biologics

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Review

Solute Carrier Family 35 (SLC35)—An Overview and Recent Progress

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Abstract: The solute carrier family 35 (SLC35) comprises multiple members of transporters, including a group of proteins known as nucleotide sugar transporters (NSTs), an adenosine triphosphate (ATP) transporter, 3′-phosphoadenosine 5′-phosphosulfate (PAPS) transporters, and transporters of unknown function. To date, seven subfamilies (A to G) and 32 members have been classified into this large SLC35 family. Since the majority of glycosylation reactions occur within the lumen of the endoplasmic reticulum (ER) and Golgi apparatus, the functions of NSTs are indispensable for the delivery of substrates for glycosylation. Recent studies have revealed the diverse functions of this family of proteins in the regulation of numerous biological processes, including development, differentiation, proliferation, and disease progression. Furthermore, several congenital disorders of glycosylation (CDGs) resulting from variations in the SLC35 family member genes have been identified. To elucidate the pathology of these diseases, a variety of knockout mice harboring mutations in the family member genes have been generated and employed as animal models for CDGs. This review presents a historical overview of the SLC35 family, with a particular focus on recent advances in research on the functions of this family and their relationship to human diseases.

Keywords: congenital disorders of glycosylation; glycosylation; nucleotide sugar transporter; PAPS transporter; SLC35 family

Citation: Kamiyama, S.; Sone, H. Solute Carrier Family 35 (SLC35)—An Overview and Recent Progress. *Biologics* **2024**, *4*, 242–279. https://doi.org/10.3390/biologics4030017

Academic Editor: Raffaele Capasso

Received: 18 June 2024
Revised: 27 July 2024
Accepted: 8 August 2024
Published: 15 August 2024

1. Introduction

The solute carrier (SLC) superfamily of membrane proteins represents a large and diverse family of transporters that facilitate the transport of a wide range of solutes across biological membranes. The SLC families and their constituent members are defined by the HUGO Gene Nomenclature Committee (HGNC) of the Human Genome Organization (HUGO), based on protein sequence similarity and phylogenetic analyses [1]. The substrates of SLC transporters include a variety of ions, sugars, amino acids, nucleotides, and other small molecules that are essential for cellular functions. The SLC35 family comprises multiple members, including a group of proteins known as nucleotide sugar transporters (NSTs), as a kind of the drug/metabolite transporter superfamily [2].

The majority of this family of proteins are involved in the transport of nucleotide sugars, which serve as essential substrates for glycosylation reactions in the endoplasmic reticulum (ER) and Golgi apparatus. In addition, the SLC35 family includes an adenosine triphosphate (ATP) transporter (SLC35B1), 3′-phosphoadenosine 5′-phosphosulfate (PAPS) transporters (SLC35B2 and SLC35B3), and a thiamine transporter (SLC35F3), in addition to transporters with unknown function (i.e., orphan transporters). To date, seven subfamilies (A to G) and 32 members (including pseudogene E2A) have been classified into this large SLC35 family (Figure 1 and Table 1). Among them, the functions of the A-D subfamily members have been well characterized, whereas little knowledge has been obtained regarding the functions of the members in the E-G subfamilies. The majority of NSTs are

multiple transmembrane proteins localized in the ER or Golgi apparatus and contribute to the delivery of substrates for glycosylation [3].

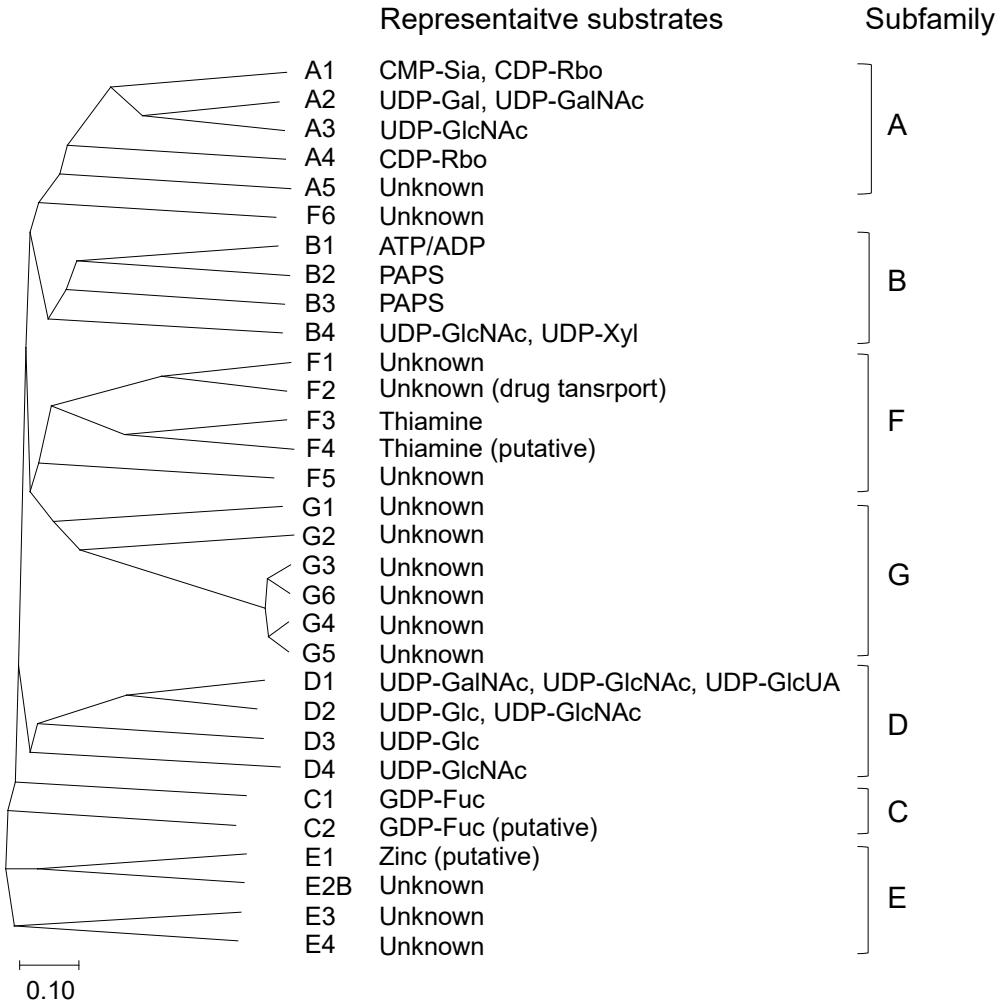

Figure 1. A phylogenetic tree of human solute carrier family 35 (SLC35). Phylogenetic tree of sequences was constructed using the neighbor-joining (NJ) method with Clustal Omega. The scale at the bottom represents evolutionary distance. ADP, adenosine diphosphate; ATP, adenosine triphosphate; CDP-Rbo, cytidine diphosphate ribitol; CMP-Sia, cytidine monophosphate sialic acid; GDP-Fuc, guanosine diphosphate fucose; GDP-Man, GDP-mannose; PAPS, 3′-phosphoadenosine 5′-phosphosulfate; UDP-Gal, uridine diphosphate galactose; UDP-GalNAc, UDP-*N*-acetylgalactosamine; UDP-Glc, UDP-glucose; UDP-GlcNAc, UDP-*N*-acetylglucosamine; UDP-GlcUA, UDP-glucuronic acid; UDP-Xyl, UDP-xylose.

Glycosylation is a common modification of proteins and lipids that is catalyzed by glycosyltransferases. In eukaryotes, sugars are activated into nucleotide sugars, including cytidine monophosphate sialic acid (CMP-Sia), guanosine diphosphate fucose (GDP-Fuc), GDP-mannose (GDP-Man), uridine diphosphate galactose (UDP-Gal), UDP-*N*-acetylgalactosamine (UDP-GalNAc), UDP-glucose (UDP-Glc), UDP-*N*-acetylglucosamine (UDP-GlcNAc), and UDP-xylose (UDP-Xyl), as the substrates for glycosylation reaction. Glycosyltransferases utilize these nucleotide sugars as donor substrates for the enzymatic attachment of sugar residues. These nucleotide sugars are synthesized in the cytosol (in the case of CMP-Sia, the nucleus), and most glycosylation reactions occur in the ER and Golgi lumens, where the glycosyltransferases are localized [4]. In the ER lumen, UDP-glucuronic acid (UDP-GlcUA) serves as a substrate for glucuronidation, which is catalyzed by UDP-glucuronosyltransferases.

As the ER and Golgi apparatus are separated from the cytosol by a membrane, the functions of NSTs are essential for the translocation of these nucleotide sugars across the membrane. Furthermore, ATP and PAPS transporters are also localized and function in the membrane of these organelles [3]. In early studies, the transport functions of NSTs, PAPS transporters, and ATP transporters have been demonstrated using Golgi vesicles isolated from mammalian tissues and cell lines [3]. In addition, mutant cell lines that lack CMP-Sia or UDP-Gal transport activity have been identified and utilized for the cloning of NSTs through a complementation approach [5].

The first molecular cloning and identification of NSTs were reported in 1996. The milk yeast *Kluyveromyces lactis* UDP-GlcNAc transporter [6], murine CMP-Sia transporter [7], and human UDP-Gal transporters [8,9] were identified and characterized. Following these discoveries, numerous studies have identified NST genes in a range of eukaryotic organisms. Initially, it was hypothesized that a single monospecific NST would be sufficient for the transport of each corresponding nucleotide sugar. However, subsequent studies demonstrated that the majority of NSTs are multisubstrate-specific transporters, and multiple NSTs exhibit functional redundancy.

NSTs employ an antiport mechanism to facilitate the transport of nucleotide sugars. This process entails the utilization of a corresponding luminal nucleoside monophosphate as an antiport molecule, including CMP, GMP, and UMP, which are generated through a glycosyltransferase reaction and subsequent luminal nucleoside diphosphatase reaction [10] (Figure 2). However, recent studies have proposed more variable antiport mechanisms. Furthermore, a number of studies have demonstrated that the functions of NSTs are interrelated and that NSTs and glycosyltransferases form complexes and regulate nucleotide sugar supply in a coordinated manner [5].

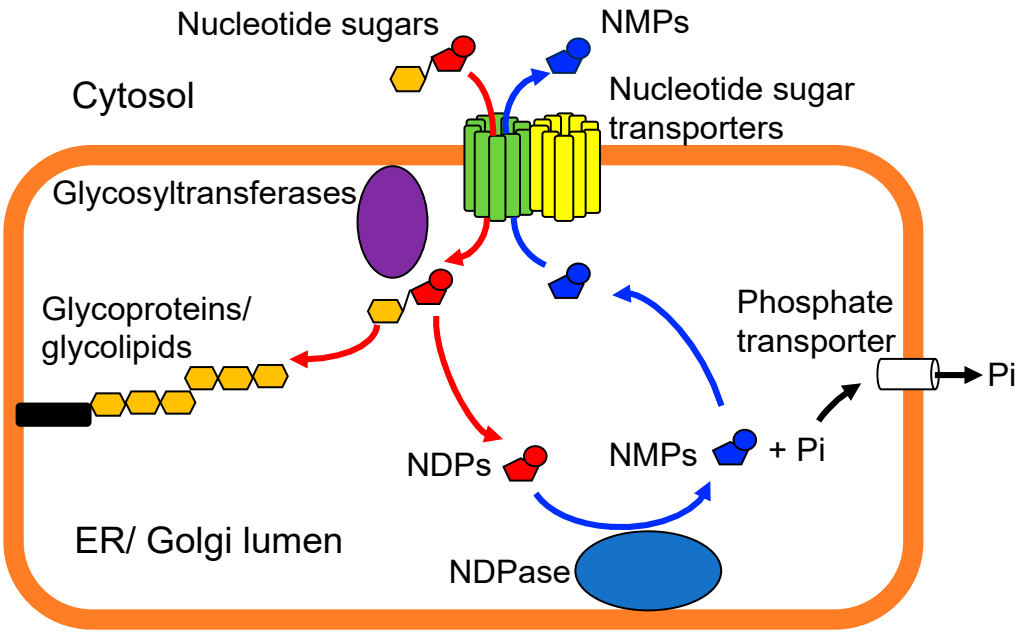

Figure 2. A schematic illustration of the function of typical nucleotide-sugar transporters (NSTs). NSTs translocate specific nucleotide sugars from the cytosol into the endoplasmic reticulum (ER) or Golgi lumens using an antiport mechanism. Glycosyltransferases transfer a sugar residue from corresponding donor substrate to a specific hydroxyl group of its acceptor molecules. Nucleoside diphosphatase (NDPase) catalyzes the hydrolysis of nucleoside diphosphate (NDP) to yield nucleoside monophosphate (NMP) and inorganic phosphate (Pi). NSTs utilize MNPs as their antiport molecules. NSTs form homodimers or heterodimers with themselves or other NSTs and interact with specific glycosyltransferases. It should be noted that in the case of certain NSTs, alternative antiport mechanisms have been proposed, including UDP-sugar/UDP-sugar countertransport.

