Serican Journal of Medicine
2024, VOL. 1, NO. 1, 23104
https://doi.org/10.17161/sjm.v1i1.23104

Sideroflexin family genes in human diseases: an update

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ABSTRACT

The Sideroflexin (SFXN) family consists of five mitochondrial membrane proteins, SFXN1 through SFXN5. These proteins were initially considered mitochondrial solute carriers, however, SFXN proteins are now recognized as crucial for various cellular functions, including iron uptake, redox balance, amino acid transporters, and metabolic regulation. These SFXN proteins have a highly conserved structure and are integral membrane proteins with multiple transmembrane helices, facilitating their role in transporting small molecules across the mitochondrial inner membrane. Although the precise structure varies slightly between family members, most SFXNs share a characteristic feature of four to six transmembrane domains. They are located primarily within the mitochondrial inner membrane. The genes encoding these proteins are widely conserved across eukaryotes, indicating their fundamental biological roles. SFXN1 is an iron importer, particularly for heme synthesis within the mitochondria. It facilitates the transport of serine and other amino acids that are precursors in metabolic pathways. Defects in SFXN1 function are associated with anemia and mitochondrial dysfunctions because of disrupted heme synthesis. SFXN2 is implicated in the modulation of iron homeostasis and likely contributes to redox balance, although its exact transport function is less defined. Dysregulation in SFXN2 gene expression was linked to iron overload disorders and oxidative stress-related diseases, potentially impacting neurodegenerative conditions. SFXN3 is similar in function to SFXN1 but may have a more prominent role in amino acid metabolism within neurons. Alterations in SFXN3 function are associated with neurological disorders, potentially affecting conditions such as Parkinson's disease. SFXN4 supports one-carbon metabolism by facilitating serine transport, which is essential for nucleotide synthesis and cellular growth. Mutations in SFXN4 have been implicated in mitochondrial disease. SFXN5 gene is the least characterized of the SFXN family, it likely plays a role in iron homeostasis and amino acid transport based on homology to other family members. SFXN1-SFXN4 genes were associated with the disease progression of multiple human cancers and exerted a strong potential for predicting patient outcomes as either a favorite or unfavorite prognostic factor.

ARTICLE HISTORY
Received: Nov. 19, 2024
Revised: Dec. 7, 2024
Accepted: Dec. 8, 2024

KEYWORDS
Sideroflexin, human cancer, iron metabolism, mitochondria

EDITED BY
Jindan Yu

REVIEWED BY
Jianhua Xiong
Ka-wing Fong

Introduction

The sideroflexin (SFXN) gene family encodes a group of mitochondrial membrane proteins. These proteins play significant roles in various mitochondrial processes, particularly related to iron and amino acid metabolism, which are crucial for maintaining cellular health and energy production. The **SFXN** proteins have five transmembrane helices, which span the inner mitochondrial membrane, anchoring the protein and facilitating its role as a transporter [1]. This structure is typical of solute carrier (SLC) proteins that often operate through conformational changes in response to molecule binding. The SFXN family is a growing area of research, particularly in understanding its role in metabolism and mitochondrial disorders, as well as potential therapeutic interventions for related diseases [1].

1. Discovery of SFXN family genes

SFXN1 was first cloned as a mutant gene responsible for sideroblastic anemias in the flexed-tail (f) mouse [2]. The human homologous SFXN1/SFXN4

