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STUDY OF NONSENSE MUTATIONS IN THE HUMAN *CD36* GENE

CD36 serves as a receptor for a wide range of ligands, including thrombospondin, fibronectin, collagen, oxLDL, anionic phospholipids, and long-chain fatty acids. Numerous studies have shown that CD36 deficiency leads to reduced insulin resistance and exerts a protective effect against atherosclerosis. In this regard, the question arises whether the rare variants could mediate an individual metabolic response (for instance, protection against muscle insulin resistance) within the modern dietary context, acting as rare Loss-of-Function (LoF) mechanism. The aim of the study was to investigate the functional role of nonsense mutations in the CD36 gene and their frequency in the human population. ***Methods.*** *Allele frequencies (MAF) were analyzed using the data from gnomAD consortium, and pathogenicity was assessed using CADD and GERP scores.* ***Results.*** *It has been established that most identified nonsense mutations are rare and exhibit high pathogenicity scores (CADD > 20). Using SpliceAI tools and transcript-specific analysis, the variants that escape the NMD (nonsense-mediated decay) mechanism were identified, leading to the synthesis of truncated protein isoforms.* ***Conclusions.*** *The identified nonsense mutations in the CD36 gene are rare (MAF < 0.01) and characterized by high pathogenicity scores on the CADD (>20) and GERP scales. A number of variants, localized primarily in the final exons, were found to escape the NMD-degradation mechanism, yet they result in the loss of interaction sites with cytoplasmic tyrosine kinases.*

Keywords: *CD36, nonsense mutations, transcripts, NMD, atherosclerosis, bioinformatic analysis.*

Introduction

The *CD36* gene encodes a multifunctional transmembrane glycoprotein CD36, which plays a pivotal role in lipid uptake, macrophage function control, and innate immunity [1]. CD36 acts as a receptor for a wide range of ligands, including thrombospondin, fibronectin, collagen, oxidized low-density lipoproteins (oxLDL), anionic phospholipids, long-chain fatty acids, and bacterial diacylated lipopeptides [2—4]. The molecule consists of a short cytoplasmic N-terminus (1—5 aa),

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a first transmembrane helix (6—26 aa), a large extracellular loop (27—439 aa) for ligand binding (specifically fatty acids), a second transmembrane helix (440—461 aa), and a signaling cytoplasmic C-tail (462—472 aa). Despite being only 11 amino acids in length, this C-terminal domain serves as a critical signaling hub: through cysteine palmitoylation, it anchors the receptor within lipid rafts and directly interacts with Src family kinases (Fyn, Lyn, Yes), focal adhesion kinase PTK2, and paxillin, thereby triggering lipid internalization and cytoskeleton reorganization cascades. Depending on the ligand, CD36 initiates signal transduction pathways that mediate angiogenesis, inflammation, fatty acid metabolism, taste perception, and the uptake of alimentary lipids in the intestine, among others [5]. CD36 is expressed by a broad spectrum of cells, including adipocytes, cardiac and skeletal myocytes, microvascular endothelial and smooth muscle cells, erythroid precursors, mammary, intestinal and renal epithelia, as well as phagocytic cells (Fig. 1).

Numerous studies have demonstrated that CD36 plays a vital role in glucose homeostasis and the development of metabolic syndrome; it has been identified as a gene associated with insulin resistance and type 2 diabetes mellitus [5]. It facilitates intracellular lipid accumulation. Under conditions of