The first crystal structure of an NST, the yeast Vrg4, was published in 2017. Parker and Newstead presented the crystal structures of the GDP-mannose transporter of *S. cerevisiae* in both the substrate-free and substrate-bound states [11]. The typical NST has a conserved architecture comprising 10 transmembrane domains, arranged in the form of two inverted topology repeats of five transmembrane helices around a central ligand-binding site [12]. Additionally, the researchers demonstrated the indispensable functions of short-chain lipids in the activation of the transporter in the Golgi membrane. The lipids facilitate the dimerization of NSTs in the membrane by forming an integral part of the dimer [11,13]. The crystal structures of NSTs also revealed the crucial roles of conserved sequence motifs in substrate recognition and transport, such as the consensus motifs for Man (GALNK), Fuc (GTAKA), and guanine (FYNN). Subsequently, the structures of the mouse and *Zea mays* CMP-Sia transporters have been reported [14,15]. These three-dimensional structural analyses yielded insights into the mechanisms underlying the diverse functions of NSTs and disease-causing mutations. For a more comprehensive understanding of the mechanisms of the structure and function of NSTs, we recommend other excellent reviews [5,12,16].

Because the structures and functions of SLC35 family members have been conserved in a variety of eukaryotes throughout evolution, numerous studies have investigated the biological functions of each NST using invertebrate mutant models, such as *Caenorhabditis elegans* and *Drosophila melanogaster*. More recently, congenital disorders of glycosylation (CDGs) caused by variations of the SLC35 family member genes have been identified, including SLC35A1-CDG, SLC35A2-CDG, SLC35A3-CDG, SLC35B2-CDG, SLC35C1-CDG, and SLC35D1-CDG. Consequently, knockout mice of the family member genes have been created and analyzed as animal models for the study of the pathology of these CDG and the elucidation of the functions of these transporters. This review presents a historical overview of the SLC35 family, with a particular focus on recent advances in research on the functions of this family and their relationship to human diseases.

Table 1. Human SLC35 family members.

Member		Aliases	Known Substrates	Chromosome	Cellular Localization	Tissue Specificity [1]	CDG Name and MIM Number [2]	Identified *Drosophila* Genes [3]	Identified *C. elegans* Genes [4]
A	1	CST	CMP-Sia CDP-Rbo	6q15	Golgi	Low tissue specificity	SLC35A1-CDG (CDG-IIf) MIM: 603585	*ugalt/dmugt* (CG2675) UDP-Gal UDP-GalNAc	*srf-3* (CE43555) UDP-Gal UDP-GlcNAc
	2	UGT	UDP-Gal UDP-GalNAc	Xp11.23	Golgi (UGT1) ER (UGT2)	Low tissue specificity	SLC35A2-CDG (CDG-IIm) MIM: 300896		*nstp-4* (CE32110) UDP-GalNAc UDP-GlcNAc
	3	UGTREL2	UDP-GlcNAc	1p21.2	Golgi	Low tissue specificity	SLC35A3-CDG MIM: 615553		*nstp-5* (CE15465) UDP-Gal UDP-Glc UDP-GalNAc UDP-GlcNAc
	4	CLRP UGTREL3	CDP-Rbo	5q31.3	Golgi	Low tissue specificity		*senju* (CG14040) UDP-Gal	
	5	UGTREL5	orphan	3q13.2	Golgi	Low tissue specificity			
B	1	UGTREL1 AXER	ATP/ADP (UDP-GlcUA)	17q21.33	ER	Low tissue specificity		*meigo* (CG5802) Unknown	*hut-1* (CE24129) UDP-Gal UDP-Glc
	2	PAPST1	PAPS	6p21.1	Golgi	Low tissue specificity	SLC35B2-CDG MIM: 620269	*sll* (CG7623) PAPS	*pst-1* (CE12374) PAPS
	3	PAPST2	PAPS	6p24.3	Golgi	Low tissue specificity		*dpapst2* (CG7853) PAPS	*pst-2* (CE01312) PAPS
	4	YEA4	UDP-GlcNAc, UDP-Xyl (UDP-GlcUA)	7q33	ER/Golgi	Low tissue specificity		*efr* (CG3774) GDP-Fuc UDP-GlcNAc UDP-Xyl	
C	1	FUCT1	GDP-Fuc	11p11.2	Golgi	Tissue enhanced (liver)	SLC35C1-CDG (CDG-IIc, LADII) MIM: 266265	*nac/gfr* (CG9620) GDP-Fuc	nstp-10 (CE30910) GDP-Fuc
	2	OVCOV1	GDP-Fuc (putative)	20q13.12	ER/Golgi	Low tissue specificity		CG14971 Unknown	

Table 1. *Cont.*

Member		Aliases	Known Substrates	Chromosome	Cellular Localization	Tissue Specificity [1]	CDG Name and MIM Number [2]	Identified *Drosophila* Genes [3]	Identified *C. elegans* Genes [4]
D	1	UGTREL7	UDP-GalNAc UDP-GlcNAc UDP-GlcUA	1p31.3	ER	Tissue enhanced (liver)	SLC35D1-CDG MIM: 269250	*frc* (CG3874) UDP-sugars	*sqv-7* (CE04263) UDP-Gal UDP-GalNAc UDP-GlcUA
	2	HFRC1	UDP-Glc UDP-GlcNAc GDP-Man * (* not human)	9q22.32	Golgi	Low tissue specificity			
	3	FRCL1	UDP-Glc	6q23.3	Early endosome/ Dense granule	Tissue enriched (brain)			
	4	TMEM241 C18orf45	UDP-GlcNAc	18q11.2	Golgi	Low tissue specificity			
E	1		Zinc (putative)	19p13.11		Low tissue specificity			
	2A 2B		2A: pseudogene 2B: orphan	1p36.33		Low tissue specificity			
	3	BLOV1	orphan	12q15		Low tissue specificity			
	4		orphan	22q12.2		Tissue enhanced (testis)			
F	1	C6orf169	orphan	6q22.2–q22.31	Recycling endosome	Group enriched (brain, retina)			
	2	HSNOV1	orphan	11q22.3	Plasma membrane	Tissue enhanced (salivary gland)			
	3		Thiamine	1q42.2	Plasma membrane	Tissue enriched (brain)			
	4	C14orf36	Thiamine (putative)	14q22.3–q23.1		Group enriched (brain, retina, seminal vesicle)			
	5		orphan	2q14.1		Low tissue specificity			
	6	C2orf18 ANT2BP	orphan	2p23.3	Mitochondria	Low tissue specificity			

Table 1. *Cont.*

Member		Aliases	Known Substrates	Chromosome	Cellular Localization	Tissue Specificity [1]	CDG Name and MIM Number [2]	Identified *Drosophila* Genes [3]	Identified *C. elegans* Genes [4]
G	1	TMEM20 POST	orphan	10q23.33	ER	Tissue enriched (intestine)			
	2	TMEM22	orphan	3q22.3		Low tissue specificity			
	3	TMEM21A	orphan	17q12		Tissue enriched (testis)			
	4	AMAC1L1	orphan	18p11.21		Not detected			
	5	AMAC1L2	orphan	8p23.1		Tissue enriched (testis)			
	6	AMAC1L3	orphan	17p13.1		Tissue enriched (testis)			

[1] The data were obtained from the Human Protein Atlas (HPA) database (https://www.proteinatlas.org, accessed on 18 June 2024). The tissue specificity is based on mRNA expression levels in the analyzed samples, which were derived from a combination of data from the HPA and the Genotype-Tissue Expression (GTEx) projects. The classification includes four categories: tissue enriched, group enriched, tissue enhanced, low tissue specificity, and not detected [17]. It should be noted that the expression profiles presented here are not entirely consistent with those previously reported [18]. [2] Disease name and OMIM (Online Mendelian Inheritance in Man, https://omim.org, accessed on 18 June 2024) ID. [3] Gene name, FlyBase (https://flybase.org, accessed on 18 June 2024) ID, and known substrates. [4] Gene name, WormBase (https://wormbase.org, accessed on 18 June 2024) protein ID for a representative isoform, and known substrates.

2. SLC35A Subfamily

The SLC35A subfamily comprises five members. Since the first cloning of mammalian NSTs in 1996, numerous studies have extensively characterized the function of SLC35A subfamily members. All members of this subfamily are considered to be assigned to NSTs, which have a variety of substrate specificities. These include CMP-Sia, UDP-Gal, UDP-GalNac, UDP-GlcNac, and CDP-ribitol (CDP-Rbo). To date, no substrate specificity has been identified for SLC35A5. However, studies have suggested that this protein is also involved in glycosylation and nucleotide sugar transport into the Golgi apparatus.

2.1. SLC35A1

The SLC35A1 protein functions as a CMP-Sia transporter. Additionally, it has been proposed that SLC35A1 may also transport other cytosine nucleotide conjugates, such as CDP-Rbo [19].

In 1996, Eckhardt et al. reported the molecular cloning of mouse *Slc35a1* cDNA by complementation of Lec2 mutant cells [7]. Lec2 and its subclone 6B2 are mutant cell lines derived from Chinese hamster ovary (CHO) cells that exhibit a significant reduction in sialylation of glycoproteins and glycolipids due to a defect in the CMP-Sia transport activity [20,21]. The expressed mouse SLC35A1 protein was localized in the Golgi apparatus and restored the glycosylation defects of the 6B2 mutant [7]. The CMP-Sia transport activity of the mouse SLC35A1 was confirmed by utilizing Golgi vesicles overexpressed with this protein in *Saccharomyces cerevisiae* [22]. Subsequently, the human homolog was cloned and identified as a CMP-Sia transporter by the complementation of the Lec2 cell line and its CMP-Sia transport activity into microsomal vesicles [23].

The biosynthesis of CMP-Sia occurs within the nucleus [24], and the CMP-Sia transporter facilitates its translocation from the cytosol into the Golgi apparatus for glycosyltransferases. The SLC35A1 is primarily localized in the medial Golgi and possesses two specific ER export motifs in its carboxyl-terminal cytoplasmic tail. The deletion of the C-terminal IIGV motif results in the retention of the SLC35A1 in the ER membrane [25].

NSTs have been predicted to be type III multi-transmembrane proteins with an even number of transmembrane domains and both N- and C-termini directed towards the cytosolic side of the ER or Golgi membrane. An initial computer-based structural analysis of hamster SLC35A1 predicted an eight-transmembrane-helix model [26]. However, a detailed topological analysis determined that the mouse SLC35A1 contains 10 transmembrane domains with N- and C-termini facing on the cytosolic side of the Golgi membrane [27]. It is proposed that SLC35A1 forms a homodimer in the Golgi membrane and that this dimerization is important for its transport activity. The fifth and tenth transmembrane domains are involved in the dimer formation, while the other domains are involved in the formation of transport bundles [15,28]. The seventh transmembrane domain is the key player for the CMP-Sia transport activity [29,30]. The Tyr214 and Ser216 residues located in the seventh transmembrane domain of the human SLC35A1 are of critical importance for the recognition of CMP-Sia as a transporting substrate [30]. In 2019, Ahuja and Whorton reported the first crystal structures of the mouse SLC35A1 in complex with its physiological substrates, CMP and CMP-sialic acid [14]. The analysis of these structures elucidated the fundamental principles of the structure–function relationship of NSTs, including substrate recognition and selectivity as well as the mechanism of substrate accessibility between the NST and the Golgi lumen.

In 2005, Martinez-Duncker et al. identified that a mutation in the *SLC35A1* gene is associated with the development of a syndrome characterized by macrothrombocytopenia and neutropenia [31]. The patient completely lacked sialyl Lewis X (sLeX) antigen on the surface of polymorphonuclear cells [31]. In the patient, the inactivation of the CMP-Sia transporter gene was due to genetic alterations caused by a double microdeletion in one allele and a 130-bp deletion in the other allele, resulting in the partial skipping of exon 6. The autosomal recessive disorder was designated as CDG-IIf (currently, SLC35A1-CDG) [31], and subsequently several cases of SLC35A1-CDG have been reported [32–34]. The affected

individuals displayed bleeding diathesis, macrothrombocytopenia, proteinuria, and neurological symptoms including ataxia, intellectual disability, and epilepsy. Kauskot et al. proposed that the function of SLC35A1 is not essential for proplatelet formation but is crucial for platelet lifespan [34]. Ma et al. generated *Slc35a1* conditional knockout mice and analyzed their *Slc35a1*$^{-/-}$ megakaryocytes and platelets. The *Slc35a1*$^{-/-}$ platelets exhibited thrombocytopenia, and the number of bone marrow megakaryocytes was reduced. Furthermore, impaired megakaryocyte maturation and the excessive clearance of desialylated platelets by liver Küpffer cells were observed [35]. Sialic acid is a common terminal residue of glycans on proteins and acidic sphingolipids such as gangliosides and has important biological functions. Szulc et al. reported that SLC35A1 knockout HEK293T cells had reduced but still detectable sialylated *N*-glycans, although sialylation of *O*-glycans appeared to be completely absent. The researchers postulated the existence of an SLC35A1-independent Golgi CMP-Sia uptake route [28].

