Toxicol Res. (2023) 39:341–353
https://doi.org/10.1007/s43188-023-00176-2

Online ISSN 2234-2753
Print ISSN 1976-8257

REVIEW ARTICLE

Exploring scavenger receptor class F member 2 and the importance of scavenger receptor family in prediagnostic diseases

Thuy-Trang T. Vo[1,2] · Gyeyeong Kong[1,2] · Chaeyeong Kim[1,2] · Uijin Juang[1,2] · Suhwan Gwon[1,2] · Woohyeong Jung[1,2] · Huonggiang Nguyen[1,2] · Seon-Hwan Kim[3] · Jongsun Park[1,2]

Received: 31 December 2022 / Revised: 9 March 2023 / Accepted: 14 March 2023 / Published online: 14 April 2023

Abstract

Scavenger Receptor Class F Member 2 (*SCARF2*), also known as the Type F Scavenger Receptor Family gene, encodes for Scavenger Receptor Expressed by Endothelial Cells 2 (SREC-II). This protein is a crucial component of the scavenger receptor family and is vital in protecting mammals from infectious diseases. Although research on SCARF2 is limited, mutations in this protein have been shown to cause skeletal abnormalities in both SCARF2-deficient mice and individuals with Van den Ende-Gupta syndrome (VDEGS), which is also associated with SCARF2 mutations. In contrast, other scavenger receptors have demonstrated versatile responses and have been found to aid in pathogen elimination, lipid transportation, intracellular cargo transportation, and work in tandem with various coreceptors. This review will concentrate on recent progress in comprehending SCARF2 and the functions played by members of the Scavenger Receptor Family in pre-diagnostic diseases.

Keywords Scavenger receptor class F member 2 · SCARF2 · Cancer · Biomarker · Van den Ende–Gupta syndrome (VDEGS) · Glioblastoma

Introduction

SCARF 2 was initially identified in a human endothelial cell line and classified as a member of the scavenger receptor family [1]. The scavenger receptor family includes a group of functionally defined membrane receptors that share a common ability to bind and internalize modified forms of low-density lipoproteins (LDL) such as acetylated LDL (AcLDL) and oxidized LDL(OxLDL) [2, 3]. Although SCARF2 is special in that it does not show the expected binding to modified LDL [1], SCARF2 is not a prominent member of the scavenger receptor family or class F due to lacking of research. However, recently it has been found to play a role in pathogenesis and serve as a diagnostic marker.

Measurable indicators of biological or pathological processes are known as biomarkers, and they are useful tools in disease diagnosis, monitoring, and predicting treatment response. Scavenger receptors (SRs) are a versatile group of receptors that play a vital role in many cellular processes, such as phagocytosis, signal transduction, antigen presentation, and cell adhesion. Furthermore, SRs are involved in a process called efferocytosis, which clears apoptotic cells and debris to maintain tissue homeostasis and prevent inflammation. Due to their involvement in various disease pathologies, there is an increasing interest in utilizing SRs as biomarkers for these conditions.

In this article, we will present an outline of SCARF2, its potential for research, and the usefulness of SRs in disease diagnosis and monitoring.

✉ Jongsun Park
insulin@cnu.ac.kr

1 Department of Pharmacology, College of Medicine, Chungnam National University, 266 Munhwa-ro, Jung-gu, Daejeon 35015, Republic of Korea

2 Department of Medical Science, Metabolic Syndrome and Cell Signaling Laboratory, Institute for Cancer Research, College of Medicine, Chungnam National University, Daejeon 35015, Republic of Korea

3 Department of Neurosurgery, Institute for Cancer Research, College of Medicine, Chungnam National University, Daejeon 35015, Republic of Korea

Scavenger receptor family

The large scavenger receptor family was first identified by Goldstein and Brown in 1979 [4]. The many receptors are classified into 12 classes (A–L) according to their ability to cooperate with many different coreceptors. The SRs exhibit flexible responses and play roles in pathogen elimination, lipid transportation, intracellular cargo, and transportation, and even serve as taste receptors [5]. The receptors play important roles in host defense, lipid metabolism, and the regulation of adaptive immunity. More specifically, each receptor can trigger inflammation (to control infection) or induce an anti-inflammatory response (depending on the conditions) [6]. Members of the scavenger receptor family are classified according to the order of discovery. The first SRs were termed scavenger receptor class A types I and type II (SR-AI and SR-AII, respectively) by Krieger's group in 1997 [7], despite the fact that they were first purified in 1988 [8], and later designated as macrophage scavenger receptor types I and II [9, 10]. Class B scavenger receptors, which are among the most extensively researched scavenger receptor classes alongside class A, offer protection against the detrimental effects of proteases. Their extracellular domains typically showcase N-linked glycosylation. The receptor's N and C termini are located within the cytoplasm and form an extracellular ring with two transmembrane domains. [11]. Class C is found only in invertebrates such as Drosophila [12]; these receptors have received little attention. Scavenger receptor class D has only one member (CD68), which was previously classified into class B because it is very similar to the class B receptors [13]. CD68 is strongly expressed by immune cells including free monocytes, tissue-specific macrophages, and microglia, but the functions of CD68 in immunity and inflammation (including antigen presentation and processing) remain unclear [6]. There are four class E scavenger receptors: lectin-like oxidized LDLR (LOX-1), dectin-1, a mannose receptor (CD206), and the asialoglycoprotein receptor 1 (ASGPR1) [14]. All four class E receptors are type 2 transmembrane proteins with extracellular domains having the C-type lectin-like motifs seen in the subfamily of natural killer cell C-type lectin-like proteins. However, only LOX-1 and dectin-1 have been well-studied; they both exhibit scavenger activities [15]. The class E scavenger receptors are type 2 transmembrane proteins with C-type lectin-like domains, while the Class F receptors are type 1 transmembrane proteins with epidermal growth factor (EGF)-like domains. The latter receptors are found in the endothelia of mammals and worms [13]. The scavenger receptor class F member 1 (SCARF1), also identified as scavenger receptor expressed by endothelial cells 1 (SREC-I)), is the most notable member recognized for its involvement in the elimination of apoptotic cells that occur during development. [16]. The class A receptors account for 90% of the degradation of acetylated low-density lipoprotein (LDL); SCARF1 is responsible for 6% of this degradation [2]. SR-PSOX/CXCL16 is a Class G scavenger receptor that facilitates the interaction between DCs and CD8 + T cells, guides T cell movements in the splenic red pulp [17], and plays an important role in tumorigenic processes, side-effects, and resistance to anti-cancer drugs [18]. CXCL16 is thus a candidate target for cancer therapy. Class H members include common lymphatic endothelial and vascular endothelial receptor-1 (Clever-1; also known as Stabilin-1 and FEEL-1) and the hyaluronan (HA) receptor for endocytosis (HARE; also known as Stabilin-2 and FEEL-2). Clever-1 and HARE affect lymphocyte adhesion, angiogenesis, transmigration, apoptotic cell clearance, and intracellular trafficking [14]. Class I has 18 members, including 4 in humans, of which the hemoglobin (Hb) scavenger receptor (also known as CD163A) was the first to be discovered; it indirectly contributes to the anti-inflammatory response [14, 19]. The remaining members are expressed in mice (SCART2) and cattle (WC1-1–13) [14]. Class J includes only the receptor for advanced glycation end-products (RAGE), which has ligand domains specific for the amyloid-β-protein, HMGB1, microbial PAMPs, and DAMPs [20]. In vivo and in vitro data have shown that HMGB1 enhances the proinflammatory effect of lipopolysaccharide (LPS) on macrophages, an effect mediated by phosphorylation of MAPK p38 and activation of NF-kB [21]. Class K contains only CD44 and the HA receptor [3]. Unlike HMGB1, CD44 prevents an excessive inflammatory response to LPS and acts as a phagocytic receptor (via HA signaling) [22]. The final class, i.e., class L, also has only two members: CD91 9 (SR-L1) and Megalin (SR-L2). Similar to class F, the first member of class L (SR-L1) is the most studied within its class; it is also the most studied among the entire LDLR gene family. Although SR-L1 functions uniquely as a scavenger receptor, SR-L1 can bind over 100 diverse ligands. However, the functions and interactions of these ligands with coreceptors and signal transducers remain unknown [6].

It is important to note that the functions of SRs are not static and may differ depending on the cell type and tissue in which they are present. Some members of this family may even have similar functions, and their roles may vary under different physiological or pathological circumstances. For a detailed comprehension of the primary functions of all 12 classes of the scavenger receptor family, please consult Table 1.