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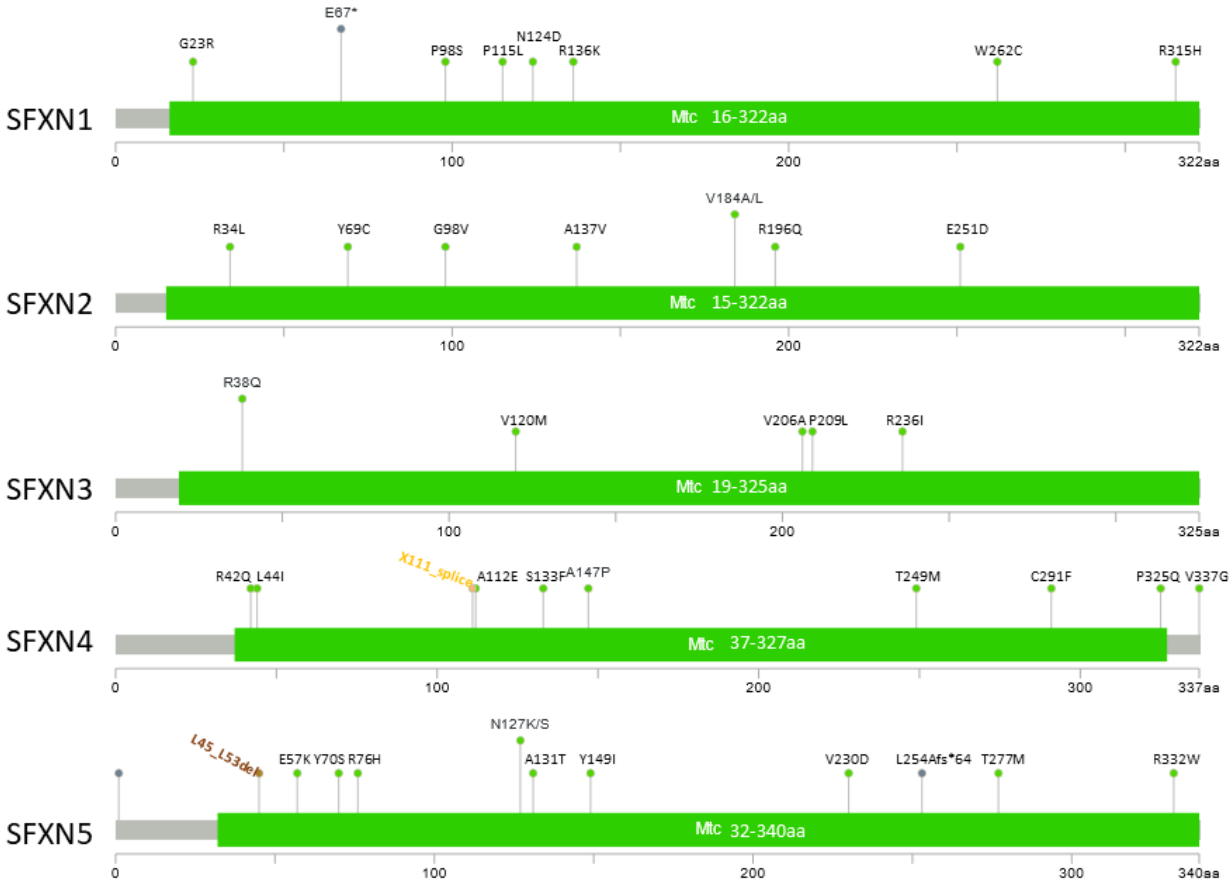

Fig 1. Schematic drawing for the structural domain and mutational alterations. Mitc: mitochondrial tricarboxylate carrier domain.

genes were cloned two years later [3, 4]. SFXN3 gene was then cloned from rat pancreatic AR42J cells with a citrate transporter protein-like property [5]. Examination of mammalian EST and genomic database identified other isoforms of this family genes SFXN1-5 [2]. SFXN2-5 (Sideroflexins 2-5) genes have a similar structure to SFXN1, they each have distinct yet somewhat overlapping roles within mitochondria [1]. SFXN2 is also involved in amino acid transport and contributes to oxidative phosphorylation. SFXN3 has roles in transporting serine into mitochondria, which is key in folate-mediated one-carbon metabolism. SFXN4 has links to iron metabolism and deficiencies in SFXN4 are linked to a condition similar to sideroblastic anemia, which involves defective iron incorporation into hemoglobin. SFXN5 is the least studied of the family but shares structural and functional similarities with other SFXN genes [6]. Their structural similarity was shown in a schematic drawing (Figure 1), which illustrates the mitochondrial tricarboxylate carrier domain and point mutations identified in human cancers.