A study utilizing haploid screening for Lassa virus entry suggested that *SLC35A1* is one of the candidate genes for α-dystroglycanopathy [36]. Although glycosylation of α-dystroglycan does not require CMP-Sia, the inactivation of *SLC35A1* in the haploid cell line HAP1 prevented functional glycosylation of α-dystroglycan and Lassa virus entry, which requires fully glycosylated α-dystroglycan. Moreover, the loss-of-function mutations in *SLC35A1* resulted in aberrant α-dystroglycan *O*-mannosylation, whereas the removal of Sia from wild-type HAP1 cells or the prevention of sialylation did not affect α-dystroglycan *O*-mannosylation [36,37].

In 2021, Ury et al. reported that the SLC35A1 can transport CDP-Rbo, a nucleotide-pentose alcohol, as well as CMP-Sia [19]. It is known that the functional *O*-mannosyl glycan on α-dystroglycan contains a tandem repeat of Rbo 5-phosphate, which is required to prime the addition of a repeated disaccharide (-Xyl-α1,3-GlcUA-β1,3-)n, called matriglycan, to the glycan chain [38] (Figure 3). This unique glycan structure of α-dystroglycan is of paramount importance in the interaction with extracellular matrix proteins, such as laminin. CDP-Rbo is synthesized by an enzyme called CDP-L-ribitol pyrophosphorylase A (CRPPA; also known as isoprenoid synthase domain-containing protein, ISPD) in the cytosol. Subsequently, enzymes FUKUTIN (FKTN) and FUKUTIN-related protein (FKRP) transfer Rbo 5-phosphate to the core M3 structure (GalNAc-β1-3-GlcNAc-β1-4-Man) on the α-dystroglycan in the Golgi apparatus [39,40] (Figure 3). The defects in CRPPA [41,42], FKTN [43], and FKRP [44,45] have been associated with muscular dystrophy due to defective glycosylation of α-dystroglycan. Although the translocation of CMP-Rbo from the cytosol into the Golgi apparatus is an essential process for the Rbo 5-phosphate modification, patients with SLC35A1-CDG did not exhibit symptoms of α-dystroglycanopathy. Another CDP-ribitol transporter, SLC35A4, is proposed to be involved in the transport of CDP-ribitol into the Golgi apparatus in a redundant manner [19].

2.2. SLC35A2

SLC35A2, also known as the UDP-Gal transporter, is one of the most extensively studied NSTs. A multitude of studies have demonstrated a correlation between the expression of *SLC35A2* and the progression and malignancy of various cancers, including colon cancer [46]. Its mutations are responsible for a rare type of CDG, CDG-IIm (currently, SLC35A2-CDG) [47,48]. The SLC35A2 and its *Drosophila* ortholog, *dm*UGT, transport UDP-Gal and UDP-GalNAc into the Golgi lumen [49]. The homologs of SLC35A2 are present in a variety of species, including nematode *C. elegans* [50], yeasts *S. cerevisiae* [51] and *Schizosaccharomyces pombe* [52,53], and protozoan parasites *Entamoeba histolytica* [54] and *Leishmania major* [55].

The human SLC35A2 was identified as the first mammalian NST based on its ability to complement the galactosylation defect of a mouse mutant cell line, Had-1 [8,9]. In 1996, Miura et al. cloned the cDNA of *SLC35A2* (*hUGT1*) from a human cDNA library [8]. Subsequently, they also cloned *hUGT2*, an alternative splicing variant of *SLC35A2* [9]. In microsomal vesicles derived from Had-1 cells, both UGT1 (SLC35A2v1) and UGT2

(SLC35A2v2) exhibited equivalent UDP-Gal transport activity [9]. The substrate specificity of SLC35A2 (hUGT1 and hUGT2) was confirmed using microsomal vesicles isolated from the yeast expression system. The SLC35A2 was found to transport UDP-GalNAc in addition to UDP-Gal [49]. A CHO mutant cell line Lec8 [56,57] and a ricin-resistant mutant MDCK cell line (MDCK-RCA^r) [57,58] also lack UDP-Gal transport activity and galactosylated glycans. Both hUGT1 and hUGT2 have the potential to restore glycosylation defects in these mutant cells [59].

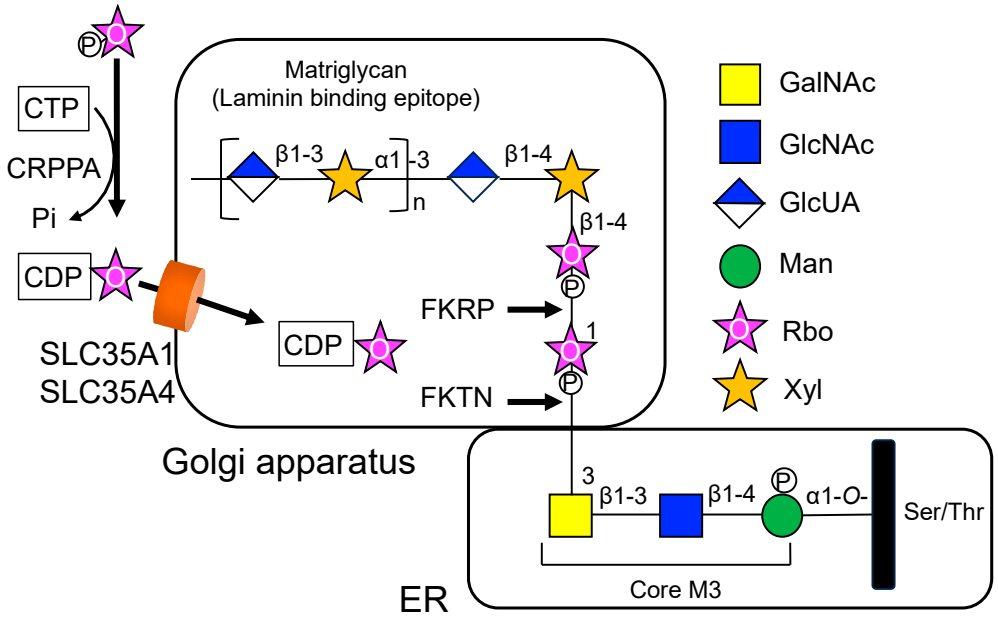

Figure 3. Potential involvement of SLC35A1 and SLC35A4 in the synthesis of *O*-mannosyl glycans on α-dystroglycan. CDP-Rbo is synthesized from CTP and Rbo-5P via the CDP-L-ribitol pyrophosphorylase A (CRPPA) enzyme and transported into the Golgi apparatus via SLC35A1 and SLC35A4. Subsequently, the enzymes FUKUTIN (FKTN) and FUKUTIN-related protein (FKRP) transfer Rbo 5-phosphate to the core M3 structure on the α-dystroglycan in a sequential manner. These modifications are essential for the addition of a repeated disaccharide matriglycan.

The amino acid sequences of these two variants differ only at their C-terminus (UGT1, SVLVK; UGT2, LLTKVKGS) [60]. The UGT1 protein exhibits Golgi localization [60,61], whereas UGT2 exhibits dual localization in the ER and Golgi apparatus due to its dilysine ER-retention motif, KVKGS [60]. The subcellular localization of SLC35A2 is also influenced by its interaction with other proteins, including glycosyltransferases and other NSTs. The localization of hUGT1 shifted from the Golgi apparatus to the ER as a consequence of the association with UDP-galactose:ceramide galactosyltransferase, a protein localized in the ER [62]. In addition, the formation of a heterodimeric complex between hUGT1 and hUGT2 proteins resulted in the relocation of hUGT1 from the Golgi apparatus to the ER due to the presence of hUGT2 [63].

A number of studies have demonstrated that SLC35A2 and SLC35A3 function in a coordinated manner. SLC35A2 and SLC35A3 are known to tightly interact with each other [64]. In SLC35A2-deficient cells, overexpression of SLC35A3 partially restored galactosylation of *N*-glycans [65]. The SLC35A2 and SLC35A3 can substitute for each other's function if appropriate regions of these transporters are conserved. The short N-terminal region of SLC35A2, comprising 35 amino acid residues, is crucial for galactosylation of *N*-glycans [66].

The *SLC35A2* gene mutations are responsible for a rare genetic disorder, SLC35A2-CDG (CDG-IIm). In 2013, Ng et al. identified mutations in the *SLC35A2* gene from three unrelated patients as an undiagnosed X-linked CDG [47]. The patients exhibited a range of symptoms, including developmental delay, hypotonia, seizures, ocular anomalies,

skeletal abnormalities, and brain malformations. Each mutation in the patients resulted in reduced UDP-Gal transport and Gal-deficient glycoproteins [47]. Additionally, Kodera et al. identified two de novo frameshift mutations and one missense mutation in *SLC35A2* in three unrelated Japanese females diagnosed with early-onset epileptic encephalopathy (EOEE), a group of epileptic encephalopathies characterized by frequent seizures accompanied by developmental retardation [48]. The missense mutant protein was correctly localized in the Golgi apparatus, whereas the two frameshift mutant proteins did not properly express [48]. Following these discoveries, researchers have identified additional mutations in *SLC35A2* that are associated with this rare form of CDG, SLC35A2-CDG.

The phenotypic manifestations of SLC35A2-CDG are variable; however, the patients diagnosed with SLC35A2-CDG commonly exhibit severe neurological symptoms. In many cases, developmental and epileptic encephalopathy with hypsarrhythmia were observed [67,68]. It is well known that a variety of CDGs present with a range of neurological symptoms, including psychomotor retardation, cognitive impairment, epileptic seizures, and hypotonia [69–71]. In particular, CDGs with aberrant *N*-glycosylation have been linked to the pathogenesis of neurological disorders and the associated symptoms [71]. Since SLC35A2 is indispensable for glycosylation processes, including those involving *N*-glycans, any disruption to its function will inevitably result in a multitude of neurological symptoms. In contrast, the majority of patients show normal glycosylation patterns of serum transferrin protein, which is a common biomarker for most types of CDGs [68,72]. Ng et al. developed an assay for the diagnosis of the disease by evaluating UDP-Gal transport into the Golgi apparatus using permeabilized patient fibroblast cells. In primary fibroblasts from affected individuals, the UDP-Gal transport activity was directly correlated with the ratio of wild-type to mutant alleles [72].

Defects in UDP-Gal transport can affect almost all galactosylated glycans, including *N*- and *O*-linked glycans, GAGs, and glycosphingolipids [73]. As the *SLC35A2* gene is located on the X chromosome (Xp11.23), the majority of SLC35A2-CDG patients are female. They have heterozygous mutant alleles of *SLC35A2*, and almost all male patients are somatic mosaics. This indicates that a wild-type *SLC35A2* allele is essential for their viability. Witters et al. reported that oral supplementation with D-Gal resulted in clinical and biochemical improvement in SLC35A2-CDG. The supplementation of Gal increased levels of a fully galactosylated *N*-glycan and decreased the ratio of incompletely formed glycans to fully formed glycans in patients [74].

2.3. SLC35A3

SLC35A3 was initially described as UDP-Gal transporter (UGT)-related protein 2 (UGTrel2) [9] and subsequently identified to be a UDP-GlcNAc transporter [75,76]. GlcNAc is a sugar found in the majority of glycoconjugates, including *N*- and *O*-linked glycoproteins, proteoglycans, and glycolipids. UDP-GlcNAc is synthesized in the cytosol and incorporated into the Golgi lumen via several transporters, including SLC35A3.

In 1998, Guillen et al. cloned the cDNA of the mammalian *SLC35A3* gene from Madin-Darby canine kidney (MDCK) cells. They discovered that this gene encodes a UDP-GlcNAc transporter by using a phenotypic correction of the *K. lactis mnn2-2* mutant [75]. *Mnn2*-2 is a mutant line of *K. lactis*, an aerobic milk yeast, lacking terminal GlcNAc in its mannan chains. The *mnn2-2* mutant's defective features were rescued by transformation with the canine *SLC35A3* gene, but not by the *SLC35A1* or *SLC35A2* genes [75]. Subsequently, the human *SLC35A3* gene was identified based on nucleotide sequence similarity to the human *SLC35A2* gene and was demonstrated to have UDP-GlcNAc transport activity [76]. The *SLC35A3* gene is ubiquitously expressed in organs, and the protein is localized to the Golgi apparatus in CHO cells [76]. The amino acid sequence of the SLC35A3 protein exhibits 53% and 40% identity to the mammalian SLC35A2 (UDP-Gal transporter) and SLC35A1 (CMP-Sia transporter) sequences, respectively.

In 2006, Thomsen et al. reported that a missense mutation in the *SLC35A3* gene causes complex vertebral malformation (CMV) in bovine [77]. CMV is an autosomal recessive

inherited disease of Holstein Friesian cattle, which is globally found in the world and causes intra-uterine or perinatal mortality [78,79]. This bovine disease is characterized by malformation of the cervical and thoracic vertebral column, craniofacial dysmorphism, malformed ribs, arthrogryposis of the lower limb joints, and cardiac anomalies. Thomsen et al. demonstrated that the aberrant protein glycosylation in tissues is associated with the bovine CMV [77]. The transformation with the wild-type *SLC35A3* gene fully complemented the defect of the *mnn2-2* mutant, whereas the mutated *SLC35A3* gene did not increase surface expression of GlcNAc. The heterozygous carriers of the missense mutation (Val180Phe) were asymptomatic, whereas its homozygous mutation typically caused death in utero [77].