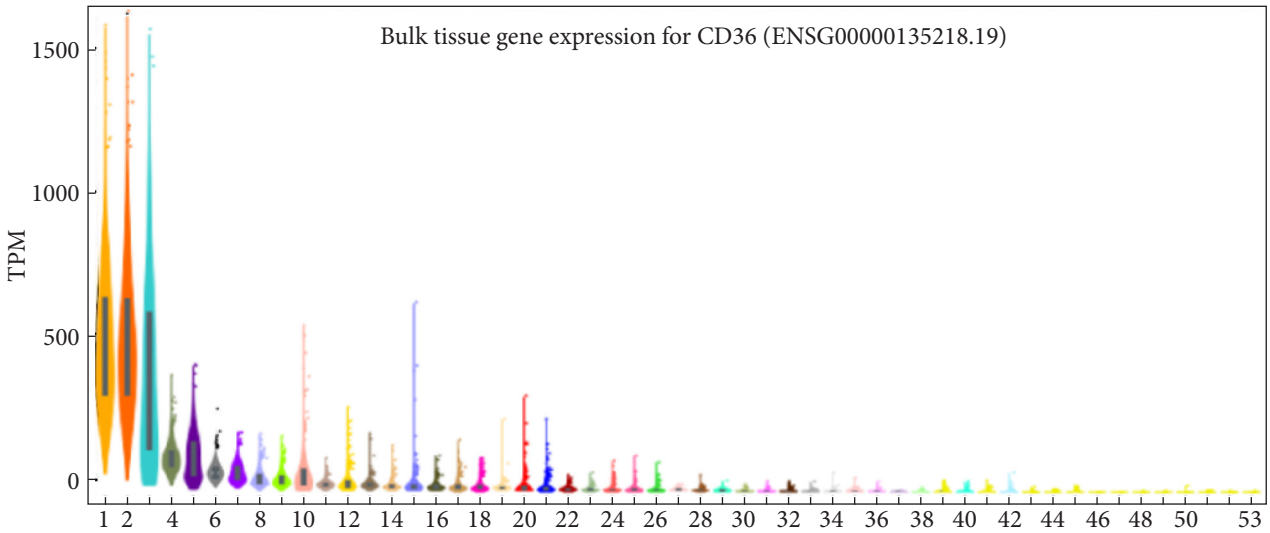

Fig. 1. *CD36* gene expression across various tissues

Data obtained from the GTExPortal (https://gtexportal.org). Expression levels are represented in TPM (transcripts per million). Tissue type: 1 — Adipose-Visceral; 2 — Adipose — Subcutaneous; 3 — Breast — Mammary Tissue; 4 – Spleen; 5 — Heart — Left Ventricle; 6 — Thyroid; 7 — Heart — Atrial Appendage; 8 — Muscle — Skeletal; 9 — Lung; 10 — Artery — Coronary; 11 — Esophagus — Muscularis; 12 — Nerve — Tibial; 13 — Esophagus — Gastroesophageal Junction; 14 — Colon — Sigmoid; 15 — Skin — Sun Exposed (Lower leg); 16 — Small Intestine — Terminal Ileum; 17 — Colon — Transverse; 18 — Whole Blood; 19 — Stomach; 20 — Artery — Tibial; 21 — Skin — Not Sun Exposed (Suprapubic); 22 — Bladder; 23 — Minor Salivary Gland; 24 — Artery — Aorta; 25 — agina; 26 — Adrenal Gland; 27 — Fallopian Tube; 28 — Pancreas; 29 — Kidney — Medulla; 30 — Liver; 31 — Uterus: 32 — Esophagus — Mucosa: 33 — Testis; 34 — Prostate; 35 — Cervix — Ectocervix; 36 — Ovary; 37 — Cervix — Endocervix; 38 — Pituitary; 39 — Brain — Hypothalamus; 40 — Kidney — Cortex; 41 — Cells — Cultured fibroblasts; 42 — Brain — Spinal cord (cervical c-1); 43 — Brain — Amygdala; 44 — Brain — Caudate (basal ganglia); 45 — Brain — Frontal Cortex (BA9); 46 — Brain — Anterior cingulate cortex (BA24); 47 — Brain — Cortex; 48 — Brain — Cerebellum, 49 — Brain — Substantia nigra; 50 — Brain — Nucleus accumbens (basal ganglia); 51 — Brain — Cerebellar Hemisphere, 52 — Brain — Putamen (basal ganglia); 53 — Cells — EBV-transformed lymphocytes

fatty acid excess, homeostasis is maintained through adipose tissue remodeling driven by CD36 activation. Furthermore, CD36 is involved in platelet activation in response to HDL oxidation. Research by Steinberg *et al.* [6] revealed that CD36-mediated lipid uptake is a crucial regulator of AMPK activation — a cellular nutrient sensor that governs metabolism with far-reaching consequences.