2. Biological importance of SFXN genes in mitochondrial iron homeostasis

Iron is essential for mitochondrial enzymes, but an imbalance can lead to oxidative stress and cell damage. While not all SFXN proteins are directly involved in iron transport, SFXN1 and SFXN4 are thought to interact with iron or iron-containing molecules due to specific amino acid residues within the transmembrane regions [2]. SFXN1's role in iron transport has been linked to sideroblastic anemia, a disorder in which iron accumulates in the mitochondria of developing red blood cells (erythroblasts), forming ringed sideroblasts [2]. This results from defects in mitochondrial iron homeostasis and leads to ineffective red blood cell production [2].

While mutations in SFXN1 itself have not been directly linked to sideroblastic anemia in humans, its functions overlap with pathways affected in this disease, and research suggests that any dysfunction in iron transport proteins like SFXN1 could contribute to related anemias. The exact mechanism of iron

transport by SFXN proteins is still under investigation, but the structure may involve specific binding sites for iron within the transmembrane domains [7]. This transport is vital because mitochondria need iron to produce heme, an essential component of hemoglobin, and to form iron-sulfur clusters required for enzymes in the mitochondrial respiratory chain [7]. Mutations or disruptions in SFXN1 can lead to iron accumulation in mitochondria or impair heme and iron-sulfur cluster synthesis, causing oxidative stress and cellular dysfunction [8].

SFXN2 has been identified as a key regulator of mitochondrial iron levels [9, 10]. Research indicates that SFXN2-deficient cells accumulate mitochondrial iron, which disrupts heme synthesis and affects cellular energy [9]. SFXN2's localization to mitochondria is crucial for its role in maintaining iron balance, thereby supporting cellular metabolism and redox homeostasis [9].

SFXN3 was recently identified as one of the mitochondrial receptors for poly(rC) binding protein 2 (PCBP2), a major cytosolic Fe(II) chaperone in human chronic myelogenous leukemia KU812 cells [11]. Silencing the SFXN3 gene expression in leukemia K562 cells reduced mitochondrial catalytic Fe(II) levels and mitochondrial maximal respiration capacity [11]. SFXN3 knockout (KO) in mouse embryonic fibroblasts decreased F-box and leucine-rich repeat protein 5 (FBXL5) and heme oxygenase-1 (HO-1) but increased transferrin uptake and induced ferritin, indicating that SFXN3 is involved in mitochondrial iron entry because FBXL5 is a subunit of the SCF^{FBXL5} ubiquitin ligase complex that targets the proteasomal degradation of iron regulatory protein IRP2, which is an important regulator in iron metabolism [12].

3. SFXN proteins in one-carbon metabolism and mitochondrial energy production

The "one-carbon metabolism" refers to biochemical reactions that transfer single carbon units (methyl groups) from donor molecules to various biosynthetic pathways [13, 14]. This process primarily utilizes the folate cycle and methionine cycle to support processes like nucleotide synthesis, amino acid metabolism, and DNA methylation [15, 16]. It was considered crucial for epigenetic regulation, essentially, it's a metabolic pathway that moves single carbon units around the cell to be used for various building blocks [14, 17]. Recent studies suggest that the SFXN1 protein is a mitochondrial serine transporter required for one-carbon metabolism and mitochondrial DNA maintenance [18, 19]. In human Jurkat and K562 cancer cells, a CRISPR-based genetic screen identified that cells null for SFXN1 are defective in glycine and purine synthesis, and purified SFXN1 transports serine in vitro [18].

In addition, SFXN1 was also found to be a TIM22 complex substrate and its deficiency led to mitochondrial respiratory chain impairments, most detrimental to complex III (CIII) biogenesis, activity, and assembly, compromising coenzyme Q levels [20]. Since the CIII dysfunction is independent of one-carbon metabolism and the known primary role for SFXN1 as a mitochondrial serine transporter, it is postulated that SFXN1-based amino acid transport impacts mitochondrial and cellular metabolic efficiency [20].