In 2013, Edvardson et al. identified deleterious mutations in *SLC35A3* in patients with arthrogryposis, impaired intellectual development, and seizures [80]. The Golgi vesicles isolated from the fibroblasts of SLC35A3-CDG patients exhibited significantly reduced UDP-GlcNAc transport activity, resulting in a substantial reduction in highly branched *N*-glycans on the cell surface. Subsequently, studies have identified that mutations in *SLC35A3* cause skeletal dysplasia in patients with a range of skeletal deformities, including CMV-like vertebral anomalies [81,82]. The presence of neurological symptoms and skeletal abnormalities in patients with SLC35A3-CDG indicates that the function of SLC35A3 is essential for the glycosylation of molecules involved in neural and skeletal development.

Saito et al. generated mutant mice lacking the *Slc35a3* gene using the CRISPR/Cas9 genome editing system [83]. The *Slc35a3*$^{-/-}$ mice exhibited chondrodysplasia accompanied by CVM-like vertebral anomalies and were perinatal lethal. In the *Slc35a3*$^{-/-}$ embryos, the extracellular matrix (ECM) in the growth plate cartilage was drastically reduced, and many flat proliferative chondrocytes were reshaped. The significant reduction in the levels of proteoglycans, including heparan sulfate (HS), keratan sulfate (KS), and chondroitin sulfate (CS)/dermatan sulfate (DS), suggests that the chondrodysplasia phenotypes observed in *Slc35a3*$^{-/-}$ mice were at least partially caused by the decreased glycosaminoglycan (GAG) synthesis [83].

Cartilage tissues are composed primarily of type II collagen, hyaluronan (HA), and a cartilage-specific proteoglycan, aggrecan. Aggrecan is a large proteoglycan composed of a core protein and numerous GAG chains of CS/DS and KS. In cartilage tissues, the major components of the ECM are produced by chondrocytes, which contribute to water retention and provide resistance to compression [84,85]. GAGs in proteoglycans receive varying degrees of sulfation and acquire a negative charge, enabling them to interact with a diverse array of molecules, including epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), Wnt, Hedgehog, and bone morphogenic protein (BMP) [86]. These GAGs are known to play crucial roles in skeletal development and bone homeostasis [87]. The decreased GAG synthesis may deteriorate the ECM quality, leading to chondrodysplasia phenotypes in CMV and *Slc35a3*$^{-/-}$ mice [83].

SLC35A3 is also involved in the biosynthesis of highly branched *N*-glycans [88]. Several studies have suggested that NSTs and glycosyltransferases form glycosylation-related complexes in the Golgi apparatus [58,64,89,90]. In the Golgi membrane, SLC35A2 and SLC35A3 form heterologous complexes and cooperate in the delivery of donor substrates for glycosyltransferases located in the Golgi apparatus [58,64]. These transporters also interact with multiple mannoside acetylglucosaminyltransferases (Mgats) [89] and *N*-acetylglucosaminyltransferase IV (GnT-IV) [91] in the Golgi membranes, and the multi-enzyme/multi-transporter complexes facilitate the efficient synthesis of complex *N*-glycans [90].

However, despite the clear demonstration of the UDP-Gal-providing activity of SLC35A2, the significance of SLC35A3 in the *N*- and *O*-glycan synthesis remains unclear. Szulc et al. analyzed *SLC35A2* and *SLC35A3* knockout cell lines and demonstrated that *SLC35A3*-knockout CHO cells showed only minor alterations in GlcNAc incorporation into *N*-glycans, whereas *SLC35A2*-deficient cells displayed significant changes in *N*- and *O*-glycan synthesis [73]. Since SLC35B4, SLC35D1, and SLC35D2 also exert UDP-GlcNAc transport activity, Szulc et al. propose that SLC35A3 may not be the primary UDP-GlcNAc transporter involved in *N*- and *O*-glycan synthesis [73].

2.4. SLC35A4

The *SLC35A4* gene encodes a Golgi-resident CDP-Rbo transporter protein [19]. Additionally, it has been postulated that SLC35A4 may play a role in regulating the intracellular trafficking of other NSTs [92].

In 2002, Pérez-Márquez et al. cloned the *Slc35a4* (*clrp*) cDNA from rat brain tissue [93]. The sequence of SLC35A4 exhibited high homology to SLC35A1 and SLC35A2, and its GFP-tagged protein was observed to localize to the Golgi apparatus. In the brain, *Slc35a4* mRNA was detected in a limited set of neurons, including the pyramidal cells of the cortex, Purkinje cells of the cerebellum, and the motoneurons of the brainstem [93]. Sosicka et al. proposed that SLC35A4 is not involved in glycosylation but rather plays a role in the intracellular trafficking of SLC35A2/SLC35A3 complexes [92]. SLC35A4 is primarily localized in the intermediate ER-Golgi compartment, which is involved in trafficking between these two organelles. In HepG2 cells, knockout of the *SLC35A4* gene did not result in glycosylation changes, but it did result in a disturbed subcellular distribution of SLC35A2/SLC35A3 complexes [92].

In 2021, Ury et al. demonstrated that the SLC35A4 protein plays a role in transporting CDP-Rbo into the Golgi apparatus. SLC35A1 has the capacity to transport both CMP-Sia and CDP-Rbo, whereas SLC35A4 only exerts CDP-Rbo transport and lacks CMP-Sia transport activity [19]. These two transporters exhibit a high degree of structural similarity, yet the amino acid sequence of the SLC35A4 protein shares no substantial sequence conservation with that of SLC35A1 within the binding site for CMP-Sia. The structural homology model indicated that SLC35A1 has a large binding pocket that can accommodate both bulky CMP-Sia and smaller CDP-Rbo, whereas SLC35A4 only accepts the CDP-Rbo [19]. In *SLC35A1* knockout cells, the deficiency of Rbo 5-phosphate in the glycan on α-dystroglycan was rescued by SLC35A4, while it did not complement the loss of CMP-Sia transport activity. The researchers proposed that CDP-Rbo transport is mainly reliant on the function of SLC35A1, whereas SLC35A4 plays a redundant role in the CDP-Rbo incorporation [19].

It has been reported that *SLC35A4* mRNA contains an upstream open reading frame (uORF) that encodes a functional microprotein [94–97]. uORF is a cis-acting element within the 5′-untranslated region upstream (5′-UTR) of the main protein coding sequence. It has a regulatory function in the translation of the downstream open reading frames (ORFs). In the 5′-UTR of *SLC35A4*, the uORF encodes a 103 amino acid peptide sequence that contains the PFAM domain DUF4535 (PFAM ID: PF15054) and is highly conserved across vertebrates [95]. Moreover, the uORF of *SLC35A4* mRNA produces a single-pass transmembrane microprotein that is targeted to the inner mitochondrial membrane. The loss of function of the microprotein significantly diminished maximal cellular respiration and ATP generation in the mitochondria [96,97].

2.5. SLC35A5

To date, the substrate specificity of SLC35A5 has not been identified. However, it is postulated that this orphan transporter protein modulates the functions of other NSTs by forming complexes [98].

Sosicka et al. reported that the SLC35A5 protein is a Golgi-resident multiprotein complex member involved in nucleotide sugar transport. Inactivation of the *SLC35A5* gene resulted in a decreased uptake of UDP-GlcUA, UDP-GlcNAc, and UDP-GalNAc in the Golgi apparatus, with no effect on UDP-Gal transport activity [98]**.** Nevertheless, in HepG2 cells, the deletion of *SLC35A5* did not significantly alter glycosylation. The SLC35A5 protein formed homomers as well as heteromers with other members of the SLC35A protein subfamily [92,98].

In the fruit fly *Drosophila*, a homolog of *SLC35A4* and *SLC35A5*, *senju* (CG14040), encodes a UDP-Gal-specific transporter [99]. In *senju* mutants, the reduction of Gal-containing glycans resulted in the hyperactivation of immune responses via the Toll signaling pathway in the absence of immune challenges [99].

3. SLC35B Subfamily

The SLC35B subfamily comprises four member genes. Due to the high homology of these members with the UDP-Gal transporter (UGT, SLC35A2), they were initially considered to be putative NSTs. Since the first identification of SLC35B2 as a PAPS transporter, studies have revealed a diverse array of their substrate specificity, including ATP and PAPS. However, the functions and substrate specificities of some members in this group have not yet been fully elucidated.

3.1. SLC35B1

SLC35B1 is proposed to act as a transporter, facilitating the import of UDP-GlcUA into the ER. This process contributes to glucuronidation by providing substrate for UDP-glucuronosyltransferases [100,101]. Additionally, recent studies have demonstrated that SLC35B1 functions as an ATP/ADP exchanger within the ER and is involved in protein folding and ER quality control (ERQC) [102,103].

In 1996, Ishida et al. first reported the sequence of human SLC35B1 as a putative NST with unknown function and named it UGT-related protein 1 (UGTrel1) [9]. The *SLC35B1* gene is conserved in various eukaryotic species, including yeast, nematode, plant, and fruit fly. Yeasts have highly homologous genes of human *SLC35B1*, namely *hut-1*. The overexpression of *hut-1* in *S. cerevisiae* and *S. pombe* resulted in increased galactosyl modification, and the proteins exhibited UDP-Gal and UDP-Glc transport activity [104,105]. The function of HUT-1 is involved in protein folding in the ER under stress conditions, although it is not essential for cell growth under normal conditions [105]. In addition, *ce*HUT-1 in the *C. elegans* is involved in maintaining ER homeostasis and is essential for its development [106]. The *cehut-1* deletion mutant worms exhibited larval growth defects and lethality with disrupted intestinal morphology. Of greater significance, the lethality and the ER stress phenotype of the mutant were rescued by the introduction of the human *SLC35B1* gene [106]. In *Drosophila*, MEIGO (CG5802) is an ER-resident protein that regulates ER folding capacity and protein *N*-glycosylation. MEIGO modulates neuronal dendrite targeting specificity by regulating the protein level and *N*-glycosylation of ephrin, a regulator of axon guidance [107]. Moreover, MEIGO is involved in regulating the dendrite targeting of projection neurons by modulating the amount and localization of cell surface receptors, including Toll-6 [108].

In human cells, Kobayashi et al. reported that the SLC35B1 protein exhibits counter-transport activity of UDP-GlcUA:UDP-GlcNAc in the ER membrane [100]. Ondo et al. proposed that SLC35B1 is a principal transporter for the translocation of UDP-GlcUA into the ER, thereby contributing to glucuronidation through the delivery of substrate for UDP-glucuronosyltransferases [101]. In contrast, Klein et al. recently demonstrated that human SLC35B1 functions as an ATP/ADP exchanger in the ER membrane and plays a role in ERQC and protein folding [102]. The protein, designated AXER, was proposed to provide ATP to BiP, a molecular chaperone in the ER [102]. Schwarzbaum et al. reported that SLC35B1 did not transport any mononucleotides or nucleotide sugars directly [103]. Furthermore, they identified di- and tri-nucleotides as potential suitable counter-substrates for the ATP transport process, in addition to ATP/ADP exchange. The researchers proposed that the reduction in UDP-GlcUA-dependent glucuronosyltransferase activity observed in the ER lumen following the knockdown of *SLC35B1* might be attributable, at least in part, to an impaired UDP export mechanism [103].

3.2. SLC35B2

The *SLC35B2* gene encodes a protein that transports PAPS from the cytosol into the Golgi apparatus [109]. Impairment of its function results in a severe autosomal recessive form of chondrodysplasia (SLC35B2-CDG) [110].

PAPS is a high-energy sulfate donor substrate for enzymes called sulfotransferases, which catalyze sulfation reactions by transferring sulfate groups from PAPS to acceptor molecules. Sulfation is an essential modification for various biomolecules, including proteo-

glycans, glycoproteins, glucolipids, and protein tyrosine residues, and regulates numerous biological processes of the cells. PAPS is synthesized from ATP and inorganic sulfate through a series of enzymatic reactions in the nuclear and cytosol. As sulfotransferases for proteins, glycoproteins, and proteoglycans are localized in the Golgi lumen, the presence of saturated PAPS transporters in the Golgi apparatus has long been postulated in mammalian cells [3,111–114].

In 2003, Kamiyama et al. first cloned the cDNA of human *SLC35B2* and identified its substrate specificity, tissue distribution, and functions [109]. The SLC35B2 protein, which they termed PAPST1, is a PAPS-specific transporter with a K_m value of 0.8 μM and no transport activity for nucleotide sugars. SLC35B2 is found to be localized to the Golgi apparatus and is expressed ubiquitously in human organs [109]. Furthermore, its single *Drosophila* ortholog, SLALOM (SLL, CG7623), was identified as a PAPS-specific transporter with a K_m value similar to that of human SLC35B2. The SLL protein plays a role in sulfating the GAG chain of HS, and its functionality is essential for viability [109]. Lüders et al. independently reported that the *Drosophila sll* gene encodes a PAPS transporter [115]. *Drosophila sll* mutants exhibited segment polarity defects as a result of abnormalities in multiple signaling pathways, including Wingless and Hedgehog [115]. In *C. elegans*, an *SLC35B2* ortholog, *pst-1*, has also been identified as a gene that encodes a PAPS transporter and demonstrated to be essential for viability and involved in HS sulfation [116].