Table 1 The main functions of the 12 classes of the scavenger receptor family

No.	Division	Name of members	Main functions	References
1	Scavenger receptor class A	MSR1, SCARA3, COLEC12, SCARA5, MARCO	Involved in the recognition and internalization of modified low-density lipoproteins (LDL) and other ligands, such as bacteria and immune complexes, to contribute to the clearance of harmful substances from the body and play a role in immune responses	[6, 64, 101]
2	Scavenger receptor class B	CD36, SR-BI, SR-BII	Involved in the selective uptake of high-density lipoprotein (HDL) cholesterol and recognition of a wide range of ligands, including oxidized LDL and thrombospondin, to play a key role in lipid metabolism and prevent the accumulation of excess cholesterol in the blood and prevent damage to the surrounding tissues	
3	Scavenger receptor class C	SR-C	Involved in the recognition and internalization of bacteria and other microorganisms, as well as other ligands, to play a role in the innate immune response and contribute to the clearance of harmful substances from the body and maintain normal cellular function	
4	Scavenger receptor class D	CD68	Functions as a lysosomal transmembrane protein, playing a role in the phagocytosis of cellular debris and pathogens, as well as in the regulation of inflammation and immune responses	
5	Scavenger receptor class E	OLR1	Functions as a pattern recognition receptor for oxidized phospholipids and plays a role in the innate immune response, promoting inflammation and apoptosis, and regulating foam cell formation and atherosclerosis	
6	Scavenger receptor class F	SCARF1, SCARF2, MEGF10	Involved in the recognition and internalization of modified lipoproteins, such as oxidized LDL, to contribute to the clearance of harmful substances from the body and maintain normal lipid levels in the circulation	
7	Scavenger receptor class G	CXCL16	Functions as a chemoattractant for immune cells, particularly natural killer cells and T cells, and plays a role in the regulation of immune responses, such as inflammation, angiogenesis, and tumorigenesis	
8	Scavenger receptor class H	STAB1, STAB2	Involved in the recognition and internalization of various ligands, including bacteria and immune complexes, to play a role in the innate immune response and contribute to the clearance of harmful substances from the body and maintain normal cellular function	
9	Scavenger receptor class I	CD163A, CD163B, CD163c-a, CD163c-b	Involved in the recognition and internalization of various ligands, including modified low-density lipoproteins (LDL) and other lipoproteins, to contribute to the clearance of harmful substances from the body and play a role in lipid metabolism	
10	Scavenger receptor class J	RAGE	Functions as a pattern recognition receptor for various ligands, including advanced glycation end-products, high-mobility group box 1 protein, and amyloid-beta peptides, playing a role in the regulation of inflammation, oxidative stress, and cell survival in response to cellular damage	
11	Scavenger receptor class K	CD44	Functions as a cell adhesion molecule and receptor for hyaluronic acid and other extracellular matrix components, playing a role in cell-cell and cell-matrix interactions, cell migration, and the regulation of immune responses, tumorigenesis, and wound healing	
12	Scavenger receptor class L	CD91, Megalin	Play a role in the uptake and clearance of a diverse range of ligands, including modified low-density lipoproteins, and contribute to the regulation of cholesterol homeostasis and innate immune response	

SCARF2 structure

Previous studies suggested that SCARF2, is a paralog of SCARF1 (35% overall homology to SCARF1, rising to 53% in the extracellular domain) [1, 23]. SCARF2 is encoded on human chromosome 22 and expressed predominantly in human endometrium, fat, gall bladder, kidney, lung, ovary, placenta, prostate, and spleen [24]. SCARF2 is a type I transmembrane protein (871 amino acids [aa] in length) encoded by 11 exons. It has a 43-aa signal peptide, 398-aa extracellular region, 21-aa helical transmembrane segment, and relatively long cytoplasmic domain (409 aa) [1, 23]. The

extracellular domain contains seven EGF-like repeats and the cytoplasmic domain is rich in serine, proline, glycine, and arginine residues. SCARF2 also contains two extracellular N-glycosylation sites and several potential intracellular phosphorylation sites [1, 25] (Fig. 1)

Scavenging function of SCARF2

The scavenger receptor family class F (SR-F) is a group of transmembrane proteins found in many different cell types, including immune cells and cells in the cardiovascular system. SR-F has three members: SCARF1, SCARF2, and Megf10 or SCARF3 (encoded by MEGF10) [26]. The sole purpose of the second member of the SR-F, SCARF2, is to serve as a brain receptor for amyloid-β protein. As a result, it plays a role in the development of Alzheimer's disease. [27]. Although SCARF1 has been extensively studied, SCARF2 has received little attention at either the protein or functional level. SCARF2 is expressed by endothelial cells and macrophages but, unlike SCARF1, shows limited internalization of modified LDL [1, 28] and binds and degrades acetylated LDL (Ac-LDL) less effectively. Therefore, the homophilic and heterophilic interactions mediated by SCARF 2 are less marked than those of SCARF1 [1]. Wicker-Planquart et al. recently suggested that SREC-II interacted strongly with maleylated BSA (MalBSA; (a common ligand of SRs) via the extracellular domain. This domain of SCARF1 binds endogenous complement C1q and the calcium-binding chaperone calreticulin (CRT) [28].

SCARF2 mutations and diseases

Mutations in SCARF2 are associated with 22q11.2 deletion syndrome, which is the most common chromosomal microdeletion syndrome, affecting approximately 1 in every 3000 live births [29]. Diseases associated with SCARF2 mutations are very rarely seen, as the mutations tend to be fatal.

Van den Ende–Gupta syndrome (VDEGS)

The exact biological functions of SCARF2 have yet to be fully understood. However, uncovering these functions is crucial, as mutations in SCARF2 have been linked to Van den Ende–Gupta Syndrome (VDEGS), a rare condition first reported in 2010 by Anastasio et al. [23]. VDEGS inheritance is autosomal-recessive, and is characterized by craniofacial dysmorphism, severe mental retardation, various skeletal abnormalities (long and slender fingers, hooked clavicles, slender ribs, and bowed long bones), respiratory problems (associated with laryngeal abnormalities) and, occasionally, an enlarged cerebellum and sclerocorneal, and heart defects [23, 30, 31]. Known VDEGS-causing SCARF2 mutations include homozygous missense mutations in exons 2, 4, and 11; a homozygous insertion in exon 11; and homozygous deletions in exons 4, 8, and 11 (see Table 2). A

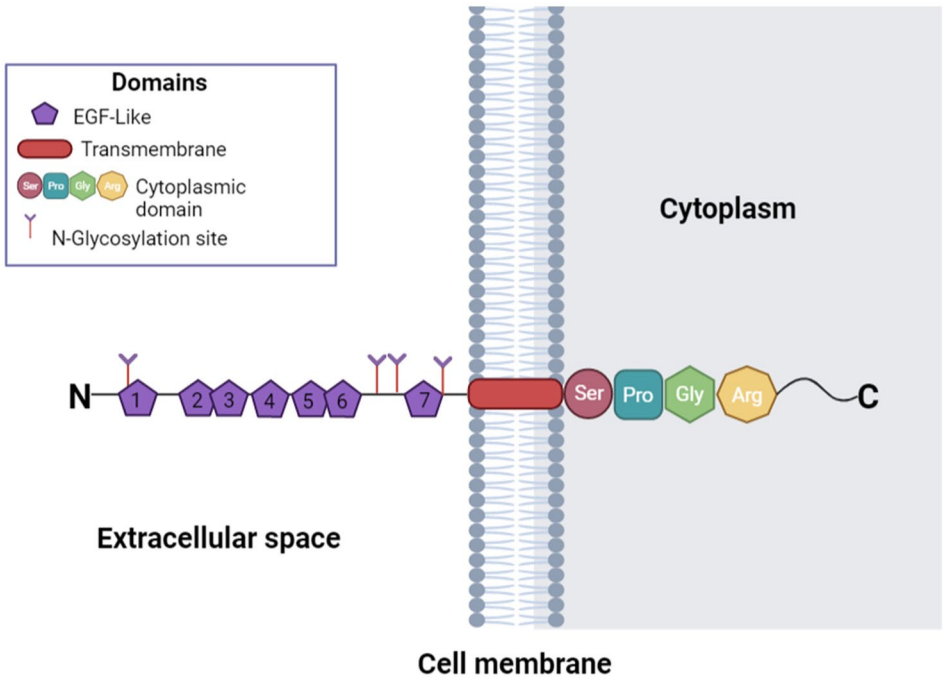

Fig. 1 Structure of SCARF2. The SCARF2 type I transmembrane protein has three main regions: (1) An extracellular domain (with the N-terminus) contains seven EGF-like repeats (purple pentagons) and several N-glycosylation sites by which biophysical properties could be modulated, thereby regulating protein function after post-translational modification. (2) One transmembrane domain (red oval) penetrates the phospholipid bilayer (blue). 3: The relatively long cytoplasmic domain (with the C-terminus) is rich in serine, proline, glycine, and arginine residues

heterozygous VDEGS mutation (a compound heterozygous SCARF2 splice site mutation combined with heterozygosity of the common microbiome 22q11.2) has also been reported [32]. The association between SCARF2 mutation and skeletal abnormalities was confirmed in SCARF2 knockout mice; the long bones were longer than normal [33, 34], mirroring the long metacarpals seen in humans with VDEGS. Homozygous knockout mice also showed decreased bone mineral density, erythrocyte cell expression, and hemoglobin levels [34]. Furthermore, homozygous knockout mice display mutations in various organs, including the chest bone, kidney, skin, trachea, cecum, colon, ileum, large intestine, small intestine, and stomach (with a frequency of 66.67%) and the epididymis, jejunum, testis, and vas deferens (with a frequency of 33.33%) [34].

Cancer

The buildup of mutated genes can result in tumors, but only a small percentage, approximately 10%, are responsible for driving carcinogenesis. SCARF2 somatic mutations have been identified in breast cancer (c.1495 C > T) [35] and pancreatic tumors (frameshift c.2239_2240insG) [36]. The impact of these mutations on tumorigenesis remains uncertain. Nevertheless, since higher levels of SCARF2 expression have been linked to better prognosis, SCARF2 could be a possible diagnostic indicator and treatment target for treatment-resistant cancers, such as glioblastoma (GBM) [37]. On the other hand, renal (Fig. 2A) and urothelial (Fig. 2B) cancers, which are generally less aggressive, may benefit from early detection since early diagnosis often leads to better treatment outcomes. Cancers can often be cured (or the survival rate improved) if detected prior to metastasis. Early diagnosis based on biomarkers such as SCARF2 is very important.