4. SFXN gene expression in other human diseases

SFXN1 interactome of 96 proteins was reported in a recent study utilizing co-immunoprecipitation followed by a shotgun mass spectrometry approach in breast cancer MCF7 cells [21]. These interacting proteins are involved in biological processes linked to mitochondrial organization, electron transport chains, and transmembrane transport. Among these proteins, ATAD3 and 17β-HSD10 were involved in neurological processes [21]. This interaction network highlights SFXN1's role in mitochondrial health, which is crucial for cellular energy and disease resistance. Disruptions in SFXN1 and its interactions are linked to neurodegenerative disorders, indicating a broader relevance [21].

SFXN1 participates in iron overload in mitochondria and plays a crucial role in ferroptosis-related pathways through its involvement in mitochondrial metabolism and iron homeostasis, both of which are central to the ferroptotic process [22]. Ferroptosis is a form of regulated cell death characterized by the accumulation of lipid peroxides and is tightly linked to iron metabolism [23]. As a mitochondrial inner membrane transporter, SFXN1 is responsible for importing serine into the mitochondria [18], which contributes to the synthesis of one-carbon units and other metabolites, producing glutathione (GSH), a key antioxidant that counteracts lipid peroxidation . It is postulated that a deficiency in SFXN1 may disrupt this pathway, lowering GSH levels and increasing vulnerability to ferroptosis.

Patulin (PAT) is a fungi-derived mycotoxin that is commonly present throughout the ecosystem and was recently found to induce myocardial inflammation and fibrosis through ferroptosis [24]. After PAT

treatment, the master regulator of ferritinophagy nuclear receptor coactivator (NCOA) 4 induced ferritin degradation and ferrous iron accumulation, leading to SFXN1-dependent mitochondrial iron overload and lipid peroxides accumulation [24]. These studies suggest that SFXN1-dependent mitochondrial iron overload is involved in PAT-induced myocardial ferroptosis and consequent cardiotoxicity. Similarly, SFXN1-transported cytoplasmic $Fe2^{+}$ into mitochondria is also responsible for inducing mitochondrial ROS and ferroptosis in sepsis-induced cardiac injury [22].

SFXN1 was found to modulate mitochondrial ROS production [25]. Apelin-13 is a 13 amino acid oligopeptide and the ligand for the apelin receptor (also known as the APJ receptor) [26]. It exhibits hypotensive and neuroprotective effects and may be a potential prognostic biomarker for acute ischemic stroke and multiple sclerosis [26]. It has a role as an antihypertensive agent, a biomarker, an autophagy inhibitor, and a neuroprotective agent [26]. A recent study showed that Apelin-13 promoted ferric citrate (FAC)-induced total cellular and mitochondria ion production, as well as mitochondria ROS contents through apelin-13-induced expression of SFXN1 and NCOA4 in the dose and time-dependent manner, resulting in ferroptosis [25].

SFXN1 was also implicated in mitochondrial iron homeostasis [1]. Mitochondria are central to iron-sulfur cluster (ISC) assembly, which supports various cellular processes, including enzymatic activities and redox balance [27]. Disruptions in ISC biosynthesis can lead to iron overload and oxidative stress, both hallmarks of ferroptosis. SFXN1 indirectly influenced lipid peroxidation [24]. Excess mitochondrial iron due to SFXN1 dysfunction activated the Fenton reaction, producing reactive oxygen species that drive lipid peroxidation and ferroptosis [24].

SFXN2 is also reported to modulate mitochondrial iron metabolism. In SFXN2-knockout (KO) cells mitochondrial iron content was elevated but the heme content and heme-dependent enzyme activities were decreased [9]. However, iron-sulfur cluster-dependent enzymes remained unchanged in SFXN2-KO cells. These alterations led to impaired mitochondrial respiration and accelerated iron-mediated death of these cells, indicating SFXN2 as a modulator of mitochondrial iron metabolism by regulating heme biosynthesis [9]. In addition, SFXN2 gene variants were identified as one of the risk factors for hypertension and stroke incidence [28-30].