It is well known that the sulfated state of GAGs is a key factor in determining the function of PGs [117]. PAPS synthesis and transport are essential for the sulfation process. The initial step involves the transport of sulfate ions into the cell by sulfate transporters. This is followed by the conversion of the sulfate ion to an activated sulfate donor, PAPS, by PAPS synthases. The subsequent step involves the translocation of PAPS from the cytosol into the Golgi apparatus by PAPS transporters. Finally, sulfotransferases transfer sulfate from PAPS to GAGs (Figure 4). In humans, it is known that anomalies in the PAPS synthesis cause a range of dysplasias. SLC26A2 (DTDST) is a plasma-membrane sulfate transporter that is responsible for four different osteochondrodysplasias: diastrophic dysplasia (DTD) [118], achondrogenesis type IB [119], atelosteogenesis type II [120], and multiple epiphyseal dysplasia (MED) [121]. DTD is a disease that is characterized by clinical features of dysplasia, including dwarfism, spinal deformation, and abnormalities of the joints [118]. In addition, it has been demonstrated that mutations in the human PAPS synthase 2 (*PAPSS2*) gene are associated with a specific form of spondyloepimetaphyseal dysplasia (SEMD) [122]. In a study using zebrafish, Wiweger et al. reported that the mutation of *SLC35B2* ortholog *pinscher* (*pic*) resulted in defective sulfation of GAGs and other molecules and was potentially involved in skeletal dysplasia [123,124]. The homozygote *pic* mutant displayed a complete absence of sulfation of proteoglycans in the ECM and other sulfated molecules. Furthermore, the mutant displayed dwarfism and severe cartilage and bone defects that closely resembled those observed in human skeletal dysplasia, as well as pronounced ultrastructural abnormalities [123].

In 2022, Guasto et al. first reported that functional impairment of human SLC35B2 causes a severe autosomal recessive form of chondrodysplasia (SLC35B2-CDG) [110]. They identified homozygous variants in *SLC35B2* that cause a novel syndromic chondrodysplasia with severe intellectual disability and hypomyelinating leukodystrophy in two patients. The loss-of-function variants in *SLC35B2* resulted in decreased CS sulfation due to decreased gene expression and protein mislocalization of SLC35B2 [110].

It is notable that patients with chondrodysplasia and biallelic *SLC35B2* variants exhibit neurological features, including a severe psychomotor delay and a hypomyelinating leukodystrophy with thin corpus callosum [110]. It is known that sulfated proteoglycans play a critical role in the development of the nervous system [125,126]. In *C. elegans*, the *SLC35B2* ortholog *pst-1* is essential for neuronal connectivity and specific aspects of nervous system development [116]. The *pst-1* mutants exhibited highly specific neuronal defects in the formation of collateral axonal branches and motor synapses. These defects were correlated with reduced complexity of sulfation patterns in HS [116]. Shimazu et al. reported

that *dsm-1* (D-serine modulator-1), the rat ortholog of *SLC35B2*, is predominantly expressed in the forebrain and involved in the translocation of D-serine, an endogenous co-agonist for the N-methyl-D-aspartate (NMDA) receptor [127]. Furthermore, Uezato et al. proposed the potential involvement of human SLC35B2 in the pathophysiology of bipolar disorder and schizophrenia [128]. They identified significant associations between single nucleotide polymorphisms (SNPs) in the *SLC35B2* and these disorders. The mRNA expression of *SLC35B2* was found to be significantly reduced in the postmortem dorsolateral prefrontal cortex of bipolar disorder patients, whereas no change was observed in schizophrenia [128].

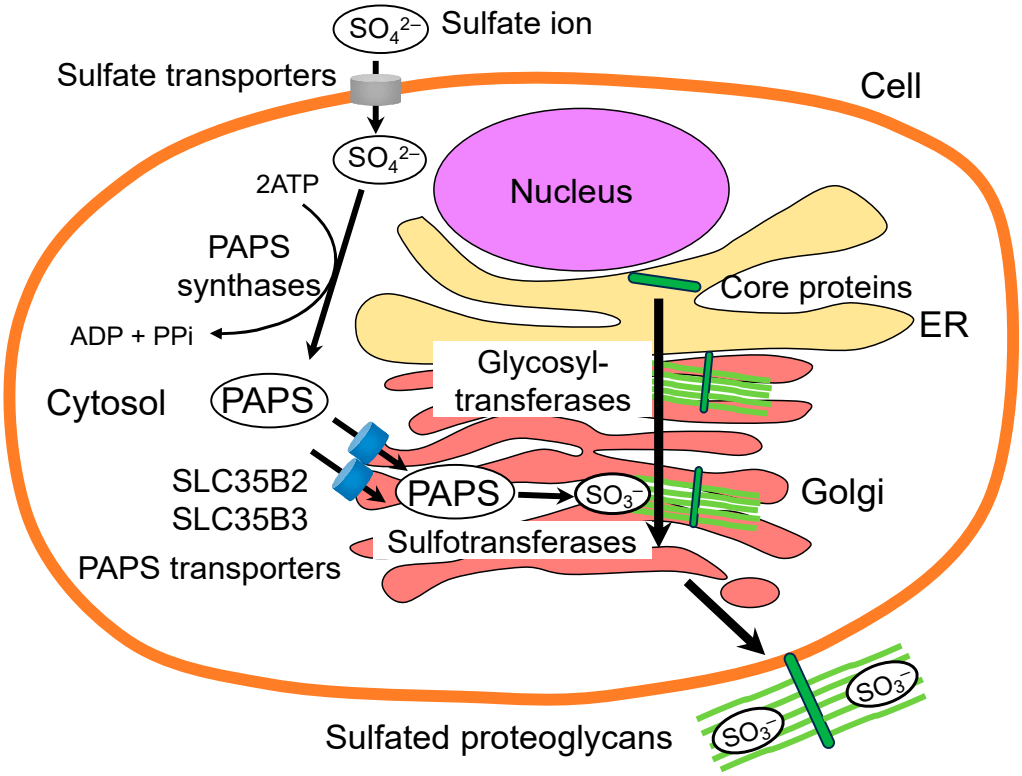

Figure 4. The role of PAPS transporters in the sulfation of proteoglycan GAGs. PAPS is utilized as a universal sulfate donor for the sulfation modification. PAPS is synthesized in the cytosol or nucleus with ATP by PAPS synthases. Subsequently, PAPS transporters translocate PAPS from the cytosol into the Golgi lumen, where the sulfotransferases are localized. Sulfotransferases transfer sulfate from PAPS to the defined positions on the sugar residues of GAGs.

A number of studies have indicated that SLC35B2 is associated with cancer progression. Kamiyama et al. demonstrated that SLC35B2 plays a role in the proliferation of colorectal carcinoma cells by controlling their sulfation status [129]. In the colorectal carcinoma tissues, the expression of SLC35B2 was increased in fibroblasts in the vicinity of invasive cancer cells. The silencing of PAPS transporter genes resulted in a reduction in FGF signaling and the proliferation of colorectal DLD-1 cells [129]. Chim-ong et al. reported that the upregulation of SLC35B2 serves as a prognostic biomarker for breast cancer, and its expression is associated with a poor prognosis of invasive ductal breast carcinoma [130].

The function of SLC35B2 has also been implicated in tyrosine sulfation [131], a post-translational modification that regulates a variety of cellular functions [132]. High expressions of *SLC35B2* and tyrosylprotein sulfotransferase 2 (*TPST2*) were found to be correlated with poor survival rates among patients diagnosed with pancreatic ductal adenocarcinoma [133]. Furthermore, the knockdown of *SLC35B2* or *TPST2* expression was observed to attenuate the growth and metastasis of pancreatic ductal adenocarcinoma cells [133]. In hepatocellular carcinoma, oxidative stress has been shown to upregulate *SLC35B2* expression and increase tyrosine sulfation of SAV1, a scaffold protein involved in the Hippo

signaling pathway [134]. The sulfation of SAV1 resulted in the subsequent inactivation of Hippo signaling, which in turn fostered the growth of hepatocellular carcinoma cells [134].

3.3. SLC35B3

In 2006, Kamiyama et al. identified human SLC35B3 as another PAPS transporter and named it PAPST2 [135]. Similar to SLC35B2, the SLC35B3 protein exhibited Golgi localization, while it was highly expressed in the colon, where *SLC35B2* is less expressed. The overexpression of the SLC35B3 protein in the HCT116 colon cancer cell line resulted in an increase in PAPS transport activity [135]. In human colorectal carcinoma DLD-1 cells, RNA interference (RNAi) of either *SLC35B2* or *SLC35B3* genes resulted in a reduction in the level of sulfation of cellular proteins and a suppression of cell proliferation [129]. Furthermore, both SLC35B2 and SLC35B3 have been demonstrated to play a role in the maintenance and differentiation of mouse embryonic stem cells [136]. These observations indicate that SLC35B3 may serve a redundant function to SLC35B2 in sulfation modification.

SLC35B3 has a single *Drosophila* ortholog gene (*dpapst2*, CG7853), which was identified to encode a PAPS-specific transporter with a K_m similar to that of the human SLC35B3 [137]. *Drosophila dpapst2* exhibited a similar expression pattern to *Drosophila sll*, an ortholog of the human *SLC35B2* gene, although *dpapst2* showed low levels of expression in most tissues. Unlike *sll*, RNAi-mediated knockdown of the *dpapst2* gene resulted in a weak phenotype. However, it genetically interacted with genes involved in HS synthesis during wing or eye formation [137]. In contrast, the *C. elegans* PST-1 (SLC35B2 ortholog) and PST-2 (SLC35B3 ortholog) proteins have distinct and non-redundant functions under physiological conditions, despite their similar PAPS transport activities in the Golgi apparatus [116]. The *pst-1* deletion mutant exhibited defects in cuticle formation, post-embryonic seam cell development, vulval morphogenesis, cell migration, and embryogenesis, whereas the *pst-2* mutant exhibited a wild-type phenotype. These *C. elegans* PAPS transporters exhibited distinct tissue distributions and subcellular localizations, and the phenotypes of double mutants of these genes were similar to those of the *pst-1* single mutant [138].

3.4. SLC35B4

SLC35B4 was initially reported as a human gene homologous to yeast *Yea4*, a gene for an ER-resident UDP-GlcNAc transporter required for cell wall chitin (poly β1,4-GlcNAc) synthesis in *S. cerevisiae* [139].

In 2005, Ashikov et al. identified the human SLC35B4 protein as a bifunctional transporter with specificity for UDP-Xyl and UDP-GlcNAc [140]. They showed that SLC35B4 is localized to the Golgi apparatus and proposed a role in the delivery of substrates for proteoglycan synthesis [140]. However, subsequent studies have reported that endogenous SLC35B4 is also localized to the ER [63,141], and that its C-terminal dilysine motif (KDSKKN) is critical for ER localization [142]. In the HepG2 cell line, knockout of the *SLC35B4* gene did not affect the major UDP-Xyl- and UDP-GlcNAc-dependent glycosylation pathways [142]. Moreover, studies have indicated that SLC35B4 also transports UDP-GlcUA, in addition to UDP-Xyl and UDP-GlcNAc. Kobayashi et al. showed that both SLC35B1 and SLC35B4 could transport UDP-GlcUA via UDP-GlcUA:UDP-GlcNAc countertransport in the ER membrane [100,101]. The expression of *SLC35B4* in human liver tissues was found to be significantly lower than that of *SLC35B1*. This indicates that SLC35B4 may play only a minor role in the supply of UDP-GlcUA [101].

In *Drosophila*, an SLC35B4 homolog protein, EFR (CG3774), is found to be capable of transporting GDP-Fuc in addition to UDP-GlcNAc and UDP-Xyl [143]. EFR was observed to localize specifically to the ER and demonstrated functional redundancy with GFR, a GDP-Fuc transporter homologous to human SLC35C1, despite their different cellular localizations [143]. However, human SLC35B4 lacks both GDP-Fuc transport activity and the ability to complement GDP-Fuc transporter-deficient fibroblast cells [140].

A number of studies have indicated a possible association between the *SLC35B4* gene and both obesity and type 2 diabetes mellitus [141,144–146]. In humans, an SNP in the

SLC35B4 gene (rs1619682) has been identified that is significantly associated with waist circumference [144]. Moreover, an elevated *SLC35B4* expression in subcutaneous adipose tissue was observed in obese humans [146]. A quantitative trait locus analysis of congenic mouse strains identified that *Slc35b4* is a regulator of obesity, insulin resistance, and gluconeogenesis in mice [145]. A reduction in hepatic *Slc35b4* expression was associated with decreased gluconeogenesis in the liver, which may contribute to hepatic insulin resistance [145]. Wex et al. reported that SLC35B4 acts as an inhibitor of gluconeogenesis in response to glucose stimulation [141]. The expression of SLC35B4 protein was increased by glucose stimulation, while the knockdown of *SLC35B4* resulted in a decrease in the expression of several proteins implicated in the pathogenesis of diabetes, including HSP60, which is known to have *O*-GlcNAc modification [147]. The researchers postulated that the uptake of UDP-GlcNAc into the ER and Golgi apparatus by SLC35B4 reduces *O*-linked glycosylation in the cytosol or nuclear by depleting the substrate for the glycosyltransferases, thereby leading to a decrease in glucose production [141].