Thus, as evidenced by numerous studies, CD36 plays a pivotal role in the fine-tuning of cellular metabolism depending on lipid and glucose availability, the development of immune responses, and atherogenesis. Its polymorphisms can significantly influence the emergence of specific phenotypes depending on dietary intake. Numerous studies in both laboratory animals and humans have shown that CD36 deficiency or reduced expression leads to the decreased insulin resistance and exerts a protective effect against atherosclerosis. In this regard, the question arises whether these rare variants could confer an individual metabolic response (for instance, protection against muscle insulin resistance) within the modern dietary context, acting as rare Loss-of-Function (LoF) mechanisms.

The aim of our study was to investigate the functional role of *CD36* gene nonsense mutations and their frequency in the human population.

Materials and Methods

To analyze minor allele frequencies (MAF), the data from gnomAD consortium were obtained via the Ensembl platform. To evaluate the functional consequences of *CD36* SNVs, we utilized CADD, GERP, and SpliceAI metrics, along with an algorithm for predicting the probability of nonsense-mediated mRNA decay (NMD). CADD (Combined Annotation Dependent Depletion) is an integrative metric designed to predict the deleteriousness (pathogenicity) of genetic variants across the human genome. GERP (Genomic Evolutionary Rate Profiling) is a bioinformatics method and algorithm used to assess the evolutionary conservation of each specific nucleotide position in the genome. SpliceAI is an artificial intelligence-based bioinformatics tool developed to predict the impact of mutations on splicing. We used the MANE Select reference transcript (ENST00000447544.7 / NM_001001548.3) for the analysis.

We calculated the likelihood of nonsense-mediated mRNA decay (NMD) based on the generally accepted model of EJC-dependent NMD. During splicing, an exon junction complex (EJC) remains at each exon-exon junction. As the ribosome moves along the mRNA, it displaces these complexes. Upon encountering a stop codon, the ribosome terminates translation. If at least one EJC remains downstream (toward the 3'end), NMD-mediated mRNA degradation is triggered. To estimate the probability of NMD, the position of the mutation was calculated relative to the final exon-exon junction. If a mutation was located more than 50—55 nucleotides upstream of the last exon-exon junction, we assumed that the mRNA would undergo NMD-mediated degradation. NMD analysis was performed for 28 *CD36* transcripts identified using Ensembl VEP data. These include transcripts NM_001001548.3 (MANE Select), NM_000072.3, NM_001001547.3, NM_001127443.2, NM_001127444.2, NM_001289908.1, NM_001289909.1, NM_001289911.2, NM_001371074.1, NM_001371078.1, NM_001371079.1, NM_001371080.1, NM_001371081.1, NR_110501.1, NM_001371075.1, NM_001371077.1, XM_005250715.6, XM_024447002.2, XM_024447003.2, XM_047421041.1, XM_047421042.1, XM_047421043.1, XM_047421044.1, XM_047421045.1, XM_047421046.1, XM_047421047.1, XM_047421048.1, and XM_047421049.1.

Results and Discussion

A comprehensive bioinformatic analysis was conducted to identify and evaluate the functional significance of *CD36* gene nonsense variants. The search for variants was performed using the dbSNP and gnomAD (v2.1.1) databases. Given the low minor allele frequency (MAF) and the limited clinical data available in the ClinVar repository, an integrative in silico approach was applied for pathogenicity prediction. We analyzed 1,138 *CD36* SNVs registered in the gnomAD database. To identify

