
49. Choquet H, Labrune Y, De Graeve F, et al. Lack of association of CD36 SNPs with early onset obesity: a meta-analysis in 9,973 European subjects. Obesity (Silver Spring) 2011;19:833-9.
50. Martin C, Passilly-Degrace P, Gaillard D, et al. The lipid-sensor candidates CD36 and GPR120 are differentially regulated by dietary lipids in mouse taste buds: impact on spontaneous fat preference. PLoS One 2011;6:e24014.
51. Mrizak I, Šerý O, Plesnik J, et al. The A allele of cluster of differentiation 36 (CD36) SNP 1761667 associates with decreased lipid taste perception in obese Tunisian women. Br J Nutr 2015;113:1330-7.
52. Daoudi H, Plesník J, Sayed A, et al. Oral fat sensing and CD36 gene polymorphism in algerian lean and obese teenagers. Nutrients 2015;7:9096-104.
53. Fujii R, Hishida A, Suzuki K, et al. Cluster of differentiation 36 gene polymorphism (rs1761667) is associated with dietary MUFA intake and hypertension in a Japanese population. Br J Nutr 2019;121:1215-22.
54. Bajit H, Ait Si Mohammed O, Guennoun Y, et al. Single-nucleotide polymorphism rs1761667 in the CD36 gene is associated with orosensory perception of a fatty acid in obese and normal-weight Moroccan subjects. J Nutr Sci 2020;9:e24.
55. Chmurzynska A, Mlodzik-Czyzewska MA, Galinski G, et al. Polymorphism of CD36 determines fat discrimination but not intake of high-fat food in 20- to 40-year-old adults. J Nutr 2020;150:2016-22.
56. Enciso-Ramírez M, Reyes-Castillo Z, Llamas-Covarrubias

MA, et al. CD36 gene polymorphism -31118 G > A (rs1761667) is associated with overweight and obesity but not with fat preferences in Mexican children. Int J Vitam Nutr Res 2021;91:513-21.
57. Meng T, Kubow S, Nielsen DE. Common variants in the CD36 gene are associated with dietary fat intake, high-fat food consumption and serum triglycerides in a cohort of Quebec adults. Int J Obes (Lond) 2021;45:1193-202.
58. Boghdady A, Arafa UA, Sabet EA, et al. Association between rs1761667 polymorphism of CD36 gene and risk of coronary atherosclerosis in Egyptian population. Cardiovasc Diagn Ther 2016;6:120-30.
59. Momeni-Moghaddam MA, Asadikaram G, Akbari H, et al. CD36 gene polymorphism rs1761667 (G > A) is associated with hypertension and coronary artery disease in an Iranian population. BMC Cardiovasc Disord 2019;19:140.
60. Yuan Y, Pang CJ, Xiao CQ, et al. Relationship between the polymorphism of rs17154181 and rs1761667 sites of CD36 gene and macroangiopathy in patients with type 2 diabetes mellitus in Guangxi province. Chinese General Practice 2015;18:2421-5.
61. Yang Q, Li H, Zhuang L, et al. Association between gene polymorphisms of CD36 and type 2 diabetes combined with carotid atherosclerosis of Han population in north of Anhui province. Journal of Guangxi Medical University 2020;37:87-92.
62. Corpeleijn E, van der Kallen CJ, Kruijshoop M, et al. Direct association of a promoter polymorphism in the CD36/FAT fatty acid transporter gene with Type 2 diabetes mellitus and insulin resistance. Diabet Med 2006;23:907-11.
63. Zeng R, Yan X, Song D, et al. Correlation between fatty acid translocase gene polymorphism and Chinese type 2 diabetes mellitus. Chinese Journal of Clinicians (Electronic Edition) 2008;2:276-83.
64. Kuriki K, Hamajima N, Chiba H, et al. Increased risk of colorectal cancer due to interactions between meat consumption and the CD36 gene A52C polymorphism among Japanese. Nutr Cancer 2005;51:170-7.
65. Kuriki K, Hamajima N, Chiba H, et al. Relation of the CD36 gene A52C polymorphism to the risk of colorectal cancer among Japanese, with reference to with the aldehyde dehydrogenase 2 gene Glu487Lys polymorphism and drinking habit. Asian Pac J Cancer Prev 2005;6:62-8.
66. Yun YM, Song EY, Song SH, et al. CD36 polymorphism and its relationship with body mass index and coronary artery disease in a Korean population. Clin Chem Lab Med 2007;45:1277-82.
67. Rać ME, Suchy J, Kurzawski G, et al. Polymorphism of the CD36 gene and cardiovascular risk factors in patients with coronary artery disease manifested at a young age. Biochem Genet 2012;50:103-11.
68. Du Y, Chen K, Liu E, et al. Gender-specific associations of CD36 polymorphisms with the lipid profile and susceptibility to premature multi-vessel coronary artery heart disease in the Northern Han Chinese. Gene 2020;753:144806.
69. Šerý O, Janoutová J, Ewerlingová L, et al. CD36 gene polymorphism is associated with Alzheimer's disease. Biochimie 2017;135:46-53.
70. Morii T, Ohno Y, Kato N, et al. CD36 single nucleotide polymorphism is associated with variation in low-density lipoprotein-cholesterol in young Japanese men. Biomarkers 2009;14:207-12.
71. Tanase C, Gheorghisan-Galateanu AA, Popescu ID, et al. CD36 and CD97 in pancreatic cancer versus other malignancies. Int J Mol Sci 2020;21:5656.
72. Proulx C, Zhang J, Sabatino D, et al. synthesis and biomedical potential of azapeptide modulators of the cluster of differentiation 36 receptor (CD36). Biomedicines 2020;8:241.
73. Geloen A, Helin L, Geeraert B, et al. CD36 inhibitors reduce postprandial hypertriglyceridemia and protect against diabetic dyslipidemia and atherosclerosis. PLoS One 2012;7:e37633.
74. Glatz JFC, Wang F, Nabben M, et al. CD36 as a target for metabolic modulation therapy in cardiac disease. Expert Opin Ther Targets 2021;25:393-400.

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