4. SLC35C Subfamily

The SLC35C subfamily comprises two members, SLC35C1 and SLC35C2. SLC35C1 is a GDP-Fuc transporter, while SLC35C2 is a putative GDP-Fuc transporter. Fuc is a terminal residue widely found in *N*- and *O*-glycans, and GDP-Fuc is a nucleotide sugar that acts as a donor substrate for fucosyltransferases. Defects in the GDP-Fuc transporter are known to cause an inherited recessive disorder, leukocyte adhesion deficiency type II (LADII, currently SLC35C1-CDG) [148,149]. Mice lacking *Slc35c1* exhibit a phenotype similar to that observed in human LAD II patients [150,151].

4.1. SLC35C1

SLC35C1 encodes a Golgi-localized GDP-Fuc transporter. In mammalian cells, GDP-Fuc is synthesized by two pathways in the cytosol. The de novo pathway produces GDP-Fuc from L-Man, and the salvage pathway uses exogenous or recovered L-Fuc via lysosomal degradation of glycoconjugates [152–154]. Subsequently, the synthesized GDP-Fuc is translocated from the cytosol into the Golgi lumen, where the fucosyltransferases are localized. The existence of a Golgi GDP-Fuc transporter has long been suggested, and the protein has been partially purified from rat liver Golgi membranes [155]. The identification of the GDP-Fuc transporter was achieved in 2001 as the gene responsible for the human hereditary recessive disorder, LADII [150,151].

LADII (CDG-IIc, currently SLC35C1-CDG) is a disorder that is characterized by a deficiency of fucosylated glycoconjugates on proteins. Individuals with this disorder exhibit features of severe mental retardation, slow growth, and facial and skeletal dysplasia. Additionally, they suffer from immunodeficiency and recurrent infections due to reduced leukocyte adhesion caused by the absence of fucosylated selectin ligands on leukocytes. In 1999, Lübke et al. demonstrated that LADII is caused by a generalized fucosylation defect resulting from impaired GDP-fucose transport into the Golgi apparatus [156]. Subsequently, two independent research groups reported in 2001 that *SLC35C1* encodes a GDP-Fuc transporter and that its mutations are responsible for LADII [148,149]. Lübke et al. cloned *SLC35C1* cDNA by complementation of the fucosylation defect in skin fibroblasts from LADII patients and verified its GDP-fucose transport activity. They identified two missense mutations in *SLC35C1* in the patients and classified the disease as a new type of CDG [148]. Lühn et al. also reported that *SLC35C1* encodes a Golgi-localized GDP-fucose transporter protein [149]. The LADII patient had an R147C amino acid change in the conserved fourth transmembrane region of the SLC35C1 protein. The *SLC35C1* gene was conserved in diverse species, and its *C. elegans* ortholog could restore fucosylation in the fibroblast cells derived from the LADII patient. In contrast, overexpression of the mutant protein from the LADII patient could not rescue its fucosylation defects [149]. Subsequently, several mutations in *SLC35C1* have been identified in LADII patients [157–162]. Helmus et al. classified *SLC35C1* mutations in LADII patients into two groups [163]. Patients in one

group had single amino acid substitutions that only affected its transport function, and another group lost two important regions of the protein, causing defects in both function and Golgi localization [163].

The existence of SLC35C1-independent GDP-Fuc transport pathways in the Golgi apparatus has been discussed. It is known that high-dose oral Fuc supplementation partially rescues the symptoms of certain types of LADII patients [158,164,165]. Lübke et al. demonstrated that Fuc supplementation in the culture medium of fibroblasts from LADII patients results in restoration of fucosylation [148]. Furthermore, LADII patient fibroblasts did not exhibit impaired protein *O*-fucosylation, including on Notch proteins, although fucosylation on *N*-linked glycans was severely reduced [165]. Hellbusch et al. reported that *Slc35c1* knockout mice exhibited reduced fucosylation and abnormalities such as growth retardation and impaired lymphocyte assembly and adhesion, which are similar to those observed in human LADII patients [150,151]. As in human LADII patients, oral supplementation of Fuc ameliorated the fucosylation defect in *Slc35c1* knockout mice. Nevertheless, the elimination of the *Slc35c1* gene did not result in any notable defects in Notch signaling during development [150]. In addition, neither LADII patients nor *Slc35c1* knockout mice exhibit alterations in T cell development, which is dependent on Notch signaling.

Notch signaling is a conserved pathway in animals that is involved in a multitude of biological processes, including embryonic development, cell differentiation, and cell proliferation [166,167]. The *O*-fucosylation of epidermal growth factor-like (EGF) tandem repeats in the extracellular domain of Notch is essential for Notch protein folding and its cell surface presentation. In mice, targeted mutation of the protein *O*-fucosyltransferase 1 (*Pofut1*) gene leads to global Notch signaling defects and causes mid-gestation embryonic lethality [168]. In *Drosophila*, the removal of the *O*-fucosyltransferase 1 (*ofut1*) gene results in global Notch signaling defects [169,170]. In contrast, the *Drosophila* null mutants of *gfr* (CG9620), an *SLC35C1* ortholog gene, exhibit only mild Notch signaling defects [171], although the cDNA can recover the defects in GDP-fucose transport in fibroblast cells from the LADII patient [171,172]. Skurska et al. reported that fucosylation was significantly reduced but not completely abolished in the *SLC35C1*-deficient cell lines [173]. Supplementation with high concentrations of Fuc restored fucosylation of *N*- and *O*-glycans in the *SLC35C1*-deficient cells. The SLC35C1-dependent pathway appears to primarily use GDP-Fuc derived from the de novo pathway, whereas the SLC35C1-independent pathway preferentially uses GDP-Fucose derived from the salvage pathway [173].

4.2. SLC35C2

SLC35C2 is closely related to the GDP-Fuc transporter SLC35C1 and has been proposed to be a putative GDP-Fuc transporter. However, the function and substrate specificity of the protein remain unclear.

SLC35C2 was initially identified as a gene that is overexpressed in ovarian cancer (*OVCOV1*) [174]. In 2010, Lu et al. reported that SLC35C2 promotes Notch1 fucosylation and is required for optimal Notch signaling in cultured mammalian cells [175]. SLC35C2 is shown to localize predominantly to the Golgi apparatus, but a small subset is found in the ER and the ER-Golgi intermediate compartment. Lu et al. proposed that SLC35C2 is a potential transporter specifically required for *O*-fucosylation of certain proteins, including the Notch receptor [175].

However, the *Slc35c2* null mice were viable and fertile and exhibited no evidence of defective Notch signaling during skeletal or T cell development [176]. Furthermore, the deletion of both the *Slc35c1* and *Slc35c2* genes did not result in any defects in Notch signaling or Notch1 afucosylation [176]. Furthermore, Skurska et al. observed that *SLC35C1* and *SLC35C2* double knockout HEK293T cells exhibit fucosylated glycans that are comparable to those in *SLC35C1* single knockout cells [173]. SLC35C2 may serve as a non-redundant GDP-Fuc supplier for the fucosylation of *N*- and *O*-glycans in the Golgi lumen and may also exist as an additional GDP-Fuc transport pathway in the mammalian Golgi membrane [5,173].

In a study, Gao M. et al. reported that SLC35C2 is a specific transporter for the uptake of CDyB (Compound of Designation yellow for B cell), a small molecule probe used for the selective detection of live B lymphocytes [177]. The knockout of the SLC35C2 transporter eliminated the ability of target cells to internalize the molecule into the ER or Golgi apparatus. Moreover, SLC35C2 expression was found to be positively correlated with the B cell maturation process, whereas it was not involved in the development of T and NK cells [177].

5. SLC35D Subfamily

The SLC35D subfamily comprises four member genes. Among them, *SLC35D1* and *SLC35D2* are closely related and encode multisubstrate-specific transporters involved in GAG synthesis. Both *C. elegans* and *Drosophila* have single corresponding genes encoding for UDP-sugar transporters, which are involved in proteoglycan synthesis and essential for development [178–181]. It is known that loss-of-function mutations in the *SLC35D1* gene are associated with Schneckenbecken dysplasia (SLC35D1-CDG) [182].

5.1. SLC35D1

SLC35D1 is a multisubstrate-specific transporter for UDP-GalNAc, UDP-GlcNAc, and UDP-GlcUA [183,184]. As these nucleotide sugars are substrates for GAG synthesis, SLC35D1 has been considered to be essential for the production of proteoglycans and skeletal development. Loss-of-function mutations in this gene are responsible for the human disorder known as Schneckenbecken dysplasia (SLC35D1-CDG) [182].

In 2001, Muraoka et al. first reported the *SLC35D1* gene as UDP-Gal transporter-related 7 (UGTrel7) and identified that it encodes a transporter for UDP-GalNAc and UDP-GlcUA [183]. Subsequently, the researchers reported that SLC35D1 also transports UDP-GlcNAc via an UDP-sugar/UDP-sugar antiport mechanism [184]. SLC35D1 protein shows an ER localization in mammalian cells [183,185], suggesting a potential role in glucuronidation via the supply of UDP-GlcUA into the ER lumen, where glucuronosyltransferases are localized [186–188]. Furthermore, SLC35D1 can provide the donor substrates for the synthesis of the repeating disaccharide unit of CS, namely UDP-GlcUA and UDP-GalNAc [184], although the elongation of repeating disaccharides of GAG chains occurs within the Golgi lumen [189,190] (Figure 5).

In 2007, Hiraoka et al. demonstrated that SLC35D1 plays a critical role in CS synthesis in cartilage and is indispensable in skeletal development in mice and humans [182]. The *Slc35d1*$^{-/-}$ homozygous knockout mice exhibited a skeletal dysplasia with severe shortening of limbs and facial structures, as well as neonatal lethality. The *Slc35d1*$^{-/-}$ mice also exhibited hypoplastic craniofacial bones, vertebral bone flattening, longitudinally short ilia, and extremely short long bones. Moreover, epiphyseal cartilage in *Slc35d1*$^{-/-}$ mice showed a decreased proliferating zone with round chondrocytes, scarce matrices, and reduced proteoglycan aggregates. The immunohistological examination of the epiphyseal cartilage in the mutant mice revealed a markedly reduced content of CS. The production of short, sparse CS chains due to a defect in CS biosynthesis resulted in the disorganization of a functional ECM in epiphyseal cartilage [182].

The researchers also revealed that loss-of-function mutations of *SLC35D1* are associated with Schneckenbecken dysplasia in humans [182]. Schneckenbecken dysplasia is an autosomal recessive skeletal dysplasia classified as a severe spondylodysplastic dysplasia group disease. The disease is characterized by the presence of snail-shaped hypoplastic iliac bones, limbs with extremely short, long bones, and flat vertebral bodies. These defects are associated with perinatal lethality. In two typical cases of Schneckenbecken dysplasia, three mutations were identified that were predicted to produce truncated proteins. These truncated proteins exhibited loss of function with respect to transport activity toward UDP-GalNAc, UDP-GlcUA, and UDP-GlcNAc [182]. Moreover, the skeletal and histological phenotypes observed in *Slc35d1*$^{-/-}$ mice were analogous to those observed in human patients with Schneckenbecken dysplasia.