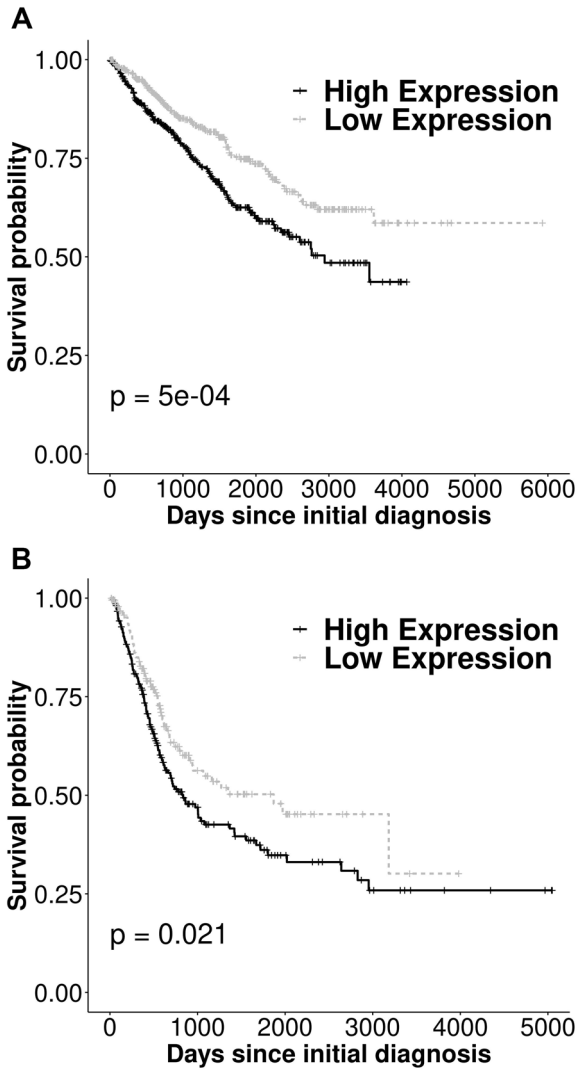

Fig. 2 mRNA levels and *SCARF2* mutation-associated survival rates revealed by analysis of the Human Protein Atlas database. The Kaplan-Meier survival curve shows the overall survival rate according to the SCARF2 expression level. **a** SCARF2 status is prognostic factor for renal cancer. **b** SCARF2 status is a prognostic factor for urothelial cancer prognosis

Table 2 *SCARF2* mutations associated with VDEGS

SCARF2 mutation	Genetic variant	Protein variant	Affected exon	References
Homozygous missense mutation	c.190T > C	Cys64Arg	2	[31, 102]
	c.651 C > G	Cys217Trp	4	[31]
	c.488G > A	Cys63Tyr	4	[103]
	c.773G > A	Cys258Tyr	4	[23, 104]
	c.2190T > C	Cys64Arg	11	[102]
Homozygous insertion	c.2291_2292insC	Ser765LeufsTer6	11	[103]
Homozygous deletion	c.438_454del17	Trp148Alafs*20	4	[30]
	c.472_477del	Cys158_Gln159del	4	[31]
	c.1328-1329delTG	V443DfsX83	8	[23]
	c.2543del	Gln848Argfs*95	11	[102]
	c.2607_2608del	Leu870Val	11	[105]

Disorders related to the brain and cardiovascular system

Passenger mutations are genetic alterations that do not contribute to disease development, while driver mutations drive disease progression by altering biological processes. SCARF2 driver mutations fall into this latter category and have been linked to brain-related disorders and cardiovascular diseases. Fine mapping of the copy number variants (CNVs) of carriers suggested that SCARF2 (locus 22q11.2) is a driver of schizophrenia [38, 39]. A 2021 study using large genotyped cohorts found that SCARF2 gene Copy Number Variations (CNVs) on chromosome 22q11.2 were associated with mood disorders [40]. CNV evaluation combined with next-generation sequencing (NGS) and the use of the eXome hidden Markov model (XHMM) allowed Overwater et al. to detect a deletion of the entire *SCARF2* gene (thus including 22q11.2) in a patient with hereditary, thoracic aortic disease [41].

The utility of scavenger receptor family proteins as biomarkers in human diseases

Comprising a vast and diverse array of proteins, the scavenger receptor family plays a crucial role in numerous cellular processes, including immune response, lipid metabolism, and pathogen recognition. Some members of this family have the potential to serve as biomarkers for a range of conditions and diseases, such as atherosclerosis, Alzheimer's disease, and cancer. Moreover, elevated SR expression has also been linked to cardiovascular disease. [42, 43].

Scavenger receptor class A

Numerous studies have explored the possibility of scavenger receptor class A (SR-A) as a biomarker for various diseases. In 1998, Khoury and colleagues have identified SR-A as the primary receptor involved in the interaction of microglia with beta-amyloid fibrils. The elevated levels of SR-A were present in both activated microglia and senile plaques, which led to the production of reactive oxygen species (ROS), contributing to the neuronal degeneration and death observed in Alzheimer's disease. These findings suggest that SR-A could serve as a promising biomarker and therapeutic target for the disease [44]. In addition, it was also demonstrated as a biomarker of rheumatoid arthritis [45]. A 2008 study by Nakayama et al. found that patients with coronary artery disease (CAD) had significantly higher levels of soluble SR-A in their plasma compared to healthy individuals. The study concluded that soluble SR-A could potentially serve as a biomarker for CAD and atherosclerosis [46]. Similarly, Ichimura and colleagues found that a high expression of SR-A was significantly associated with shorter metastasis-free and cancer-specific survival of upper urinary tract cancer [47]. Moreover, a study featured in BioMed Research International revealed that individuals with lung cancer displayed significantly elevated levels of SR-A in their serum compared to healthy subjects, suggesting that SR-A could potentially serve as a prognostic marker for clinical stage I lung adenocarcinoma. [48]. However, further research is necessary to validate and confirm the utility of SR-A as a biomarker for these and other diseases.

Scavenger receptor class B

Scavenger receptor class B (SR-B) is a group of membrane receptors that play a crucial role in regulating lipid metabolism and transport in various cells and tissues, including macrophages, endothelial cells, and steroidogenic cells. Among its many functions, SR-B can be utilized as a biomarker to diagnose or monitor disease progression. Notably, SR-B1 is integral to regulating cholesterol homeostasis and the development of atherosclerosis. Macrophages expressing elevated levels of SR-B1 have been linked to lower risk of cardiovascular disease [43, 49]. However, in certain types of cancer, such as lung, breast, ovarian, colorectal, pancreatic, and prostate, high levels of SR-B1 expression in cancer cells have been associated with increased tumor growth and metastasis [50–52]. Furthermore, the expression of SR-B at both mRNA and protein levels is linked to an unfavorable prognosis for patients with GBM, suggesting that SR-B could be used as a biomarker to predict patient survival [53]. In oral squamous cell carcinoma patients, those with high expression of SR-B also had a lower probability of progression-free survival, which was 34% [54]. Additionally, in the ovary, SR-B1 expressed in theca cells is critical for the uptake of cholesterol and its conversion into steroid hormones [55]. Therefore, SR-B1 expression serves as a useful biomarker for ovarian function. In the liver, reduced expression of SR-B1 has been linked to the development of nonalcoholic fatty liver disease (NAFLD), a condition characterized by the accumulation of fat in the liver [56].

Scavenger receptor class C

The effectiveness of scavenger receptor classes C as dependable biomarkers has not been confirmed. Further investigation is required to determine their efficacy as biomarkers and how their expression levels may relate to the advancement of the disease or response to treatment.

Scavenger receptor class D

Expressed in various tissues such as the liver, lung, and brain, scavenger receptor class D (SR-D) is a receptor that may hold promise as a biomarker for certain diseases, despite being less researched than other SRs. Research has indicated that SR-D could play a role in the advancement and onset of neurodegenerative conditions, including Alzheimer's disease. [57]. Additionally, elevated levels of SR-D in tumor samples were associated with a negative prognosis in several cancers, including glioblastoma, kidney renal clear cell carcinoma, lower-grade glioma, liver hepatocellular carcinoma, lung squamous cell carcinoma, thyroid carcinoma, and thymoma, but with a favorable prognosis in kidney chromophobe [58].

Scavenger receptor class E

A cell surface receptor known as scavenger receptor class E (SR-E) is mainly found in macrophages and contributes to regulating inflammatory responses and lipid metabolism. Research has indicated that SR-E may play a role in the growth and advancement of cardiovascular disease, as evidenced by its upregulation in atherosclerotic plaques. [59, 60]. Moreover, there is a suggestion that SR-E could serve as a promising biomarker for breast cancer since it is frequently overexpressed in breast cancer tissues and has been linked to an unfavorable prognosis. [61]. Furthermore, studies have shown that SR-E levels are elevated in patients with nonalcoholic fatty liver disease (NAFLD), a condition characterized by the accumulation of fat in the liver that can progress to more severe forms of liver disease SR-E has been suggested as a potential biomarker for NAFLD and its associated complications, as it may be involved in the pathogenesis of the disease [62]. In a recent study, SR-E also shows potential as a predictor or a regulator in non-small cell lung cancer (NSCLC) immunotherapy [63].