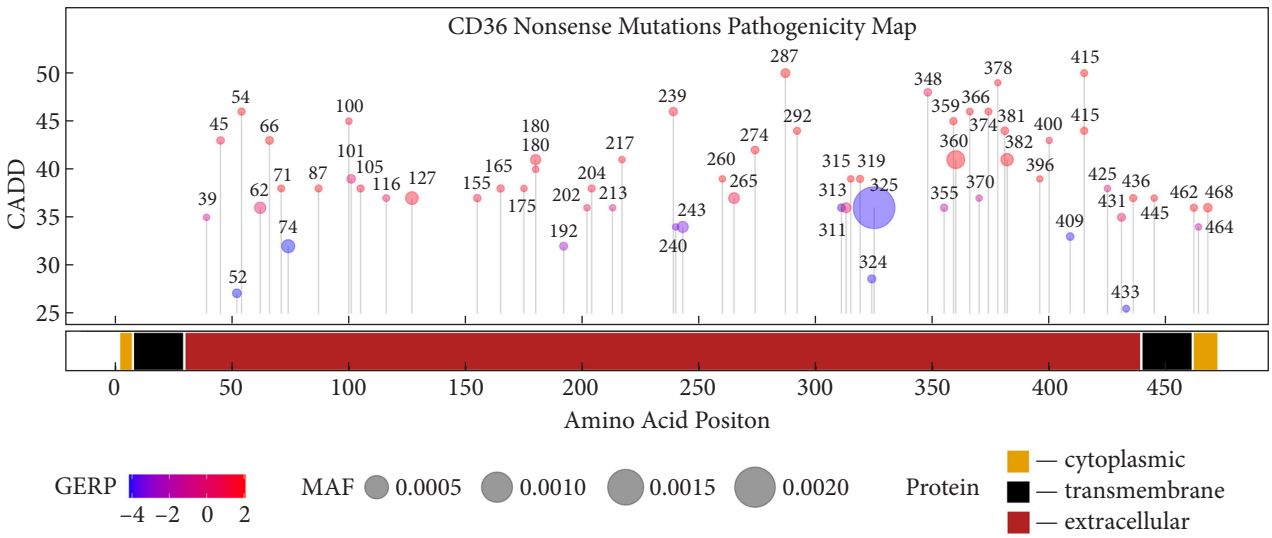

Fig. 2. Distribution of nonsense mutations across the functional domains of the CD36 protein. (Description in the text)

nonsense-mutations among the detected variants, the following steps were implemented. From all *CD36* SNVs, we filtered those designated as «stop_gain» in the Consequence section. This step yielded 79 *CD36* SNVs that resulted in a premature stop codon. Subsequently, further selection based on CADD scores was performed. From the initial pool of variants, 15 transcripts were excluded due to the lack of population frequency data in the gnomAD and TOPMed repositories. These variants include rs745978010, rs756628279, rs1356475716, rs1797717920, rs765646557, rs766760770, rs1554346177, rs752886472, rs767729808, rs1797917229, rs774967939, rs1584475666, rs779622793, rs1291812134, and rs747104060. The presence of reference identifiers for these variants in the absence of a calculated allele frequency indicates their ultra-rare (possibly sporadic) nature or origin from restricted clinical isolates, which precludes their correct use in systemic statistical and correlation analyses of the *CD36* gene frequency characteristics. As a result, a final list of 64 SNVs was obtained. Figure 2 presents the distribution of these genetic variants according to their localization within the functional domains of the protein, as well as their CADD pathogenicity scores and GERP conservation values.

CD36 is a gene consisting of 15 exons with 28 transcript variants, according to Ensembl VEP data. Analysis of *CD36* mRNA expression level in subcutaneous adipose tissue using GTEx portal (v8) data revealed significant transcript heterogeneity. The highest activity was observed for the MANE Select transcript NM_001001548.3, with a median expression in adipose tissue of 231.2 TPM (Fig. 3). Three alternative isoforms also demonstrate high expression: NM_000072.4 (isoform 3) at 115.5 TPM in adipose tissue, NM_001001547.3 (isoform 2) at 77.1 TPM, and NM_001127443.2 (isoform 4) at 43.6 TPM. Among the remaining 24 transcripts, all are classified as splice minor variants; according to GTEx and The Human Protein Atlas, their expression levels (nTPM) do not exceed 1%, making a negligible contribution to the total *CD36* expression in adipose tissue. A slightly different transcriptional landscape is observed in the myocardium: cardiac tissue demonstrates a significantly lower total *CD36* mRNA level compared to adipocytes, with the primary functional load distributed among only three isoforms. Notably, there is a complete absence of NM_000072.4 expression (0 TPM) in the heart, whereas it remains one of the key transcripts in adipose tissue