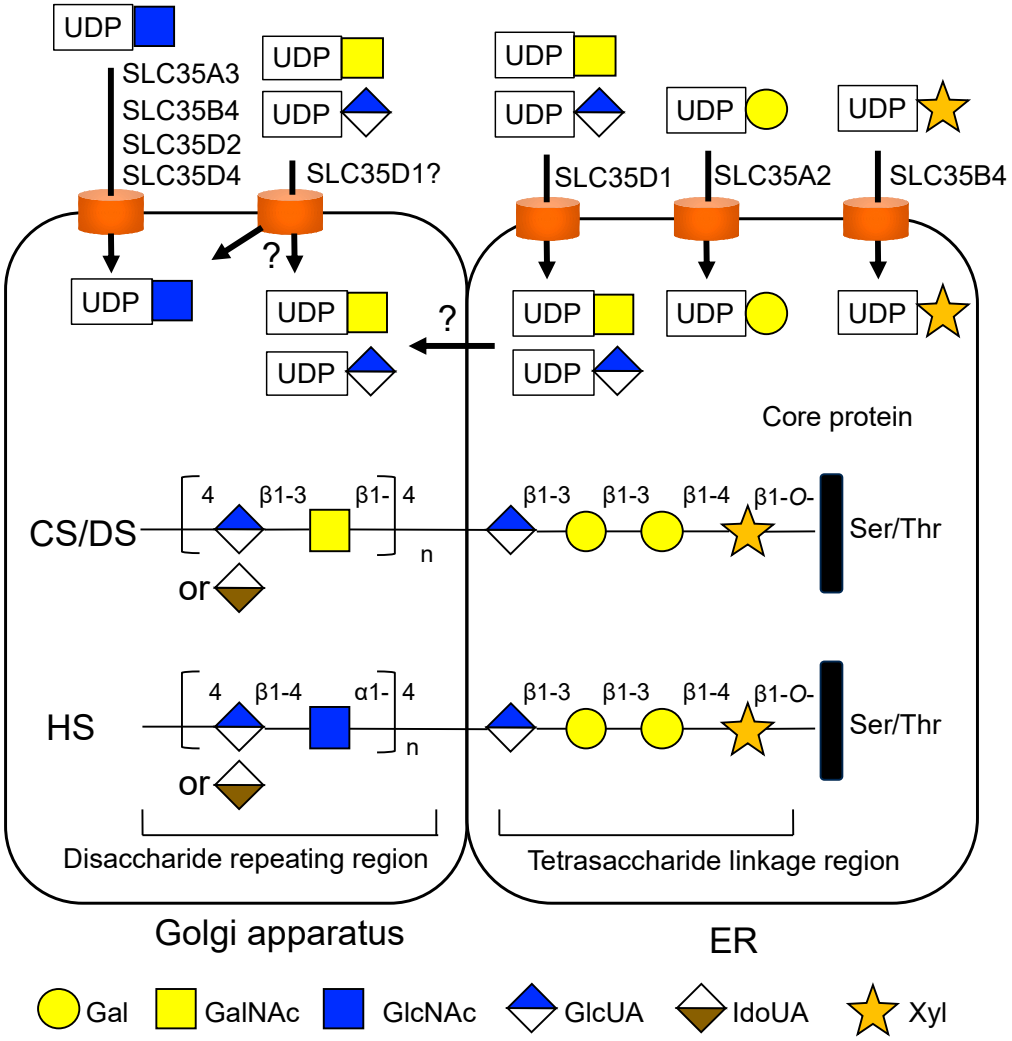

Figure 5. Potential involvement of NSTs in the synthesis of chondroitin sulfate (CS), dermatan sulfate (DS), and heparan sulfate (HS) glycosaminoglycans (GAGs). The biosynthesis of GAG is initiated by the formation of the *O*-linked tetrasaccharide structure, which is common to CS/DS and HS. CS/DS and HS contain different types of repeated disaccharide units. HS and DS contain a high content of iduronic acid (IdoUA), which is converted from glucuronic acid (GlcUA) by C5 epimerization. SLC35D1 can provide the donor substrates for the elongation of CS/DS-type disaccharide units; however, SLC35D1 is localized to the ER, and the elongation of repeating disaccharides occurs within the Golgi lumen. SLC35A3, SLC35B4, SLC35D2, and SLC35D4 can transport UDP-GlcNAc, which serves as a donor substrate for the elongation of HS-type disaccharide units.

Subsequently, several additional mutations in *SLC35D1* have been identified in patients with Schneckenbecken dysplasia [191–193]. These loss-of-function mutations of *SLC35D1* appear to be exclusively associated with Schneckenbecken dysplasia and not in other severe spondylodysplastic dysplasia-related diseases [191]. Rautengarten et al. reported that SLC35D1 acts as a general UDP-sugar transporter [194]. They observed that its hypomorphic missense variants of Pro133Leu and Thr65Pro resulted in a significant decrease in transport activity and Schneckenbecken-like dysplasia. The researchers also proposed that SLC35D1 may have an expanded role beyond CS biosynthesis, participating in a variety of important glycosylation reactions occurring in the ER [194].

5.2. SLC35D2

In 2004, Suda et al. identified human *SLC35D2* as a *Drosophila frc* homolog and named it *hfrc1* (human fringe connection 1) [185]. SLC35D2 is closely related to human

SLC35D1, with 54.3% identity of their amino acid sequences. However, in contrast to SLC35D1, SLC35D2 was found to localize to the Golgi apparatus [185]. The SLC35D2 protein exhibited multi-substrate transport activity towards UDP-GlcNAc, UDP-Glc, and GDP-Man [185]. However, the GDP-Man transport activity was only observed in the yeast expression system, which contains a high level of the antiport molecule GMP in the Golgi apparatus but not in the mammalian cells [185].

Both *SLC35D1* and *SLC35D2* mRNAs are expressed in all adult and fetal tissues [18,185]. The tissue distribution of *SLC35D2* is highly similar to that of *SLC35D1*, while the expression level of *SLC35D2* is consistently higher than that of *SLC35D1* in most tissues [185]. Ishida et al. independently reported that SLC35D2 can transport UDP-GlcNAc to the Golgi apparatus [195]. Sesma et al. demonstrated that overexpressed SLC35D2 protein is localized to the Golgi apparatus in human bronchial epithelial cells and enhances the expression of cell surface GlcNAc-rich glycans, as well as the cellular release of UDP-sugar signaling molecules [196]. Suda et al. also demonstrated that overexpression of the *SLC35D2* gene in HCT116 cells modulates cell surface HS levels by providing UDP-GlcNAc for GAG synthesis in the Golgi lumen [185]. In MDA-MB-231 breast cancer cells, the expression of *SLC35D1* and *SLC35D2* affected breast cancer cell behavior in conjunction with the expression of glycosyltransferases for HS synthesis [197]. However, unlike *SLC35A3*, no disease associated with *SLC35D2* impairment has yet been identified.

SLC35D2 also exerts a UDP-Glc transport activity in the Golgi apparatus [185]. The Golgi-localized UDP-Glc transporter has been postulated to be involved in glycosylation processes in the Golgi apparatus, such as the addition of *O*-linked glucose [198]. Gehre et al. demonstrated that human SLC35D2 exhibits UDP-Glc transport activity in glycogen-rich vacuoles [199]. In cells infected with the pathogen *Chlamydia trachomatis*, SLC35D2 was recruited to the inclusion membrane and translocated UDP-Glc into the lumen for de novo glycogen synthesis of the bacteria. The knockdown of the *SLC35D2* gene resulted in a significant reduction of intraluminal glycogen staining [199]. However, because the reduction was only partial, the researchers proposed the existence of other UDP-Glc transporter(s) in the Golgi apparatus. Indeed, UDP-Glc transport activity has also been found in another subfamily member, SLC35D3 [200] (see the next section).

In both *Drosophila* and *C. elegans*, the human SLC35D1 and SLC35D2 genes share a single highly homologous gene, namely the *fringe connection* (*frc*, CG3874) and *sqv-7*, respectively. The *sqv-7* gene encodes a multisubstrate-specific transporter for UDP-Gal, UDP-GalNAc, and UDP-GlcUA [179]. In *C. elegans*, *sqv-7* mutants exhibit defects in both chondroitin and HS biosynthesis and display the squashed vulva (sqv) phenotype, which is characterized by a defect in epithelial invaginations of the vulva during early embryogenesis [178]. In *Drosophila*, the *frc* gene encodes a multisubstrate transporter that transfers UDP sugars, including UDP-GlcUA, UDP-GlcNAc, and UDP-Xyl, from the cytosol into the Golgi lumen [180,181]. The *frc* mutant embryos display defects in Wingless, Hedgehog, and FGF signaling [181], as well as a Notch signaling defect [180]. It has been proposed that FRC and SLC35D1 utilize UDP-sugars and UDP as well as UMP as antiport molecules for countertransport [184].

5.3. SLC35D3

SLC35D3 has been identified as a UDP-Glc transporter [200] and proposed to be involved in platelet dense granule formation, synaptic vesicular neurotransmitter transport, and adipocyte differentiation. SLC35D3 has been proposed to be involved in the pathogenesis of some recessive metabolic disorders, including Hermansky–Pudlak syndrome (HPS) and Chediak–Higashi syndrome (CHS). HPS is a rare genetic disorder that is characterized by albinism, which is the absence of pigment in the skin, hair, and eyes. It is also associated with bleeding problems due to a deficiency of the platelet δ-storage pool, which is caused by malformation of platelet dense granules and pigment cell melanosomes [201].

In 2007, Chintala et al. first reported that mutation of *Slc35d3* causes platelet dysfunction by regulating the content of platelet dense granules in *Roswell* (*ros*) mutant mice [201].

The *ros* is a mouse model of HPS and CHS in which the lysosome-related organelles, including dense granules, are dysfunctional. Due to its genetic heterogeneity, several candidate genes have been identified in both human HPS and mouse models [202]. In hypopigmentation mouse models, the *ashen* strain exhibits typical features of HPS, including prolonged bleeding time accompanied by a substantial platelet-dense granule deficiency due to a mutation on the *Ashen* gene (*Rab27a*), which is a critical gene for organelle-specific protein trafficking in melanocytes and platelets [203]. The *ros* mutant mice possess an additional mutation on the *Slc35d3* gene due to an insertion of an IAP element within exon 1. This mutation results in a possible alteration of membrane topology by amino acid substitutions at the N-terminus [201].

Chintala et al. demonstrated that the platelet-dense granule defect observed in $ros^{-/-}$ mice was effectively reversed in transgenic mice that expressed the normal *Slc35d3* gene. However, the effect was specific to platelet-dense granules and had no effect on melanosomes (i.e., pigmentation defect) or lysosomes. Furthermore, no *SLC35D3* mutations were identified in 22 HPS patients who presented with albinism and prolonged bleeding symptoms of unknown etiology [201]. In a study using $ros^{-/-}$ mutant mice, Meng et al. observed that the delivery of SLC35D3 protein from early endosomes of megakaryocytes is required for platelet dense granule biogenesis, which is differentially defective in HPS models [204]. Epitope-tagged and endogenous SLC35D3 was predominantly localized to early endosomes and subsequently delivered to nascent, dense granules. Alternatively, it may function in dense granule biogenesis directly from early endosomes [204].

In 2021, Qian et al. identified that SLC35D3 transports UDP-Glc as a major substrate by combining metabolite profiling with a radiolabeled substrate transport assay [200]. They also found that SLC35D3 is localized to synaptic vesicles and functions as a vesicular neurotransmitter transporter by ultrastructural analysis [200]. In the mouse brain, *Slc35d3* mRNA is highly enriched in striatonigral medium spiny neurons (MSNs) [205,206]. Its expression is restricted to dopamine receptor D1 but not D2 in the brain [207]. Zhang et al. reported that the *ros* mutant mice exhibit obesity and metabolic syndrome, as well as reduced membrane dopamine receptor D1 [207]. The mice showed impaired dopamine signaling in striatal neurons, which are involved in metabolic control in the central nervous system by regulating dopamine signaling. Additionally, the researchers identified two mutations in *SLC35D3* (K404X and insL201) in patients with metabolic syndrome. The mutations resulted in altered subcellular localization of SLC35D3 and impaired dopamine signaling in striatal neurons [207].

In humans, a locus near the sequence tagged site (STS) marker D6S1009, located in the intergenic region between *SLC35D3* (55,419 bp apart on the centromeric side) and *NHEG1* (867 bp apart on the telomeric side), has been associated with obesity or body mass index (BMI) [208–210]. Li et al. proposed that *SLC35D3* is a specific transcriptional regulatory factor during porcine intramuscular preadipocyte differentiation [211]. In porcine tissues, *SLC35D3* exhibited high expression in various tissues, including leaf fat and subcutaneous adipose tissue. Gene silencing with *SLC35D3* siRNA resulted in increased adipogenic processes in intramuscular adipocytes [211]. Wang et al. also reported that SLC35D3 can promote white adipose tissue browning and ameliorate obesity by inhibiting Notch signaling in mice [212]. They showed that white adipocyte-specific *Slc35d3* knockin protected against diet-induced obesity, whereas its knockout inhibited white adipose tissue browning and caused decreased energy expenditure and impaired insulin sensitivity. SLC35D3 directly interacted with the extracellular domain of Notch1, resulting in the accumulation of Notch1 protein in the ER and the inhibition of its transport to the plasma membrane [212].

5.4. SLC35D4

The *SLC35D4* gene, previously known as *TMEM241* (Transmembrane Protein 241, synonyms *C18orf45* or *hVVT*), has been recently added to the SLC35D subfamily. The *SLC35D4* gene encodes a UDP-GlcNAc transporter that is localized in the Golgi apparatus [213].

In 2023, Zhao et al. reported that the SLC35D4 (TMEM241) is required for the mannose-6-phosphate (Man-6P) modification of NPC2 and cholesterol transport from lysosomes [213]. This modification is necessary for the lysosomal targeting of proteins, including NPC2, which mediates cholesterol exit from lysosomes. In HeLa cells, the knockout of the *SLC35D4* gene resulted in impaired sorting of NPC2 protein, which in turn caused cholesterol accumulation in lysosomes. The SLC35D4 protein is closely related to SLC35A3, and both proteins are localized to the cis-Golgi network. Cells lacking either *SLC35A3* or *SLC35D4* exhibited a 70–80% reduction in UDP-GlcNAc content in the Golgi apparatus compared to wild-type cells. In *SLC35A3* knockout cells, Man-6P modification of total cellular proteins was also reduced, resulting in cholesterol accumulation in lysosomes. Furthermore, overexpression of *SLC35A3* rescued intracellular cholesterol accumulation and NPC2 sorting abnormalities caused by *SLC35D4* knockout. Mice deficient in *SLC35D4* exhibited cholesterol accumulation in pulmonary cells and displayed pulmonary injury and hypokinesia, indicating the crucial role of this transporter protein in maintaining lysosome homeostasis and lung function [213].