SFXN3 was found abundantly in the brain, neuronally enriched in synaptic terminals, and regulated by key synaptic proteins, including α-synuclein [31, 32]. SFXN3 protein uses the carrier import pathway to insert into the inner mitochondrial membrane and Sfxn3-KO mice exhibited neurodegenerative events and cell death, resembling neurological conditions like Parkinson's disease and Alzheimer's disease [33]. In addition, Sfxn3 is also involved in retinal function. Single-cell RNA sequencing of retinal cells isolated from C57BL/6J mice showed that Sfxn3 is expressed in bipolar cell subtypes, retinal ganglion cells, and some amacrine cell subtypes but not significantly in Müller cells or photoreceptors [34]. Consistently, CRISPR/Cas9 technology-based Sfxn3-KO mouse lines developed progressive and severe outer retinal degeneration [34]. GSEA pathway analysis indicated Sfxn3's association with synaptic homeostasis [34].

SFXN4 is a co-factor for the assembly of complex I, and its mutation has been shown to cause mitochondrial disease [35]. Because SFXN4 belongs to a family of amino acid transporter proteins, these data indicate a dramatic shift in function through evolution. In addition, genome-wide association meta-analysis of stroke in > 22,000 individuals of African ancestry revealed that suggestive association with variants in the SFXN4 gene represents potential novel ischemic stroke loci [36].

SFXN5 was recently shown to be involved in neutrophil recruitment [37], while cell spreading is a critical step in neutrophil migration, leading to neutrophil recruitment to inflammatory tissues [38]. Mechanistically, Sfxn5 deficiency impaired neutrophil spreading-associated cellular phenotypes, such as cell adhesion, chemotaxis, and ROS production [37]. Moreover, SFXN5 was also found to be one of the modulators of brown adipose tissue thermogenesis [39].

5. SFXN dysregulation in human cancers

SFXN1 has been identified as a potential biomarker in multiple cancers, including lung adenocarcinoma [34, 40-43]. It was initially reported as one component of multi-gene signatures in disuse infiltrating gliomas [44], and then for lung cancer [45] and papillary thyroid cancer [46]. Its high expression is correlated with factors like tumor size and metastasis, and it is associated with immune infiltration [43]. In lung cancers, SFXN1 overexpression promoted tumor progression *via* the mTOR signaling pathway

[47]. In addition, SFXN1 expression may influence the tumor microenvironment by interacting with immune cells, such as T and B cells, and immune checkpoints [48], suggesting SFXN1 is a target for immune-based therapies in cancers like lung cancer [48]. Similarly, SFXN1 was an unfavorite prognostic factor in human breast cancers, and two SFXN1 CpG sites (5'-UTR-S_Shelf-cg06573254 and TSS200-Island-cg17647431) were related to breast cancer progression [49]. Further analysis revealed that SFXN1 protein levels were increased and associated with unfavorable outcomes in triple-negative breast cancers [50]. Mechanistically, SFXN1 inhibited the autophagy receptor TOLLIP (toll interacting protein)-mediated autophagic degradation of cellular inhibitor of PP2A (CIP2A), which was partially prevented by lapatinib-mediated inhibition of the CIP2A/PP2A/p-AKT pathway [50]. However, SFXN1 expression was reduced in hepatocellular carcinomas (HCC), and reduced SFXN1 expression correlated to recurrence-free and overall survival in non-viral HCC patients [51]. Furthermore, SFXN1 knockout (KO) in HCC cells enhanced cell viability, lowered fat intake, and diminished reactive oxygen species (ROS) production in response to palmitate treatment. In nude mice xenograft models derived from SFXN1-KO cells, high-fat diet feeding lost tumorigenic potential compared to the control cells [51].