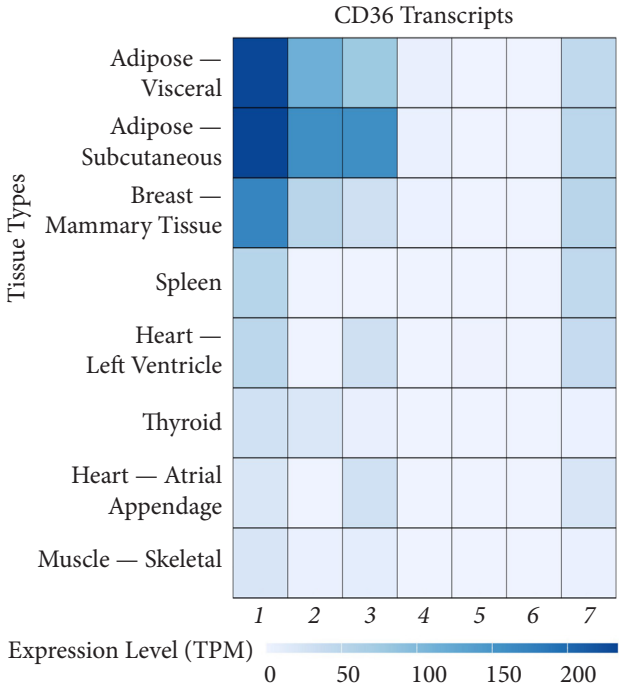

Fig. 3. Expression of individual *CD36* isoforms. Data obtained from the GTExPortal. Captions are analogous to Fig. 1: *1* — NM_001001548.3; *2* — NM_000072.3; *3* — NM_001001547.3; *4* — NM_001127444.2; *5* — NM_001289911.2; *6* — NM_ 001289908.1; *7* — NM_001127443.2

(115.5 TPM). It was established that the major transcript (NM_001001548.3) remains the leading variant, though its level reaches only 48.7 TPM. NM_001127443.2 is expressed at 38.9 TPM, and NM_001001547.3 is expressed at 30.3 TPM.

We analyzed the presence of identified nonsense mutations across all transcripts and found that certain transcripts avoid specific nonsense mutations of the gene (Table 1). However, all such transcripts are classified as splice minor variants and exhibit very low expression levels in the target tissues. Consequently, they cannot be considered a source of functional CD36 protein in cases where major transcripts are impaired.

Furthermore, we analyzed the probability of NMD for the nonsense-mutations. It was demonstrated that a portion of the transcripts indeed escapes NMD; however, these are classified as splice minor variants and cannot ensure CD36 synthesis. According to our calculations, the dominant isoform NM_001001548.3 escapes NMD in the following mutations: rs543879836, rs140728267, rs563772337, rs977068707, rs1307971636, and rs766072001. The CADD scores for these mutations ranged between 34 and 38, representing a relatively moderate manifestation of probable pathogenicity. The MAF did not differ from other *CD36* nonsense mutations. Mutations rs543879836, rs140728267, and rs563772337 are located in the extracellular domain, while rs977068707, rs1307971636, and rs766072001 are situated in the cytoplasmic domain, which mediates binding to PTK2, PXN, and LYN. Even if such a protein is synthesized, it will be truncated and lack the transmembrane domain and/or the C-terminus, which is essential for intracellular signaling. According to our calculations, the isoforms NM_000072.3, NM_001001547.3, and NM_001127443.2 escape NMD in rs1797918768, rs1463817861, and rs1385635045, all of which are located in the extracellular domain. However, they exhibit high CADD scores (35—50), and their MAF does not differ from other nonsense mutations. The isoforms NM_000072.3, NM_001001547.3, and NM_001127443.2 are expressed in adipose tissue, while NM_001001547.3 and NM_001127443.2 are also expressed in cardiac tissue; these could partially support CD36 synthesis, yet the resulting protein would be truncated and devoid of the transmembrane domain and the C-terminus.

Further analysis of nonsense mutation pathogenicity was conducted for the NM_001001548.3 transcript, as it is the MANE Select variant and exhibits the highest expression levels. The identified SNVs were predominantly located in the extracellular domain of the CD36 protein (60 identified nonsense mutations). Among these, four (rs1399769891, rs556438655, rs754102777, rs748962842) were situated within the binding sites for thrombospondin, THBS1, and THBS2. Additionally, three variants (rs1306255488, rs569959776, rs1001057012) map to the lipid-binding pocket, which is critical for interaction with fatty acids. The extracellular loop is

responsible for interactions with oxLDL and fatty acids; thus, the presence of mutations in this region is of critical importance for transporter function. Even if NMD is evaded, premature translation termination in this region results in the loss of not only the transmembrane segment but also key binding sites, effectively neutralizing CD36 receptor function. Among the identified nonsense mutations, one (rs1798012630) is located in the transmembrane region, which would lead to the disconnection