Scavenger receptor class F

Proteins belonging to the SR-F group have been discovered to have diverse functions in biological processes, including the elimination of apoptotic cells, the regulation of immune responses, and the identification and absorption of modified low-density lipoproteins (LDLs). However, the malfunctioning of this latter process may play a role in the progression of atherosclerosis, a condition characterized by the accumulation of fatty deposits in the walls of arteries, which may increase the risk of heart disease [64, 65]. In addition to their role in the uptake of modified LDLs, SR-F proteins have also been implicated in other physiological processes, such as the regulation of immune response and the clearance of cellular debris [66, 67].

SCARF1 has attracted significant research attention within the SR-F group, with studies indicating that it is expressed in various cancer cell types, including breast, lung, pancreatic, and prostate cancer. In comparison to normal cells, cancer cells often exhibit increased expression levels of SCARF1 [68]. More specifically, Patten and colleagues looked at the expression of SCARF in tissue samples from patients with hepatocellular carcinoma (HCC). They found that SCARF1 expression was downregulated in HCC tumor tissues, compared to non-tumoral tissues, and loss of SCARF1 expression was associated with poorly differentiated/aggressive tumors. The authors suggest that SCARF1 may serve as a prognostic biomarker for HCC [69]. Moreover, Li et al. discovered a correlation between SCARF3 expression levels and IDH mutation in glioma. The study demonstrated that the methylation level and mRNA expression of MEGF10 in glioma were not only associated with IDH mutation, but also had a notable impact on the clinical prognosis of patients. Therefore, MEGF10 might be utilized as a promising tool for further investigation on the function of IDH in glioma and serve as a biomarker for glioma advancement [70, 71]. These studies have suggested that SR-F may play a role in the suppression of the immune response in cancer cells. This suppression is thought to allow cancer cells to evade recognition and destruction by the immune system, potentially contributing to the progression of cancer.

Scavenger receptor class G

Scavenger receptor class G (SR-G) is a chemokine protein that exhibits potential as a biomarker for diverse conditions. For example, A 2017 study by Xing et al. revealed that elevated levels of SR-G were linked to increased severity of coronary atherosclerotic heart disease, implying that SR-G might be an advantageous biomarker for assessing the prognosis and advancement of the disease in patients with coronary heart disease. [72]. Other studies, including those by Lin et al. and Zhao Lin et al., have also found that SR-G levels are significantly elevated in patients with chronic kidney disease and renal injury in type 2 diabetes mellitus [73, 74]. These findings suggest that SR-G could serve as a useful biomarker for the early detection and monitoring of renal disease. Additionally, in hemodialysis patients, SR-G could be used in conjunction with C-reactive protein as an inflammatory biomarker [75]. Furthermore, Ayyappan and colleagues conducted a study in 2020 and discovered that the levels of SR-G were notably higher in individuals

with rheumatoid arthritis as compared to healthy individuals [76]. Nevertheless, more research is necessary to fully establish its potential as a biomarker and determine its clinical usefulness.

Scavenger receptor class H

Scavenger receptor class H (SR-H) proteins are involved in various biological processes, including the clearance of endogenous and exogenous ligands, as well as immune cell trafficking and antigen presentation. SR-H proteins have been implicated in several diseases, including cancer, atherosclerosis, and inflammatory disorders [77]. Therefore, some studies have suggested that SR-H proteins expression may be a prognostic biomarker for certain cancers, such as liver and lung cancer, and may also be useful in predicting the efficacy of certain cancer treatments [78, 79].

Scavenger receptor class I

Scavenger receptor class I (SR-I) proteins are cell surface receptors primarily expressed on macrophages and monocytes. They are involved in the phagocytosis of apoptotic cells, bacteria, and other foreign particles, as well as in the regulation of inflammatory responses. SR-I proteins have been proposed as a potential biomarker for a variety of conditions, including cancer, infectious diseases, and inflammatory disorders. Notably, according to a study conducted by Cheng and colleagues in 2017, high expression of SR-I was found to be linked with an unfavorable prognosis in patients suffering from gastric cancer. The study suggested that SR-I may serve as a useful biomarker for predicting the prognosis and therapeutic target of gastric cancer [80]. In addition, SR-I is a prognostic predictor of short-term and long-term outcomes in decompensated cirrhosis patients. Accordingly, the addition of SR-I to the original clinical scoring systems improved their prognostic performance [81]. SR-I may be also correlated with disease severity and the disease progression in hemorrhagic fever with renal syndrome patients; however, the underlying mechanisms should be explored further [82]. Moreover, a 2013 study by Jude et al. found that plasma levels of soluble SR-I were elevated in patients with rheumatoid arthritis and were associated with disease activity. The study suggested that SR-I may serve as a useful biomarker for monitoring disease activity and predicting treatment response in patients with rheumatoid arthritis [83].

Scavenger receptor class J

Scavenger receptor class J (SR-J) is a transmembrane receptor that is expressed on a wide range of cell types and is involved in various physiological and pathological processes, including inflammation, oxidative stress, and tissue damage. In 2005, Emanuele et al. found that plasma levels of SR-I were significantly lower in patients with Alzheimer's disease compared to healthy controls. The study suggested that soluble SR-I could be a useful biomarker for the early diagnosis and monitoring of Alzheimer's disease [84]. An earlier study by Falcone and colleagues also reported that a low plasma SR-J concentration could be a marker for vascular disease [85]. In addition, the notable decrease in SR-I expression observed in multiple sclerosis patients when compared to healthy controls highlights the potential involvement of the SR-I axis in the clinical pathology of multiple sclerosis. This decrease in SR-I expression may lead to heightened inflammatory responses. The study proposes that SR-I may serve as a promising marker of disease severity in multiple sclerosis [86, 87].

Scavenger receptor class K

Scavenger receptor class K (SR-K) is a cell surface glycoprotein that plays a pivotal role in several cellular processes, such as cell adhesion, migration, and signaling. Moreover, SR-K is known to be involved in a range of pathological conditions, such as inflammation, immune disorders, and cancer. SR-K is a versatile biomarker that has widespread usage in diagnosing, predicting, and treating diverse diseases. Its specific expression patterns in different cell types and involvement in numerous signaling pathways make it a valuable resource for research and clinical applications. As a biomarker, SR-K has been extensively studied for several cancer types, including breast, prostate, pancreatic, and colorectal cancer. The receptor is overexpressed in cancer cells and is associated with tumor progression, invasion, and metastasis [88]. SR-K expression is used to identify cancer stem cells, which are thought to be responsible for tumor initiation, maintenance, and resistance to therapy. SR-K is also used to predict the prognosis of cancer patients and to monitor their response to treatment [89, 90]. Furthermore, SR-K is expressed on the surface of many types of stem cells, including hematopoietic stem cells, mesenchymal stem cells, and neural stem cells. It is used as a biomarker for the identification and isolation of stem cells from different tissues, as well as for the characterization of their properties and differentiation potential [90]. Additional, SR-K is expressed on the surface of many types of immune cells and is involved in the recruitment and activation of leukocytes. It has been shown to be upregulated in inflammatory conditions such as rheumatoid arthritis [91], asthma [92], and allergic reactions [93]. SR-K is used as a biomarker for these conditions, as well as a target for therapeutic intervention. Not only that, SR-K has also been shown to be involved in

the development of atherosclerosis and other cardiovascular diseases [94, 95]. It is expressed on the surface of vascular smooth muscle cells and is involved in the migration and proliferation of these cells. SR-K is used as a biomarker for the diagnosis and prognosis of these conditions, as well as a target for therapeutic intervention. Recent studies have also identified SR-K as a novel biomarker and therapeutic target for liver fibrosis in patients with congestive hepatopathy [96].

Scavenger receptor class L

LRP-1 (low-density lipoprotein receptor-related protein 1), which is one of the two members of scavenger receptor class L (SR-L), is a transmembrane protein that participates in numerous physiological processes, including lipoprotein metabolism, extracellular matrix component clearance, and regulation of cell signaling. This protein is expressed in various cell types and tissues. Recent investigations have demonstrated that LRP-1 expression is markedly higher in NSCLC (non-small cell lung cancer) cells and can also be detected in extracellular vesicles released from these cells. Moreover, LRP-1 expression is elevated in lung cancer biopsy tissues and exosomes of NSCLC patients. As such, LRP-1 holds potential as an important tool for investigating the development of diagnostic and prognostic biomarkers for NSCLC disease [97]. LRP-2 (low-density lipoprotein receptor-related protein 2), the second member of scavenger receptor class L, is highly expressed in the proximal tubules of the kidney and has been shown to play a crucial role in the reabsorption of several vital proteins, including albumin. Multiple studies have demonstrated that LRP-2 levels are significantly reduced in the kidneys of patients with chronic kidney disease and diabetic nephropathy, indicating that LRP-2 may be a valuable biomarker for diagnosing and monitoring these conditions[98]. Besides, the LPR-2 mutation signature is a potential predictor of patients' prognosis after immunotherapy [99]. Furthermore, there is evidence suggesting that LRP-1 and LRP-2 play a role in the pathogenesis of Alzheimer's disease. Research has indicated that the expression levels of these proteins are notably reduced in the brain tissue of individuals affected by Alzheimer's disease. [100]. This suggests that SR-L could be a useful biomarker for diagnosing and monitoring Alzheimer's disease.

Conclusion and perspective

Overall, SCARF2 is an important target for developing therapeutic strategies aimed at preventing or treating cardiovascular disease and brain-related disorders, including glioblastoma. However, similar to SCARF1, SCARF2 has many positively charged residues (potential phosphorylation sites) in the long cytoplasmic tail [1]; ligand binding may differentially affect cellular signaling. The 22q11.2 deletion syndrome is associated with deficiencies in several genes, including SCARF2, and with various human congenital malformations. The role played by SCARF2 in homeostasis, immunity, and disease pathology should be further explored. Therefore, more research is needed to fully understand the role of this protein in various biological processes and to determine how they can be effectively targeted for therapeutic purposes.