SFXN2 overexpression has been associated with poor outcomes in multiple myeloma patients [10]. Elevated SFXN2 promotes myeloma cell proliferation by limiting mitophagy and increasing iron-based energy production [10]. This suppression of autophagy appears to involve heme oxygenase-1 (HO1), an antioxidant protein, suggesting that SFXN2 helps MM cells resist cellular stress [10]. Knockdown of SFXN2 in experimental models has shown promise in reducing tumor growth, indicating SFXN2 as a potential therapeutic target in MM [10]. In human breast cancers, higher levels of SFXN2 expression were significantly associated with a favorite survival outcome [49].

SFXN3 has revealed its role in different types of cancer, making it a protein of interest for tumor prognosis and therapeutic targeting [49, 52-55]. In head and neck squamous cell carcinoma (HNSC), SFXN3 expression correlates with poor prognosis, chemotherapy resistance, and an immunosuppressive tumor microenvironment [52]. This regulation is thought to involve a non-coding RNA pathway (LINC01270/hsa-miR-29c-3p/SFXN3), suggesting that SFXN3 contributes to aggressive tumor behaviors by modulating immune responses and drug resistance [56]. In addition, the SFXN3 CpG site (Body-S_Shelf-cg17858697) was associated with breast cancer prognosis [49]. In papillary thyroid carcinoma cells, silencing SFXN3 gene expression significantly reduced cell viability [57].

SFXN4 expression was previously used as one of the 9-gene signatures for glioma prognosis [58]. This capacity was recently confirmed in osteosarcoma [59]. SFXN4 gene was overexpressed in cancer tissues derived from the ovary and liver, which was correlated with clinicopathological characteristics and predicted poor outcomes [60, 61]. In ovarian cancer cells, SFXN4 inhibition increased their sensitivity to DNA-damaging drugs such as cisplatin and PARP inhibitors [61], indicating that SFXN4 is a new target in ovarian cancer therapy. In liver cancers, SFXN4 expression was mainly associated with oxidative phosphorylation, reactive oxygen species, and metabolic pathways and was regulated by various transcription factors and miRNAs [60]. Consistently, SFXN4 knockdown in liver cancer cells suppressed xenograft tumor growth in nude mice [60]. However, loss of heterozygosity was reported in familial colorectal cancers [62].

SFXN5 is the least studied SFXN family gene in human cancers. In a recent report [49], multivariable survival analysis using DNA methylation data (MethSurv database) identified nine SFXN5 CpG loci that are associated with the prognosis of breast cancer patients. Among the four different medulloblastoma subgroups (MB-WNT, MB-SHH, MB-G3, and MB-G4), the SFXN5 (and AHCYL1) gene was the most significantly expressed genes in the MB-SHH and MB-G4 groups [63]. The clinical significance of these alterations was under further investigation.

6. Conclusion and future directions

The Sideroflexin protein family is a class of important mitochondrial membrane transporter proteins and plays a crucial role in iron metabolism, mitochondrial function, and the development of various diseases. Significant progress has been made in current research, but many unanswered questions remain. Future in-depth studies are needed to elucidate the functional mechanisms of SFXN proteins in iron metabolism, mitochondrial energy production, and oxidative homeostasis. The development of SFXN-specific drugs or therapies and exploration of their interactions with other biomolecules will provide new ideas and methods for research and clinical applications in related fields.