Analysis of CD36 gene transcripts for the presence of nonsense-mutations

Exon number in the MANE Select NM_001001548.3 transcript	Variant RSID	Transcripts lacking the specified mutation and escaping NMD (calculated)
3	rs1262349151	NM_001289911.2, NM_001371080.1
4	rs763504892, rs768992385, rs748289963, rs574416705, rs139067066, rs748202229, rs545489204, rs764713274	NM_001371079.1, NM_001371080.1
5	rs1399769891, rs556438655, rs754102777, rs748962842, rs201765331	—
6	rs373217513, rs369405900, rs146120263, rs202075359, rs746071954, rs1306255488, rs569959776	NM_001289909.1
7	rs1001057012, rs373829578, rs200067322	—
8	rs1393025883, rs1797103824, rs149985988	NM_001289908.1
9	rs760518458, rs964493808	NM_001289908.1
10	rs763513155, rs747098468, rs760212344, rs1797629734, rs762366674, rs1175585168, rs770214805, rs751804837, rs3211938	NR_110501.1
11	rs1175328132, rs151044699, rs981228197, rs56381858, rs1797725544, rs780637878, rs1406028281	—
12	rs1378994947, rs775478465, rs201657731, rs1167195397, rs1797840166	—
13	rs1797918768, rs1463817861, rs1385635045	NM_000072.3, NM_001001547.3, NM_001127443.2, NM_001127444.2, NM_001289908.1, NM_001289909.1, NM_001289911.2, NM_001371074.1, NM_001371078.1, NM_001371079.1, NM_001371080.1, NM_001371081.1, NR_110501.1
14	rs543879836, rs140728267, rs563772337	NM_001001548.3
14	rs1803256, rs1798012630	—
14	rs977068707, rs1307971636, rs766072001	NM_001001548.3, NM_001371075.1, NM_001371077.1, XM_005250715.6, XM_024447002.2, XM_024447003.2, XM_047421041.1, XM_047421042.1, XM_047421043.1, XM_047421044.1, XM_047421045.1, XM_047421046.1, XM_047421047.1, XM_047421048.1, XM_047421049.1

between the extracellular domain and the cytoplasmic tail, thereby disrupting association with kinases. Three nonsense mutations (rs977068707, rs1307971636, rs766072001) were located in the cytoplasmic domain, which mediates binding to PTK2, PXN, and LYN. Binding to LYN kinase is essential for caveolar endocytosis of fatty acids [8]. Truncated CD36 proteins may still anchor into the plasma membrane, but the lack of cytoplasmic tails renders them incapable of downstream signaling.

All analyzed SNVs demonstrated CADD PHRED scores >20, indicating their high destructive potential and probable pathogenicity [9]. Evolutionary conservation analysis using GERP scoring revealed more heterogeneous results: for 17 variants, the GERP value exceeded 2 (Fig. 2), confirming the localization of these substitutions within highly conserved regions of the *CD36* gene. Population frequency analysis of the investigated *CD36* variants confirmed their classification as rare, as the minor allele frequency (MAF) did not exceed 0.25% in any case. The highest prevalence was observed for the rs3211938 variant, with a MAF of 0.25%. For the remaining identified SNVs, the frequency was significantly lower than 0.1% (Fig. 2), suggesting a low prevalence of these potentially pathogenic substitutions in the general population.

Using the SpliceAI algorithm, four variants (rs1175328132, rs760212344, rs748289963, rs763504892) were identified, characterized by a high probability of splicing disruption. Notably, all these SNVs demonstrated extremely high pathogenicity scores (CADD > 40). The combination of high SpliceAI and CADD scores suggests that the negative impact of these mutations may result not only from the emergence of a premature stop codon but also from severe aberrations in pre-mRNA processing, significantly enhancing their probable pathogenicity.