Ongoing research is exploring the potential of SRs as biomarkers and imaging targets in various diseases, making the role of SRs in diagnostic medicine a subject of active investigation. It should be noted that the clinical use of biomarkers requires rigorous validation and standardization, and should not replace other diagnostic tools in making informed decisions about patient care. The suitability of biomarkers, including SRs, for clinical use should be based on well-designed studies that consider their specificity, sensitivity, and predictive value. Further investigation is needed to determine whether SRs meet these criteria and could be a valuable biomarker for disease.

Acknowledgements The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/g4Mmp4.

Funding Please add: This research was funded by research fund of Chungnam National University (2020-ParkJ) and by the National Research Foundation of Korea (NRF) grant funded by the Korea Government (MEST) (NRF-2021R1A2C1008492, NRF-2020R1F1A1049801, NRF-2021R1C1C200845611).

Declarations

Conflict of interest The authors declare that they have no competing interests.

References

1. Ishii J, Adachi H, Aoki J, Koizumi H, Tomita S, Suzuki T, Tsujimoto M, Inoue K, Arai H (2002) SREC-II, a new member of the scavenger receptor type F family, trans-interacts with SREC-I through its extracellular domain. J Biol Chem 277:39696–39702. https://doi.org/10.1074/jbc.M206140200
2. Greaves DR, Gordon S (2005) Thematic review series: the immune system and atherogenesis. Recent insights into the biology of macrophage scavenger receptors. J Lipid Res 46:11–20. https://doi.org/10.1194/jlr.R400011-JLR200
3. Horiuchi S, Sakamoto Y, Sakai M (2003) Scavenger receptors for oxidized and glycated proteins. Amino Acids 25:283–292. https://doi.org/10.1007/s00726-003-0029-5
4. Brown MS, Goldstein JL (1979) Receptor-mediated endocytosis: insights from the lipoprotein receptor system. Proc Natl Acad Sci U S A 76:3330–3337. https://doi.org/10.1073/pnas.76.7.3330
5. Canton J, Neculai D, Grinstein S (2013) Scavenger receptors in homeostasis and immunity. Nat Rev Immunol 13:621–634. https://doi.org/10.1038/nri3515

6. Taban Q, Mumtaz PT, Masoodi KZ, Haq E, Ahmad SM (2022) Scavenger receptors in host defense: from functional aspects to mode of action. Cell Communication and Signaling 20:2. https://doi.org/10.1186/s12964-021-00812-0
7. Krieger M (1997) The other side of scavenger receptors: pattern recognition for host defense. Curr Opin Lipidol 8:275–280. https://doi.org/10.1097/00041433-199710000-00006
8. Kodama T, Reddy P, Kishimoto C, Krieger M (1988) Purification and characterization of a bovine acetyl low density lipoprotein receptor. Proc Natl Acad Sci U S A 85:9238–9242. https://doi.org/10.1073/pnas.85.23.9238
9. Kodama T, Freeman M, Rohrer L, Zabrecky J, Matsudaira P, Krieger M (1990) Type I macrophage scavenger receptor contains alpha-helical and collagen-like coiled coils. Nature 343:531–535. https://doi.org/10.1038/343531a0
10. Rohrer L, Freeman M, Kodama T, Penman M, Krieger M (1990) Coiled-coil fibrous domains mediate ligand binding by macrophage scavenger receptor type II. Nature 343:570–572. https://doi.org/10.1038/343570a0
11. Asch AS, Barnwell J, Silverstein RL, Nachman RL (1987) Isolation of the thrombospondin membrane receptor. J Clin Invest 79:1054–1061. https://doi.org/10.1172/JCI112918
12. Pearson A, Lux A, Krieger M (1995) Expression cloning of dSR-CI, a class C macrophage-specific scavenger receptor from Drosophila melanogaster. Proc Natl Acad Sci U S A 92:4056–4060. https://doi.org/10.1073/pnas.92.9.4056
13. Murphy JE, Tedbury PR, Homer-Vanniasinkam S, Walker JH, Ponnambalam S (2005) Biochemistry and cell biology of mammalian scavenger receptors. Atherosclerosis 182:1–15. https://doi.org/10.1016/j.atherosclerosis.2005.03.036
14. PrabhuDas MR, Baldwin CL, Bollyky PL, Bowdish DME, Drickamer K, Febbraio M, Herz J, Kobzik L, Krieger M, Loike J, McVicker B, Means TK, Moestrup SK, Post SR, Sawamura T, Silverstein S, Speth RC, Telfer JC, Thiele GM, Wang XY, Wright SD, El Khoury J (2017) A Consensus definitive classification of scavenger receptors and their roles in Health and Disease. J Immunol 198:3775–3789. https://doi.org/10.4049/jimmunol.1700373
15. Moore KJ, Freeman MW (2006) Scavenger receptors in atherosclerosis: beyond lipid uptake. Arterioscler Thromb Vasc Biol 26:1702–1711. https://doi.org/10.1161/01.ATV.0000229218.97976.43
16. Thielens NM, Tedesco F, Bohlson SS, Gaboriaud C, Tenner AJ (2017) C1q: a fresh look upon an old molecule. Mol Immunol 89:73–83. https://doi.org/10.1016/j.molimm.2017.05.025
17. Matloubian M, David A, Engel S, Ryan JE, Cyster JG (2000) A transmembrane CXC chemokine is a ligand for HIV-coreceptor Bonzo. Nat Immunol 1:298–304. https://doi.org/10.1038/79738
18. Korbecki J, Bajdak-Rusinek K, Kupnicka P, Kapczuk P, Simińska D, Chlubek D, Baranowska-Bosiacka I (2021) The role of CXCL16 in the pathogenesis of Cancer and Other Diseases. Int J Mol Sci 22:3490. https://doi.org/10.3390/ijms22073490
19. Etzerodt A, Moestrup SK (2013) CD163 and inflammation: biological, diagnostic, and therapeutic aspects. Antioxid Redox Signal 18:2352–2363. https://doi.org/10.1089/ars.2012.4834
20. Ibrahim ZA, Armour CL, Phipps S, Sukkar MB (2013) RAGE and TLRs: relatives, friends or neighbours? Mol Immunol 56:739–744. https://doi.org/10.1016/j.molimm.2013.07.008
21. Qin YH, Dai SM, Tang GS, Zhang J, Ren D, Wang ZW, Shen Q (2009) HMGB1 enhances the proinflammatory activity of lipopolysaccharide by promoting the phosphorylation of MAPK p38 through receptor for advanced glycation end products. J Immunol 183:6244–6250. https://doi.org/10.4049/jimmunol.0900390
22. Liang J, Jiang D, Griffith J, Yu S, Fan J, Zhao X, Bucala R, Noble PW (2007) CD44 is a negative regulator of acute pulmonary inflammation and lipopolysaccharide-TLR signaling in mouse macrophages. J Immunol 178:2469–2475. https://doi.org/10.4049/jimmunol.178.4.2469
23. Anastasio N, Ben-Omran T, Teebi A, Ha KC, Lalonde E, Ali R, Almureikhi M, Der Kaloustian VM, Liu J, Rosenblatt DS, Majewski J, Jerome-Majewska LA (2010) Mutations in SCARF2 are responsible for Van Den Ende-Gupta syndrome. Am J Hum Genet 87:553–559. https://doi.org/10.1016/j.ajhg.2010.09.005
24. Fagerberg L, Hallstrom BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, Habuka M, Tahmasebpoor S, Danielsson A, Edlund K, Asplund A, Sjostedt E, Lundberg E, Szigyarto CA, Skogs M, Takanen JO, Berling H, Tegel H, Mulder J, Nilsson P, Schwenk JM, Lindskog C, Danielsson F, Mardinoglu A, Sivertsson A, von Feilitzen K, Forsberg M, Zwahlen M, Olsson I, Navani S, Huss M, Nielsen J, Ponten F, Uhlen M (2014) Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol Cell Proteomics 13:397–406. https://doi.org/10.1074/mcp.M113.035600
25. Consortium TU (2020) UniProt: the universal protein knowledgebase in 2021. Nucleic Acids Res 49:D480–D489. https://doi.org/10.1093/nar/gkaa1100
26. Prabhudas M, Bowdish D, Drickamer K, Febbraio M, Herz J, Kobzik L, Krieger M, Loike J, Means TK, Moestrup SK, Post S, Sawamura T, Silverstein S, Wang XY, El Khoury J (2014) Standardizing scavenger receptor nomenclature. J Immunol 192:1997–2006. https://doi.org/10.4049/jimmunol.1490003
27. Wilkinson K, El Khoury J (2012) Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer's disease. Int J Alzheimers Dis 2012:489456. https://doi.org/10.1155/2012/489456
28. Wicker-Planquart C, Tacnet-Delorme P, Preisser L, Dufour S, Delneste Y, Housset D, Frachet P, Thielens NM (2021) Insights into the ligand binding specificity of SREC-II (scavenger receptor expressed by endothelial cells). FEBS Open Bio 11:2693–2704. https://doi.org/10.1002/2211-5463.13260
29. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, Zackai EH, Emanuel BS, Vermeesch JR, Morrow BE, Scambler PJ, Bassett AS (2015) 22q11.2 deletion syndrome. Nat Reviews Disease Primers 1:15071. https://doi.org/10.1038/nrdp.2015.71
30. Migliavacca MP, Sobreira NL, Antonialli GP, Oliveira MM, Melaragno MI, Casteels I, de Ravel T, Brunoni D, Valle D, Perez AB (2014) Sclerocornea in a patient with van den Ende-Gupta syndrome homozygous for a SCARF2 microdeletion. Am J Med Genet A 164A:1170–1174. https://doi.org/10.1002/ajmg.a.36425
31. Hildebrandt CC, Patel N, Graham JM Jr, Bamshad M, Nickerson DA, White JJ, Marvin CT, Miller DE, University of Washington Center for, Mendelian G, Grand KL, Sanchez-Lara PA, Schweitzer D, Al-Zaidan HI, Al Masseri Z, Alkuraya FS, Lin AE (2021) Further delineation of van den Ende-Gupta syndrome: genetic heterogeneity and overlap with congenital heart defects and skeletal malformations syndrome. Am J Med Genet A 185:2136–2149. https://doi.org/10.1002/ajmg.a.62194
32. Bedeschi MF, Colombo L, Mari F, Hofmann K, Rauch A, Gentilin B, Renieri A, Clerici D (2010) Unmasking of a recessive SCARF2 mutation by a 22q11.12 de novo deletion in a patient with Van den Ende-Gupta Syndrome. Mol Syndromol 1:239–245. https://doi.org/10.1159/000328135
33. Meehan TF, Conte N, West DB, Jacobsen JO, Mason J, Warren J, Chen CK, Tudose I, Relac M, Matthews P, Karp N, Santos L, Fiegel T, Ring N, Westerberg H, Greenaway S, Sneddon D, Morgan H, Codner GF, Stewart ME, Brown J, Horner N, International Mouse Phenotyping C, Haendel M, Washington N, Mungall CJ, Reynolds CL, Gallegos J, Gailus-Durner V, Sorg T, Pavlovic G, Bower LR, Moore M, Morse I, Gao X, Tocchini-Valentini GP, Obata Y, Cho SY, Seong JK, Seavitt J, Beaudet