6. SLC35E Subfamily

Five genes (*E1*, *E2A*, *E2B*, *E3*, and *E4*; *E2A* is a pseudogene) belong to the E subfamily, yet neither their transport substrates nor their biological functions have been elucidated.

In a recent study, Huang et al. demonstrated that SLC35E1 plays a role in regulating zinc-ion-mediated keratinocyte proliferation [214]. They observed that SLC35E1 is enriched in the suprabasal layer of psoriasis lesions and that its expression is increased in keratinocytes of patients with psoriasis. Furthermore, *Slc35e1* knockout mice with imiquimod-induced psoriasis displayed a less severe psoriasis phenotype than wild-type mice. In keratinocytes, SLC35E1 regulates zinc ion concentrations and localization, and its deficiency inhibits the proliferation of keratinocytes. The researchers proposed that SLC35E1 promotes keratinocyte proliferation by regulating zinc levels, although they did not confirm its zinc ion transport activity [214].

7. SLC35F Subfamily

Six genes belong to the SLC35F subfamily. To date, no member of the SLC35F subfamily has been reported to be involved in nucleotide sugar transport. It has been proposed that these transporters may facilitate drug transport. In these members, SLC35F3 has been identified to have a thiamine (vitamin B1) transport activity [215]. Some of the SLC35F members have been proposed to be associated with a range of human diseases, such as hypertension [215] and neurodevelopmental disorders [216].

7.1. SLC35F1

Despite the absence of conclusive evidence regarding the function of SLC35F1, several studies have indicated that SLC35F1 may play a role in neurodevelopment and be associated with human neurodevelopmental disorders.

In humans, *SLC35F1* mRNA is highly expressed in the fetal and adult brain [18]. Farenholtz et al. reported that *Slc35f1* is highly expressed in a variety of brain structures, including the cortex, hippocampus, amygdala, thalamus, basal ganglia, and hypothalamus, in adult mouse forebrain [217]. The SLC35F1 protein is localized in the recycling endosome but not in the Golgi or ER, where the majority of NSTs are localized [217].

In 2015, Szafranski et al. reported that deletions in a chromosomal region, including the regulatory sequences of *SLC35F1* (6q22.1q22.31) are associated with pediatric epilepsy [218]. Furthermore, Di Fede et al. reported that a patient carrying a heterozygous missense variant in *SLC35F1* exhibited a phenotype similar to Rett syndrome (RTT) [216]. RTT is a severe neurodevelopmental disorder that results in psychomotor regression and the progressive development of a severe condition associated with motor, cognitive, and behavioral impairment. The patient with the *SLC35F1* mutation exhibited refractory seizures, severe intellectual disability, limited speech, and an inability to walk independently [216].

However, unlike humans, the knockout mice lacking the *Slc35f1* gene displayed no significant alterations in neurodevelopmental phenotypes [219]. Ehlers et al. reported that the elimination of *Slc35f1* in mice did not result in any significant impairment of learning and memory, nor did it have a substantial impact on brain morphology [219]. Furthermore, their neuroanatomical parameters of neuronal plasticity (as dendritic spines and adult hippocampal neurogenesis) remain unaltered [219]. The researchers presume that this discrepancy may be attributed to the difference in *Slc35f1* expression in astrocytes between mice and humans.

7.2. SLC35F2

SLC35F2 was initially identified as a lung squamous cell carcinoma-related gene *HSNOV1* (homo sapiens novel protein 1) [220]. The physiological function of SLC35F2 remains unclear. However, it has been reported that this protein is involved in the uptake of the anticancer drug YM155.

The *SLC35F2* mRNA is expressed at the highest levels in the adult salivary gland [18] and brain [221]. The *SLC35F2* transcripts were found to be highly enriched in brain microvascular endothelial cells (BMEC), suggesting a potential role in the construction of the brain endothelial cell-selective blood–brain barrier [221]. Additionally, *SLC35F2* is expressed at a high level in a variety of human cancers. A number of studies have reported that the expression and function of SLC35F2 are related to the development of malignant tumors in various cancers, including lung cancer [222,223], papillary thyroid cancer [224], bladder cancer [225], and pancreatic cancer [226].

In 2014, Winter et al. reported that SLC35F2 is a key factor in the biological function of an anticancer drug, YM155 (sepantronium bromide) [227]. YM155 is a drug that inhibits the transcription of the survivin promoter. The YM155 molecule is transported into cells via the SLC35F2 transporter, where it generates DNA damage through intercalation [227]. Winter et al. demonstrated a correlation between YM155 sensitivity and *SLC35F2* expression and its drug-importing activity in several cancer cell lines. SLC35F2 is identified as the primary determinant of YM155-mediated DNA damage toxicity [227]. Voges et al. also reported that the drug-resistant cell lines displayed decreased sensitivity to YM155, accompanied by downregulation of *SLC35F2* [228]. Neuroblastoma cells that have adapted to YM155 displayed reduced levels of survivin and SLC35F2, increased levels of a multidrug resistance transporter ABCB1, and decreased sensitivity to survivin depletion [228]. Furthermore, Nyquist et al. reported that androgen and its receptor signaling axis upregulate *SLC35F2* transcription and enhance sensitivity to YM155 in castrate prostate cancer patients. Since *SLC35F2* expression is correlated with androgen levels, high-dose androgens act in synergy with YM155 treatment by inducing *SLC35F2* expression in prostate cancer cells [229,230].

YM155 is also utilized as a stemotoxic molecule to eliminate undifferentiated human embryonic stem (ES) cells and induced pluripotent stem (iPS) cells for tumor-free cell therapy. In human ES cells lacking *SLC35F2*, the stemotoxic activity of YM155 was completely absent. The formation of hydrogen bonds involving the pyrazine ring structure is crucial for the recognition of YM155 by SLC35F2 [231]. Additionally, the high cytotoxicity of YM155 in human iPS cells is attributed to the high expression of *SLC35F2* in these cells. The knockout of *SLC35F2* with CRISPR-Cas9, or depletion with siRNAs, rendered the iPS cells highly resistant to YM155 [232].

7.3. SLC35F3 and F4

The SLC35F3 protein was shown to have thiamine (vitamin B1) transport activity. Furthermore, it has been reported that its SNPs are associated with an elevated risk of hypertension in humans [215]. SLC35F4 is a paralog of SLC35F3 with 92% sequence similarity and is proposed as a putative thiamine transporter [233].

In 2014, Zhang et al. identified that two SNPs (rs16842784 and rs17514104) at the *SLC35F3* gene are associated with high blood pressure and an increased risk of hypertension in a primary care population of North America and Western Europe [215]. The SLC35F3

protein, which exhibits high homology with the yeast Thi74 thiamine transporter, was found to exert thiamine transport activity. Individuals homozygous for the risk allele at *SLC35F3* (rs17514104 T/T) exhibited decreased erythrocyte thiamine content. Zang et al. also identified an association between a different missense variant of *SLC35F3* (rs34032258) and hypertension risk in the Chinese Han population [234]. Additionally, Seo and Choi found that a genetic variation in rs10910387 T>C and rs12135117 T>A genotypes in *SLC35F3* is associated with an increased risk for hypertension in females and males, respectively, in the Korean population [235]. In both studies, the genetic variation in *SLC35F3* was not a decisive predictor of hypertension risk, indicating that allele frequency may vary across different ethnic populations [234,235].

SNPs in the *SLC35F3* gene have also been identified as being associated with lifestyle-related diseases, including diabetes [236], obesity [237], and metabolic syndromes [238]. In 2016, Simonti et al. identified a replicating association between SNP rs12049593 in intron 2 of *SLC35F3*, which is one of the Neanderthal variants, and protein-calorie malnutrition [239]. Additionally, several studies have indicated that *SLC35F3* has been positively selected in East Asian populations [233,240,241]. Cheng et al. postulated that *SLC35F3* may have been an adaptive genetic variant in ancestral East Asian populations associated with the adaptation to eating polished grains [241]. Ma and Xu identified the adaptive haplotypes at three thiamine transporter genes, *SLC19A2*, *SLC35F3*, and *SLC35F4*, by analyzing genome data of 3823 individuals representing 223 global populations [233]. The putative adaptive haplotype, allele C of *SLC35F3* rs61824595, is likely of archaic origins. It reached a high frequency at least 10,000 years ago and has changed little in the recent 10,000 years in East Asian populations [233].

7.4. SLC35F5

SLC35F5 mRNA is expressed in a wide range of adult and fetal tissues [18]. However, the function of SLC35F5 remains poorly understood.

Some studies have indicated that SLC35F5 may be associated with the sensitivity of cancers to antitumor drugs. Matsuyama et al. reported that SLC35F5 is associated with 5-fluorouracil (5-FU) sensitivity in colorectal cancers. The expression of *SLC35F5* was significantly higher in 5-FU responding tumors than in nonresponding tumors [242]. Hao et al. proposed that SLC35F5 may be a key effector of chemoresistance-promoting activity [243]. In non-small cell lung cancer (NSCLC) cells, the upregulation of microRNA *MIR369-3p* and downregulation of *SLC35F5* expression were found to be associated with cisplatin resistance and the magnitude of malignancy of the cells. MIR369-3p regulates cisplatin chemoresistance in NSCLC cells by directly targeting the 3′ untranslated region of the *SLC35F5* gene. There was an inverse correlation between *SLC35F5* expression levels and *MIR369-3p* expression levels. Furthermore, the inhibition of miR-369-3p or the reactivation of epigenetically silenced *SLC35F5* in NSCLC cells resulted in sensitization to cisplatin treatment [243].

7.5. SLC35F6

SLC35F6 (formerly known as C2orf18 or ANT2BP) is an orphan transporter with a poorly understood function. Kashiwaya et al. reported that SLC35F6 is one of the key molecules involved in pancreatic carcinogenesis [244].

The *SLC35F6* mRNA is shown to have limited expression in normal adult organs, whereas it is highly expressed in pancreatic ductal adenocarcinoma (PDAC) cells. SLC35F6 protein is localized in the mitochondria and interacts with adenine nucleotide translocase 2 (ANT2) protein, which is involved in the maintenance of the mitochondrial membrane potential and energy homeostasis. RNAi-mediated knockdown of *SLC35F6* in PDAC cell lines resulted in the induction of apoptosis and suppression of cancer cell growth, indicating that this gene plays an essential role in maintaining the viability of PDAC cells [244].

8. SLC35G Subfamily

The SLC35G group has recently been classified as a member of the SLC35 family. At present, six member genes are known to belong to this subfamily, yet the functions of these genes remain largely unidentified.

In these members, SLC35G1 was reported to be involved in the store-operated calcium entry as a scaffold protein by interacting with stromal interaction molecule 1 (STIM1), an ER calcium sensor protein [245]. Krapivinsky et al. identified the SLC35G1 protein through its interaction ability with ORAI1, a calcium-selective plasma membrane ion channel, and named it POST (partner of stromal interaction molecule 1, previously called TMEM20) [245]. The researchers revealed that following the Ca^{2+} store depletion in the ER, the SLC35G1 protein binds to STIM1 within the ER and moves to the plasma membrane. The STIM1-POST complex results in sustained high cytosolic Ca^{2+} concentration through the activation of Orai1 and the inhibition of plasma membrane Ca^{2+} ATPase (PMCA) activity [245].

In a recent study, Wang et al. reported that the *SLC35G1* gene is a novel candidate gene for autism spectrum disorder (ASD) in the East Asian population [246]. The researchers identified nine novel ASD candidate genes from a large Chinese ASD cohort. One of these genes, *SLC35G1*, was examined in a mouse model to assess its function. Heterozygous *Slc35g1* deletion mice exhibited deficits in social interaction and increased stereotypic behaviors [246].

9. Conclusions

The study of NSTs has spanned approximately half a century. Following the first identification of NSTs in 1996, numerous studies have revealed the diverse and important functions of the transporters in this large family. The analysis of invertebrate model organisms, such as *Drosophila* and *C. elegans*, has yielded insights into the essential roles of these NSTs and PAPS transporters in glycosylation and biological functions during development. The subsequent identification of diseases associated with variations in SLC35 family genes has led to an increasing recognition of their importance in glycosylation over the past decade. Additionally, genome editing technology has enabled the generation of an extensive number of knockout mice and knockout cells, thereby facilitating a more comprehensive understanding of the functions of the SLC35 family members. Nevertheless, over half of the members belonging to the SLC35 family remain unelucidated with regard to their functional properties and transport substrates. Despite the considerable accumulation of knowledge about NSTs, several conflicting findings have been reported regarding their transport mechanisms, substrate specificities, subcellular localizations, and functions. It is anticipated that future investigations will provide further clarification of the mechanism underlying the functions of the SLC35 family transporters.

Author Contributions: Conceptualization, S.K.; investigation, S.K.; supervision, S.K. and H.S.; visualization, S.K.; writing—original draft preparation, S.K.; writing—review and editing, S.K. and H.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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