Among the identified SNVs, a significant portion is absent from clinical databases (such as ClinVar) and is virtually unmentioned in the literature. However, the lack of described phenotypes in public repositories does not imply a lack of pathogenicity for these variants. This can be explained by their relatively low frequency in the studied populations (MAF < 10^{-5}), according to gnomAD data. These variants were identified in large-scale genome sequencing projects, and their annotation as "stop-gain" is based on high-confidence loss-of-function (pLOF high confidence) metrics. Such a low frequency makes the detection of these SNVs a relatively rare clinical encounter. Nevertheless, they possess high CADD scores and theoretically may trigger NMD, indicating their substantial functional impact on the performance of the CD36 protein

Due to its numerous functions, CD36 can influence conditions associated with metabolic syndromes, including insulin resistance, inflammation, and atherosclerosis [10]. CD36 deficiency leads to postprandial hyperlipidemia resulting from delayed blood lipid clearance in both humans and rodents [11]. CD36 facilitates the uptake of a significant portion of fatty acids in the myocardium, adipose tissue, and skeletal muscle. Consequently, CD36 deficiency causes defective myocardial fatty acid uptake [12]. Human induced pluripotent stem cell-derived cardiomyocytes have demonstrated that loss of CD36 function reduces fatty acid uptake, disrupting cardiac metabolism and myocardial contractility [13]. These findings highlight the role of CD36 in maintaining suboptimal myocardial energetics as a common underlying cause of dilated cardiomyopathy. In *cd36-/-* knockout mice, there is an enhancement of glucose utilization alongside reduced tissue fatty acid uptake [6]. The authors of these studies view such changes as an adaptation to energetic shifts, increasing glucose uptake to ensure myocyte survival and growth [14]. Furthermore, Podrez *et al.* [15] demonstrated in thrombosis-prone mice that CD36 deletion exerts a protective effect against increased platelet reactivity associated with hyperlipidemia and the concomitant prothrombotic phenotype.

The individuals with CD36 deficiency who consume large amounts of lipids exhibit high levels of circulating fatty acids [16] and chylomicron remnants [17], carrying an increased risk of metabolic

syndrome and complicated obesity [18]. However, such individuals demonstrate better insulin-stimulated glucose uptake, suggesting that CD36 deficiency may protect against muscle insulin resistance, though this requires further investigation. The increased CD36 expression promotes the transformation of macrophages into foam cells with a lipid-associated macrophage (LAM) phenotype. CD36 facilitates the accumulation of intracellular lipid droplets within macrophages. Conversely, the reduced CD36 expression limits lipid uptake and foam cell formation [19] by altering intracellular lipid processing. CD36 plays a key role in innate immunity against infectious diseases by recognizing pathogen-associated molecular patterns (PAMPs) on infected cells and changes in the phospholipid bilayer [20], which aids in the clearance of infectious agents by macrophages [21] and the modulation of cytokine release by immune cells.

CD36 deficiency resulting from the rs3211938 nonsense-mutation has been geographically linked to the prevalence of sickle cell anemia, as CD36 functions as a receptor for malaria-infected erythrocytes [20]. It has also been demonstrated that the absence of CD36 significantly increases host susceptibility to pneumonia caused by *Klebsiella pneumoniae*. In response to *S. aureus* infection, the mice with CD36 deficiency exhibited enlarged abscesses and increased dermonecrosis. Coburn *et al.* [22] suggest that this is linked to the role of CD36 in controlling the innate host response to skin infections.

We found that the majority of the identified nonsense mutations are localized within the large extracellular loop (27—439 aa). Premature translation termination in these regions prevents the formation of the hydrophobic pockets responsible for binding long-chain fatty acids and oxidized lipoproteins. Even those mutations occurring in the transmembrane or cytoplasmic domains of the protein result in the complete loss or functional impairment of the intracellular C-tail. In cases where these SNVs do not trigger mRNA NMD, the resulting proteins remain non-functional. Consequently, all the indicated mutations, in one way or another, lead to CD36 deficiency and reduced fatty acid uptake.