AL, Dickinson ME, Herault Y, Wurst W, de Angelis MH, Lloyd KCK, Flenniken AM, Nutter LMJ, Newbigging S, McKerlie C, Justice MJ, Murray SA, Svenson KL, Braun RE, White JK, Bradley A, Flicek P, Wells S, Skarnes WC, Adams DJ, Parkinson H, Mallon AM, Brown SDM, Smedley D (2017) Disease model discovery from 3,328 gene knockouts by the International mouse phenotyping Consortium. Nat Genet 49:1231–1238. https://doi.org/10.1038/ng.3901

34. Birling MC, Yoshiki A, Adams DJ, Ayabe S, Beaudet AL, Bottomley J, Bradley A, Brown SDM, Bürger A, Bushell W, Chiani F, Chin HG, Christou S, Codner GF, DeMayo FJ, Dickinson ME, Doe B, Donahue LR, Fray MD, Gambadoro A, Gao X, Gertsenstein M, Gomez-Segura A, Goodwin LO, Heaney JD, Hérault Y, de Angelis MH, Jiang ST, Justice MJ, Kasparek P, King RE, Kühn R, Lee H, Lee YJ, Liu Z, Lloyd KCK, Lorenzo I, Mallon AM, McKerlie C, Meehan TF, Fuentes VM, Newman S, Nutter LMJ, Oh GT, Pavlovic G, Ramirez-Solis R, Rosen B, Ryder EJ, Santos LA, Schick J, Seavitt JR, Sedlacek R, Seisenberger C, Seong JK, Skarnes WC, Sorg T, Steel KP, Tamura M, Tocchini-Valentini GP, Wang CL, Wardle-Jones H, Wattenhofer-Donzé M, Wells S, Wiles MV, Willis BJ, Wood JA, Wurst W, Xu Y, Teboul L, Murray SA (2021) A resource of targeted mutant mouse lines for 5,061 genes. Nat Genet 53:416–419. https://doi.org/10.1038/s41588-021-00825-y
35. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, Mandelker D, Leary RJ, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, Markowitz SD, Willis J, Dawson D, Willson JK, Gazdar AF, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman KE, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE (2006) The consensus coding sequences of human breast and colorectal cancers. Science 314:268–274. https://doi.org/10.1126/science.1133427
36. Kim BY, Park MH, Woo HM, Jo HY, Kim JH, Choi HJ, Koo SK (2017) Genetic analysis of parathyroid and pancreatic tumors in a patient with multiple endocrine neoplasia type 1 using whole-exome sequencing. BMC Med Genet 18:106. https://doi.org/10.1186/s12881-017-0465-9
37. Kim C, Kong G, Lee H, Tran Q, Vo TT, Kwon SH, Park J, Kim SH, Park J (2022) Scavenger receptor class F member 2 (SCARF2) as a novel therapeutic target in glioblastoma. Toxicol Res 38:249–256. https://doi.org/10.1007/s43188-022-00125-5
38. Collins RL, Glessner JT, Porcu E, Niestroj L-M, Ulirsch J, Kellaris G, Howrigan DP, Everett S, Mohajeri K, Nuttle X, Lowther C, Fu J, Boone PM, Ullah F, Samocha KE, Karczewski K, Lucente D, Consortium E, Gusella JF, Finucane H, Matyakhina L, Aradhya S, Meck J, Lal D, Neale BM, Hodge JC, Reymond A, Kutalik Z, Katsanis N, Davis EE, Hakonarson H, Sunyaev S, Brand H and Talkowski ME (2021) A cross-disorder dosage sensitivity map of the human genome. medRxiv:2021.01.26.21250098. https://doi.org/10.1101/2021.01.26.21250098
39. Shprintzen RJ (2008) Velo-cardio-facial syndrome: 30 Years of study. Dev Disabil Res Rev 14:3–10. https://doi.org/10.1002/ddrr.2
40. Vysotskiy M, Zhong X, Miller-Fleming TW, Zhou D, Autism Working Group of the Psychiatric Genomics C, Bipolar Disorder Working Group of the Psychiatric Genomics C, Schizophrenia Working Group of the Psychiatric, Genomics C, Cox NJ, Weiss LA (2021) Integration of genetic, transcriptomic, and clinical data provides insight into 16p11.2 and 22q11.2 CNV genes. Genome Med 13:172. https://doi.org/10.1186/s13073-021-00972-1
41. Overwater E, Marsili L, Baars MJH, Baas AF, van de Beek I, Dulfer E, van Hagen JM, Hilhorst-Hofstee Y, Kempers M, Krapels IP, Menke LA, Verhagen JMA, Yeung KK, Zwijnenburg PJG, Groenink M, van Rijn P, Weiss MM, Voorhoeve E, van Tintelen JP, Houweling AC, Maugeri A (2018) Results of next-generation sequencing gene panel diagnostics including copy-number variation analysis in 810 patients suspected of heritable thoracic aortic disorders. Hum Mutat 39:1173–1192. https://doi.org/10.1002/humu.23565
42. Cuthbert GA, Shaik F, Harrison MA, Ponnambalam S, Homer-Vanniasinkam S (2020) Scavenger receptors as biomarkers and therapeutic targets in cardiovascular disease. Cells 9:2453. https://doi.org/10.3390/cells9112453
43. Sahebi R, Hassanian SM, Ghayour-Mobarhan M, Farrokhi E, Rezayi M, Samadi S, Bahramian S, Ferns GA, Avan A (2019) Scavenger receptor class B type I as a potential risk stratification biomarker and therapeutic target in cardiovascular disease. J Cell Physiol 234:16925–16932. https://doi.org/10.1002/jcp.28393
44. El Khoury J, Hickman SE, Thomas CA, Loike JD, Silverstein SC (1998) Microglia, scavenger receptors, and the pathogenesis of Alzheimer's Disease. Neurobiol Aging 19:S81–S84. https://doi.org/10.1016/S0197-4580(98)00036-0
45. Hu F, Jiang X, Guo C, Li Y, Chen S, Zhang W, Du Y, Wang P, Zheng X, Fang X, Li X, Song J, Xie Y, Huang F, Xue J, Bai M, Jia Y, Liu X, Ren L, Zhang X, Guo J, Pan H, Su Y, Yi H, Ye H, Zuo D, Li J, Wu H, Wang Y, Li R, Liu L, Wang X-Y, Li Z (2020) Scavenger receptor-A is a biomarker and effector of rheumatoid arthritis: a large-scale multicenter study. Nat Commun 11:1911. https://doi.org/10.1038/s41467-020-15700-3
46. Nakayama M, Kudoh T, Kaikita K, Yoshimura M, Oshima S, Miyamoto Y, Takeya M, Ogawa H (2008) Class A macrophage scavenger receptor gene expression levels in peripheral blood mononuclear cells specifically increase in patients with acute coronary syndrome. Atherosclerosis 198:426–433. https://doi.org/10.1016/j.atherosclerosis.2007.09.006
47. Ichimura T, Morikawa T, Kawai T, Nakagawa T, Matsushita H, Kakimi K, Kume H, Ishikawa S, Homma Y, Fukayama M (2014) Prognostic significance of CD204-positive macrophages in upper urinary tract cancer. Ann Surg Oncol 21:2105–2112. https://doi.org/10.1245/s10434-014-3503-2
48. Sun Y, Xu S (2018) Tumor-associated CD204-Positive macrophage is a prognostic marker in clinical stage I lung adenocarcinoma. Biomed Res Int 2018:8459193. https://doi.org/10.1155/2018/8459193
49. Gracia-Rubio I, Martín C, Civeira F, Cenarro A (2021) SR-B1, a key receptor involved in the progression of cardiovascular disease: a perspective from mice and human genetic studies. Biomedicines. https://doi.org/10.3390/biomedicines9060612
50. Feng H, Wang M, Wu C, Yu J, Wang D, Ma J, Han J (2018) High scavenger receptor class B type I expression is related to tumor aggressiveness and poor prognosis in lung adenocarcinoma: a STROBE compliant article. Medicine (Baltimore) 97:e0203. https://doi.org/10.1097/md.0000000000010203
51. Shahzad MM, Mangala LS, Han HD, Lu C, Bottsford-Miller J, Nishimura M, Mora EM, Lee JW, Stone RL, Pecot CV, Thanapprapasr D, Roh JW, Gaur P, Nair MP, Park YY, Sabnis N, Deavers MT, Lee JS, Ellis LM, Lopez-Berestein G, McConathy WJ, Prokai L, Lacko AG, Sood AK (2011) Targeted delivery of small interfering RNA using reconstituted high-density lipoprotein nanoparticles. Neoplasia 13:309–319. https://doi.org/10.1593/neo.101372
52. Traughber CA, Opoku E, Brubaker G, Major J, Lu H, Lorkowski SW, Neumann C, Hardaway A, Chung Y-M, Gulshan K, Sharifi N, Brown JM, Smith JD (2020) Uptake of high-density lipoprotein by scavenger receptor class B type 1 is associated with prostate cancer proliferation and tumor progression in mice. J Biol Chem 295:8252–8261. https://doi.org/10.1074/jbc.ra120.013694