Genes	Cancer Types	Expression Profile			
SFXN1	Diffuse Infiltrating Gliomas	as one of an iron-regulatory 8-gene signature			
	Lung Adenocarcinoma	as one of a 6-gene risk assessment model	poor prognosis	32819300	2020
	Papillary Thyroid Carcinoma	as one of a 5-genes of Soluble Carrier Family	unfavorite prognosis	34590520	2021
	Lung Adenocarcinoma	Upregulated in mRNA expression	unfavorable prognostic biomarker of OS and RFS	35116859	2019
	Lung Adenocarcinoma	mRNA overexpression, promotes tumor progression via the mTOR signaling pathway	poor prognosis and tumor progression	35878532	2022
	Lung Adenocarcinoma	markedly upregulated at both mRNA and protein levels, correlated with larger tumor size, positive lymph node metastasis, advanced clinical stage	poor prognosis	38233752	2024
	Lung Adenocarcinoma	highly expressed and closely related to FDG uptake	as a promising prognostic biomarker	38184958	2024
	Hepatocellular Carcinoma	significantly reduced and correlated to recurrence-free and overall survival in non-viral HCC, suppresses lipid accumulation and ROS generation	predicts clinical outcome of non-viral HCC patients	37296228	2023
	Breast Cancer	significantly upregulated	related to poor prognosis	37020524	2023
	Lung Adenocarcinoma	increased expression accompanied by decreased infiltration of NK and cytotoxic T cells. In vivo, targeting SFXN1 decreased Tregs infiltration and inhibited tumor growth	a potential therapeutic target	38537539	2024
	Triple-Negative Breast Cancer (TNBC)	significantly overexpressed in tumor tissues and associated with unfavorable outcomes in patients. promoted TNBC progression by inhibiting the autophagy receptor toll interacting protein-mediated autophagic degradation of CIP2A	a new targeted therapy for patients with TNBC	38849012	2024
SFXN2	Multiple Myeloma	significantly elevated and correlated to poor outcomes. promoted cell proliferation and suppressed starvation-induced autophagy/mitophagy	the therapeutic potential in combination with iron metabolism as target for treatment	32599841	2020
	Breast Cancer	high expression was significantly associated with good prognosis	a valuable biomarker and treatment target	37020524	2023
SFXN3	Lung Adenocarcinoma	not differentially expressed compared to normal samples and within different stages	no prognostic value	35878532	2022
	Colorectal Cancer	significantly highly expressed	related to the prognosis	37435199	2023
	Papillary Thyroid Carcinoma	as one of the iron-related risk gene signature, silencing SFXN3 significantly reduced cell viability	successfully predicted the disease-free survival	37361050	2023
	Acute Myeloid Leukemia	as one of the 6-gene risk model	high-risk subgroup had an immune "hot" phenotype and was related to a poor prognosis	36618700	2022
	Acute Myeloid Leukemia	expressed at higher levels and associated with decreased overall survival. SFXN3 knockdown results in enhanced cell apoptosis and dropped cell proliferation, a reduction of CyclinD1 and NFKB1.	a prognostic marker and promotes tumor growth	38877336	2024
	Acute Myeloid Leukemia	primarily overexpressed in non-M3 patients, promotes DNA methylation at transcription start sites	associated with poor clinical outcomes and sensitivity to the hypomethylating therapy	37491851	2023
	Head and Neck Cancer	upregulated	correlated with poor prognosis.	36237258	2022
	Head and Neck Cancer	non-coding RNA-mediated high expression positively associated with enriched tumor-infiltrating macrophages, suppressive cells, immune checkpoint expression and resistance to paclitaxel	an independent risk factor	36159813	2022
SFXN4	Glioma	as one of a 9-gene signature	provided a more accurate predictor of poor outcome	24279471	2014
	Osteosarcoma	as one of the robust 8 hypoxia- and lactate metabolism-related gene signature	for prognosis prediction, classification of "cold" and "hot" tumors, accessing immunotherapy response, and directing personalized treatment	39569192	2024
	Familial Colorectal Cancer	Loss of heterozygosity	with rare truncating variants	24146633	2013
	Hepatocellular Carcinoma	consistently elevated, positively correlated with clinicopathological characteristics, and predicted poor outcome, mainly related to oxidative phosphorylation, reactive oxygen species and metabolic pathways. In vivo, SFXN4 knockdown inhibited xenograft growth in mice	provide both prognostic information and therapeutic potential	37786439	2023
	Ovarian Cancer	plays a role in synthesis of iron sulfur clusters (Fe-S). inhibition of Fe-S biogenesis triggers the accumulation of excess iron, leading to oxidative stress, and reduced DNA repair	a new target in ovarian cancer therapy	36402786	2022
SFXN5	Medulloblastoma	most significantly expressed in the MB-SHH and MB-G4 groups	unknown	37886818	2023
	Breast Cancer	not significantly altered	no significance	37020524	2023

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