In summary, the animal models with complete CD36 deficiency have demonstrated dyslipidemia, defective fatty acid uptake in cardiac and skeletal muscles, altered insulin responses, protection against diet-induced atherosclerosis, thrombophilia, and reduced insulin resistance and adipose tissue inflammation. The data described in the literature regarding phenotypic changes in humans with CD36 deficiency suggest that the effect is diet-dependent. Although carriers of *CD36* nonsense-mutations may have an advantage in malaria-endemic areas, numerous studies indicate that complete CD36 deficiency leads to hyperlipidemia and is associated with cardiovascular diseases and complications in infectious processes. At the same time, CD36 deficiency exerted a protective effect in atherosclerosis and reduced insulin resistance. This impact is evidently linked to the diet-specifically, the amount of glucose and lipid intake under conditions of partial or complete deficiency. The rare prevalence and *in silico* analysis suggest that these nonsense mutations primarily have a pathogenic impact. We identified a series of mutations, localized mainly in the final exons, that escape the NMD degradation mechanism. This leads to the synthesis of truncated receptor isoforms that retain part of the extracellular domain but lack the C-terminal segment, resulting in the loss of key interaction sites with cytoplasmic tyrosine kinases (PTK2, PXN, LYN). This causes complete or partial blocking of intracellular signaling, which may serve as an evolutionary mechanism for modulating the metabolic response to dietary lipid excess. This causes a complete or partial blockade of intracellular signaling, which may confer an individual metabolic response to dietary lipid overload in the context of modern diets.

Conclusions

1. Based on the analysis of the gnomAD consortium data, nonsense-mutations of the *CD36* gene were identified, the majority of which are rare (MAF < 0.01) and characterized by high pathogenicity scores according to CADD (>20) and GERP scales. This indicates their significant

destructive potential and high evolutionary conservation of the respective positions.

2. It was established that the impact of nonsense-mutations on the *CD36* protein architecture is transcript-specific. A series of variants, localized primarily in the final exons, were found to escape the NMD degradation mechanism. This leads to the synthesis of truncated receptor isoforms that retain a portion of the extracellular domain but lack C-terminal segments, resulting in the loss of key interaction sites with cytoplasmic tyrosine kinases (PTK2, PXN, LYN). This causes complete or partial block of intracellular signaling, which may serve as an evolutionary mechanism for modulating the metabolic response to dietary lipid excess. This causes a complete or partial blockade of intracellular signaling, which may confer an individual metabolic response to dietary lipid overload in the context of modern diets.

Compliance with Ethical Standards. This study did not involve human participants as test subjects and does not contain personalized patient data. All analyzed data were obtained in an anonymized form from publicly accessible databases (gnomAD, GTEx, Ensembl). In accordance with international standards, the use of de-identified public data does not require specific approval from a bioethics committee.

Conflict of Interest. The author declare that there is no conflict of interest regarding the publication of this article.

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ВИВЧЕННЯ НОНСЕНС-МУТАЦІЙ ГЕНА *CD36* ЛЮДИНИ

CD36 слугує рецептором для широкого спектру лігандів — тромбоспондину, фібронектину, колагену, oxLDL, аніонних фосфоліпідів та довголанцюгових жирних кислот. Численними дослідженнями показано, що дефіцит CD36 призводить до зменшення інсулінорезистентності та має захисний вплив від атеросклерозу. У зв'язку з цим виникає питання, чи можуть ці рідкісні варіанти забезпечувати індивідуальну метаболічну відповідь (наприклад, захист від інсулінорезистентності м'язів) у сучасному дієтичному контексті, діючи як рідкісні Loss-of-Function (LoF) механізми. Метою дослідження стало вивчення функціональної ролі нонсенс-мутацій гена *CD36* та їхньої частоти в людській популяції. ***Методи.*** Для аналізу частот алелів (MAF) використовували дані консорціуму gnomAD, а патогенність оцінювали за допомогою балів CADD та GERP. ***Результати.*** Встановлено, що більшість ідентифікованих нонсенс-мутацій є рідкісними та мають високі показники патогенності (CADD > 20). За допомогою інструментів SpliceAI та аналізу транскрипт-специфічності виявлено варіанти, що уникають механізму NMD, та призводить до синтезу вкорочених ізоформ білка. ***Висновки.*** Ідентифіковані нонсенс-мутації гена *CD36* є рідкісними (MAF < 0,01) та характеризуються високими показниками патогенності за шкалами CADD (> 20) і GERP. Виявлено низку варіантів, локалізованих переважно в останніх екзонах, які уникають механізму NMD-деградації, проте спричиняють втрату сайтів взаємодії з цитоплазматичними тирозинкіназами.

***Ключові слова*:** *CD36*, нонсенс-мутації, транскрипти, NMD, атеросклероз, біоінформатичний аналіз.