53. Hale JS, Otvos B, Sinyuk M, Alvarado AG, Hitomi M, Stoltz K, Wu Q, Flavahan W, Levison B, Johansen ML, Schmitt D, Neltner JM, Huang P, Ren B, Sloan AE, Silverstein RL, Gladson CL, DiDonato JA, Brown JM, McIntyre T, Hazen SL, Horbinski C, Rich JN, Lathia JD (2014) Cancer stem cell-specific scavenger receptor CD36 drives glioblastoma progression. Stem Cells 32:1746–1758. https://doi.org/10.1002/stem.1716
54. Haidari S, Tröltzsch M, Knösel T, Liokatis P, Kasintsova A, Eberl M, Ortner F, Otto S, Fegg F, Boskov M, Probst FA (2021) Fatty acid receptor CD36 functions as a surrogate parameter for Lymph Node Metastasis in oral squamous cell carcinoma. Cancers (Basel) 13:4125. https://doi.org/10.3390/cancers13164125
55. Lai WA, Yeh YT, Lee MT, Wu LS, Ke FC, Hwang JJ (2013) Ovarian granulosa cells utilize scavenger receptor SR-BI to evade cellular cholesterol homeostatic control for steroid synthesis. J Lipid Res 54:365–378. https://doi.org/10.1194/jlr.M030239
56. Rivera K, Quiñones V, Amigo L, Santander N, Salas-Pérez F, Xavier A, Fernández-Galilea M, Carrasco G, Cabrera D, Arrese M, Busso D, Andia ME, Rigotti A (2021) Lipoprotein receptor SR-B1 deficiency enhances adipose tissue inflammation and reduces susceptibility to hepatic steatosis during diet-induced obesity in mice. Biochim Biophys Acta Mol Cell Biol Lipids 1866:158909. https://doi.org/10.1016/j.bbalip.2021.158909
57. Minett T, Classey J, Matthews FE, Fahrenhold M, Taga M, Brayne C, Ince PG, Nicoll JA, Boche D (2016) Microglial immunophenotype in dementia with Alzheimer's pathology. J Neuroinflammation 13:135. https://doi.org/10.1186/s12974-016-0601-z
58. Zhang J, Li S, Liu F, Yang K (2022) Role of CD68 in tumor immunity and prognosis prediction in pan-cancer. Sci Rep 12:7844. https://doi.org/10.1038/s41598-022-11503-2
59. Shaw DJ, Seese R, Ponnambalam S, Ajjan R (2014) The role of lectin-like oxidised low-density lipoprotein receptor-1 in vascular pathology. Diab Vasc Dis Res 11:410–418. https://doi.org/10.1177/1479164114547704
60. Arjuman A, Chandra NC (2013) Effect of IL-10 on LOX-1 expression, signalling and functional activity: an atheroprotective response. Diab Vasc Dis Res 10:442–451. https://doi.org/10.1177/1479164113489042
61. Sun X, Fu X, Xu S, Qiu P, Lv Z, Cui M, Zhang Q, Xu Y (2021) OLR1 is a prognostic factor and correlated with immune infiltration in breast cancer. Int Immunopharmacol 101:108275. https://doi.org/10.1016/j.intimp.2021.108275
62. Ozturk O, Colak Y, Senates E, Yilmaz Y, Ulasoglu C, Doganay L, Ozkanli S, Oltulu YM, Coskunpinar E, Tuncer I (2015) Increased serum soluble lectin-like oxidized low-density lipoprotein receptor-1 levels in patients with biopsy-proven nonalcoholic fatty liver disease. World J Gastroenterol 21:8096–8102. https://doi.org/10.3748/wjg.v21.i26.8096
63. Liu B, Wang Z, Gu M, Zhao C, Ma T, Wang J (2021) GEO data mining identifies OLR1 as a potential biomarker in NSCLC immunotherapy. Front Oncol 11:629333. https://doi.org/10.3389/fonc.2021.629333
64. Zani IA, Stephen SL, Mughal NA, Russell D, Homer-Vanniasinkam S, Wheatcroft SB, Ponnambalam S (2015) Scavenger receptor structure and function in health and disease. Cells 4:178–201. https://doi.org/10.3390/cells4020178
65. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgözoğlu L, Lewis EF (2019) Atherosclerosis. Nat Rev Dis Primers 5:56. https://doi.org/10.1038/s41572-019-0106-z
66. Gudgeon J, Marín-Rubio JL, Trost M (2022) The role of macrophage scavenger receptor 1 (MSR1) in inflammatory disorders and cancer. Front Immunol 13:1012002. https://doi.org/10.3389/fimmu.2022.1012002
67. Ramirez-Ortiz ZG, Pendergraft WF, Prasad A, Byrne MH, Iram T, Blanchette CJ, Luster AD, Hacohen N, Khoury JE, Means TK (2013) The scavenger receptor SCARF1 mediates the clearance of apoptotic cells and prevents autoimmunity. Nat Immunol 14:917–926. https://doi.org/10.1038/ni.2670
68. Sjöstedt E, Zhong W, Fagerberg L, Karlsson M, Mitsios N, Adori C, Oksvold P, Edfors F, Limiszewska A, Hikmet F, Huang J, Du Y, Lin L, Dong Z, Yang L, Liu X, Jiang H, Xu X, Wang J, Yang H, Bolund L, Mardinoglu A, Zhang C, von Feilitzen K, Lindskog C, Pontén F, Luo Y, Hökfelt T, Uhlén M, Mulder J (2020) An atlas of the protein-coding genes in the human, pig, and mouse brain. Science 367:eaay5947. https://doi.org/10.1126/science.aay5947
69. Patten DA, Wilkinson AL, O'Rourke JM, Shetty S (2020) Prognostic value and potential immunoregulatory role of SCARF1 in hepatocellular carcinoma. Front Oncol 10:565950. https://doi.org/10.3389/fonc.2020.565950
70. Li G, Wang Z, Zhang C, Liu X, Yang F, Sun L, Liang J, Hu H, Liu Y, You G, Bao Z, Zhang W, Wang Z, Jiang T (2018) MEGF10, a glioma survival-associated molecular signature, predicts IDH mutation status. Dis Markers 2018:5975216. https://doi.org/10.1155/2018/5975216
71. Kurian KM, Haynes HR, Crosby C, Hopkins K, Williams M (2013) IDH mutation analysis in gliomas as a diagnostic and prognostic biomarker. Br J Neurosurg 27:442–445. https://doi.org/10.3109/02688697.2013.771139
72. Xing J, Liu Y, Chen T (2018) Correlations of chemokine CXCL16 and TNF-α with coronary atherosclerotic heart disease. Exp Ther Med 15:773–776. https://doi.org/10.3892/etm.2017.5450
73. Lin Z, Gong Q, Zhou Z, Zhang W, Liao S, Liu Y, Yan X, Pan X, Lin S, Li X (2011) Increased plasma CXCL16 levels in patients with chronic kidney diseases. Eur J Clin Invest 41:836–845. https://doi.org/10.1111/j.1365-2362.2011.02473.x
74. Zhao L, Wu F, Jin L, Lu T, Yang L, Pan X, Shao C, Li X, Lin Z (2014) Serum CXCL16 as a novel marker of renal injury in type 2 diabetes mellitus. PLoS One 9:e87786. https://doi.org/10.1371/journal.pone.0087786
75. Abdel-Messeih PL, Alkady MM, Nosseir NM, Tawfik MS (2020) Inflammatory markers in end-stage renal disease patients on haemodialysis. J Med Biochem 39:481–487. https://doi.org/10.5937/jomb0-25120
76. Ayyappan P, Harms RZ, Seifert JA, Bemis EA, Feser ML, Deane KD, Demoruelle MK, Mikuls TR, Holers VM, Sarvetnick NE (2020) Heightened levels of antimicrobial response factors in patients with rheumatoid arthritis. Front Immunol 11:427. https://doi.org/10.3389/fimmu.2020.00427
77. Manta CP, Leibing T, Friedrich M, Nolte H, Adrian M, Schledzewski K, Krzistetzko J, Kirkamm C, David Schmid C, Xi Y, Stojanovic A, Tonack S, de la Torre C, Hammad S, Offermanns S, Krüger M, Cerwenka A, Platten M, Goerdt S, Géraud C (2022) Targeting of scavenger receptors Stabilin-1 and Stabilin-2 ameliorates atherosclerosis by a plasma proteome switch mediating Monocyte/Macrophage suppression. Circulation 146:1783–1799. https://doi.org/10.1161/circulationaha.121.058615
78. Yong J, Huang L, Chen G, Luo X, Chen H, Wang L (2021) High expression of Stabilin-2 predicts poor prognosis in non-small-cell lung cancer. Bioengineered 12:3426–3433. https://doi.org/10.1080/21655979.2021.1943109
79. Géraud C, Mogler C, Runge A, Evdokimov K, Lu S, Schledzewski K, Arnold B, Hämmerling G, Koch PS, Breuhahn K, Longerich T, Marx A, Weiss C, Damm F, Schmieder A, Schirmacher P, Augustin HG, Goerdt S (2013) Endothelial transdifferentiation in hepatocellular carcinoma: loss of Stabilin-2

expression in peri-tumourous liver correlates with increased survival. Liver Int 33:1428–1440. https://doi.org/10.1111/liv.12262
80. Cheng Z, Zhang D, Gong B, Wang P, Liu F (2017) CD163 as a novel target gene of STAT3 is a potential therapeutic target for gastric cancer. Oncotarget 8:87244–87262. https://doi.org/10.18632/oncotarget.20244
81. Zhang Y, Huang C, Nie Y, Liu Q, Xiao N, Liu L, Zhu X (2021) Soluble CD163 is a predictor of mortality in patients with decompensated cirrhosis. Front Med (Lausanne) 8:698502. https://doi.org/10.3389/fmed.2021.698502
82. Wang J, Guo W, Du H, Yu H, Jiang W, Zhu T, Bai X, Wang P (2014) Elevated soluble CD163 plasma levels are associated with disease severity in patients with hemorrhagic fever with renal syndrome. PLoS One 9:e112127. https://doi.org/10.1371/journal.pone.0112127
83. Jude C, Dejica D, Samasca G, Balacescu L, Balacescu O (2013) Soluble CD163 serum levels are elevated and correlated with IL-12 and CXCL10 in patients with long-standing rheumatoid arthritis. Rheumatol Int 33:1031–1037. https://doi.org/10.1007/s00296-012-2459-4
84. Emanuele E, D'Angelo A, Tomaino C, Binetti G, Ghidoni R, Politi P, Bernardi L, Maletta R, Bruni AC, Geroldi D (2005) Circulating levels of soluble receptor for advanced glycation end products in Alzheimer disease and vascular dementia. Arch Neurol 62:1734–1736. https://doi.org/10.1001/archneur.62.11.1734
85. Falcone C, Emanuele E, D'Angelo A, Buzzi MP, Belvito C, Cuccia M, Geroldi D (2005) Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. Arterioscler Thromb Vasc Biol 25:1032–1037. https://doi.org/10.1161/01.Atv.0000160342.20342.00
86. Sternberg Z, Weinstock-Guttman B, Hojnacki D, Zamboni P, Zivadinov R, Chadha K, Lieberman A, Kazim L, Drake A, Rocco P, Grazioli E, Munschauer F (2008) Soluble receptor for advanced glycation end products in multiple sclerosis: a potential marker of disease severity. Mult Scler 14:759–763. https://doi.org/10.1177/1352458507088105
87. Sternberg Z, Sternberg D, Drake A, Chichelli T, Yu J, Hojnacki D (2014) Disease modifying drugs modulate endogenous secretory receptor for advanced glycation end-products, a new biomarker of clinical relapse in multiple sclerosis. J Neuroimmunol 274:197–201. https://doi.org/10.1016/j.jneuroim.2014.07.005
88. Chen C, Zhao S, Karnad A, Freeman JW (2018) The biology and role of CD44 in cancer progression: therapeutic implications. J Hematol Oncol 11:64. https://doi.org/10.1186/s13045-018-0605-5
89. Xu H, Niu M, Yuan X, Wu K, Liu A (2020) CD44 as a tumor biomarker and therapeutic target. Experimental Hematol Oncol 9:36. https://doi.org/10.1186/s40164-020-00192-0
90. Thapa R, Wilson GD (2016) The importance of CD44 as a stem cell biomarker and therapeutic target in cancer. Stem Cells Int 2016:2087204. https://doi.org/10.1155/2016/2087204
91. Naor D, Nedvetzki S (2003) CD44 in rheumatoid arthritis. Arthritis Res Ther 5:105–115. https://doi.org/10.1186/ar746
92. Katoh S, Uesaka T, Tanaka H, Matsuhara H, Ohashi-Doi K, Oga T (2022) CD44 is critical for the enhancing effect of hyaluronan in allergen-specific sublingual immunotherapy in a murine model of chronic asthma. Clin Exp Immunol 208:202–211. https://doi.org/10.1093/cei/uxac024
93. Camp RL, Scheynius A, Johansson C, Puré E (1993) CD44 is necessary for optimal contact allergic responses but is not required for normal leukocyte extravasation. J Exp Med 178:497–507. https://doi.org/10.1084/jem.178.2.497
94. Cuff CA, Kothapalli D, Azonobi I, Chun S, Zhang Y, Belkin R, Yeh C, Secreto A, Assoian RK, Rader DJ, Puré E (2001) The adhesion receptor CD44 promotes atherosclerosis by mediating inflammatory cell recruitment and vascular cell activation. J Clin Invest 108:1031–1040. https://doi.org/10.1172/jci12455
95. Li J, Tan Y, Sheng Z, Zhou P, Liu C, Zhao H, Song L, Zhou J, Chen R, Chen Y, Yan H (2021) The association between plasma hyaluronan level and plaque types in ST-segment-elevation myocardial infarction patients. Front Cardiovasc Med 8:628529. https://doi.org/10.3389/fcvm.2021.628529
96. Osawa Y, Kawai H, Tsunoda T, Komatsu H, Okawara M, Tsutsui Y, Yoshida Y, Yoshikawa S, Mori T, Yamazoe T, Yoshio S, Oide T, Inui A, Kanto T (2021) Cluster of differentiation 44 promotes liver fibrosis and serves as a biomarker in congestive hepatopathy. Hepatol Commun 5:1437–1447. https://doi.org/10.1002/hep4.1721
97. Akbar S, Qadri S, Ashraf S, Parray A, Raza A, Abualainin W, Dermime S, Haik Y (2022) Expression of CD91 in extracellular vesicles: a potential biomarker for the diagnosis of non-small cell lung cancer. Adv Cancer Biol Metastasis 4:100046. https://doi.org/10.1016/j.adcanc.2022.100046
98. Nishiwaki H, Niihata K, Kinoshita M, Fujimura M, Kurosawa K, Sakuramachi Y, Takano K, Matsunaga S, Okamura S, Kitatani M, Tsujii S, Hayashino Y, Kurita N (2022) Urinary C-megalin as a novel biomarker of progression to microalbuminuria: a cohort study based on the diabetes distress and Care Registry at Tenri (DDCRT 22). Diabetes Res Clin Pract 186:109810. https://doi.org/10.1016/j.diabres.2022.109810
99. Li C, Ding Y, Zhang X, Hua K (2022) Integrated in silico analysis of LRP2 mutations to immunotherapy efficacy in pan-cancer cohort. Discover Oncol 13:65. https://doi.org/10.1007/s12672-022-00528-8
100. Spuch C, Antequera D, Pascual C, Abilleira S, Blanco M, Moreno-Carretero MJ, Romero-López J, Ishida T, Molina JA, Villarejo A, Bermejo-Pareja F, Carro E (2015) Soluble megalin is reduced in cerebrospinal fluid samples of Alzheimer's disease patients. Front Cell Neurosci 9:134. https://doi.org/10.3389/fncel.2015.00134
101. Gordon S, Neyen C (2016) Scavenger receptors. In: Bradshaw RA, Stahl PD (eds) Encyclopedia of cell biology. Academic-Press, Waltham, pp 727–740. https://doi.org/10.1016/B978-0-12-394447-4.30110-9
102. Patel N, Salih MA, Alshammari MJ, Abdulwahhab F, Adly N, Alzahrani F, Elgamal EA, Elkhashab HY, Al-Qattan M, Alkuraya FS (2014) Expanding the clinical spectrum and allelic heterogeneity in van den Ende-Gupta syndrome. Clin Genet 85:492–494. https://doi.org/10.1111/cge.12205
103. Karaer D, Karaer K (2022) Two novel variants in SCARF2 gene underlie van den Ende-Gupta syndrome. Am J Med Genet A 188:1881–1884. https://doi.org/10.1002/ajmg.a.62707
104. Al-Qattan MM, Andejani DF, Sakati NA, Ramzan K, Imtiaz F (2018) Inclusion of joint laxity, recurrent patellar dislocation, and short distal ulnae as a feature of Van Den Ende-Gupta syndrome: a case report. BMC Med Genet 19:18. https://doi.org/10.1186/s12881-018-0531-y
105. Niederhoffer KY, Fahiminiya S, Eydoux P, Mawson J, Nishimura G, Jerome-Majewska LA, Patel MS (2016) Diagnosis of Van den Ende-Gupta syndrome: Approach to the Marden-Walker-like spectrum of disorders. Am J Med Genet A 170:2310–2321. https://doi.org/10.1002/ajmg.a.37831