Published in final edited form as:
Mol Aspects Med. 2013 April ; 34(2-3): 620–628. doi:10.1016/j.mam.2012.05.012.

The SLC41 family of MgtE-like magnesium transporters

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Abstract

Magnesium is one of the most predominant intracellular divalent cations and is requisite to the regulation of a diverse array of cellular functions. Although accumulating data from multiple studies have begun to illuminate the critical role(s) played by Mg^{2+} transporters in pathways involved in cell signaling, metabolism, growth and proliferation, there is still a lack of understanding of the underlying molecular mechanisms that govern those various functions. In this review, we focus on the recently described SLC41 family of magnesium transporters, two members of which have been shown to mediate Mg^{2+} uptake and transport, and highlight what is known about their expression, localization, and function, as well as their roles and contributions to cellular Mg^{2+} transport.

Keywords

Transporter; MgtE; Magnesium; Solute carrier 41 (SLC41); TRPM7-deficient; membrane

1. Overview of Mg^{2+} uptake and transport

Intracellular Mg^{2+} exists at total cellular concentrations estimated to be in the range of several to tens of mM depending on the cell type (reviewed in (Romani, 2011; Romani and Scarpa, 2000b; Saris et al., 2000)). Mg^{2+} is involved in multiple functions including as an enzyme cofactor (comprising of every enzyme and signaling protein which utilizes a nucleotide triphosphate cofactor), maintenance of active conformations of macromolecules, regulation of phosphoinositide-derived second messengers, charge compensation for negatively charged groups (particularly phosphate), and regulation of various transporters and ion channels (Chien and Cambier, 1990; Eskes et al., 1998; Mandel and Goodman, 1999; Morrill et al., 1998; O'Rourke et al., 1992; Wolf and Cittadini, 1999, 2003).

There are two important features of Mg^{2+} biochemistry, which constrain how Mg^{2+} may function in biological systems. The first is the existence of a large Mg^{2+} buffering capacity of intracellular phosphometabolites (particularly ATP), such that only a small fraction of free Mg^{2+} entering the cytosol or other compartments is able to remain free in solution intracellularly. The second is the total amount of Mg^{2+} present within cells. Mg^{2+} exists

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within a cell's various intracellular compartments in millimolar total concentrations. Although the majority of this is bound in various forms, free Mg^{2+} is typically within the range of 0.3-1.0 mM. On account of these two factors, a total flux of Mg^{2+} into a cell equivalent in magnitude to that occurring acutely for example with a typical Ca^{2+} signal, will result in only negligible changes in total intracellular free Mg^{2+} (reviewed in (Romani and Scarpa, 2000a) and (Romani and Maguire, 2002)). However, it remains possible that Mg^{2+} may function as an intracellular messenger in localized regions near Mg^{2+} transporters, as has been recently suggested to occur following T-cell receptor activation (Li et al., 2011).

Over the past decade, a number of magnesium transporters and transport pathways have been molecularly identified or proposed to exist in vertebrate cells, and it is the coordinated function of these proteins and pathways that determines vertebrate cellular Mg^{2+} homeostasis (Figure 1). Members of the SoLute Carrier family 41 (SLC41A1 and A2) are prominent among the molecularly identified transporters, due to their recognized homology to the prokaryotic MgtE Mg^{2+} transporter family. SLC41A1 is thought to mediate Mg^{2+} transport across the plasma membrane, whereas SLC41A2 may mediate Mg^{2+} transport across either the plasma membrane or organellar membranes. In addition to SLC41A1 and SLC41A2, transporters that mediate and/or regulate Mg^{2+} uptake across the plasma membrane include, Transient Receptor Potential cation channel subfamily Melastatin 7 (TRPM7), Magnesium Transporter protein 1 (MagT1) and Ancient Conserved Domain Protein (ACDP) family proteins ((Deason-Towne et al., 2011; Goytain and Quamme, 2005a; Sahni et al., 2007; Schmitz et al., 2003; Sponder et al., 2010; Wabakken et al., 2003)). The TRPM7 homologue, TRPM6, is also a plasma membrane transporter, and has been linked to Mg^{2+} uptake from the gut lumen and urine for the purpose of maintaining organism-level Mg^{2+} homeostasis (Schlingmann et al., 2002; Voets et al., 2004). In conjunction with progress in the characterization of Mg^{2+} transport systems at the molecular level, physiological studies have accumulated evidence that Mg^{2+} transport is dynamically regulated, emphasizing the crucial role Mg^{2+} transport must play in eukaryotic cell function. While total cellular free ionized cytosolic Mg^{2+} concentrations remain relatively constant under all but extreme conditions of Mg^{2+} deprivation or supplementation (Romani and Maguire, 2002; Wolf et al., 2003), total Mg^{2+} contents have been shown to change acutely to a considerable extent in vertebrate cells subjected to various types of stimulation (Grubbs, 1991; Gunther and Hollriegl, 1993). Although significant alterations in Mg^{2+} transport may also occur for regulatory purposes between one or more cellular subcompartments, the regulation of intercompartmental Mg^{2+} transport has proven difficult to study due to a lack of compartment-specific probes.

2. SLC41 Mg^{2+} transporters: vertebrate representatives of the MgtE family

The SLC41 family of vertebrate magnesium transporters was first identified and characterized in 2003 (Wabakken et al., 2003) and comprises three members – SLC41A1, SLC41A2 and SLC41A3 (Table 1). Members of the SLC41 transporter family are found in all eukaryotes, and display distant homology to the prokaryotic MgtE family of Mg^{2+} transporters (Hattori et al., 2009; Hattori et al., 2007; Ishitani et al., 2008). The Transporter Classification DataBase (TCDB; Saier et al., 2009) categorizes SLC41 transporters in the MgtE family - 9.A.19, with 9.A being reserved for 'transporters of unknown biochemical mechanisms'. Comparison of the SLC41 transporters with protein databases (Pfam and NCBI), identified two domains - D1 and D2, homologous to Pfam10769, a domain found in the prokaryotic MgtE transporter (Wabakken et al., 2003). Two conserved motifs – PX_6GN and $P(D/A)X_4PX_6D$ with functional implications have also been identified in both D1 and D2 domains (Wabakken et al., 2003). Furthermore, SLC41 proteins appear to possess the same basic structural features of prokaryotic MgtE transporters: MgtE proteins create a

Mg^{2+}-selective pore via homodimerization (Hattori et al., 2007), and examination of the SLC41 topology suggests the presence of two five TM span MgtE domains, connected by a TM spanning linker. Similarly, the large N-terminal domains of prokaryotic MgtE proteins have been implicated in regulation of their Mg^{2+} transport, and the shorter N-terminal cytoplasmic domain of SLC41A1 has recently been implicated in regulation of SLC41A1 function (Hattori et al., 2009; Mandt et al., 2011).

3. SLC41A1

3.1 Expression and localization

SLC41A1 was the first member of the family to be described, and was identified using the modified Signal Sequence Trap (SST) method (Wabakken et al., 2003). High expression levels of SLC41A1 have been detected in the human heart and testis, whereas prostate, adrenal gland, skeletal muscle and thyroid have lower expression levels. Hematopoietic tissues, brain, lungs and colon displayed the weakest expression in surveys of primary tissue, although lymphoid cell lines including Tom-1 and Jurkat cells were observed to express SLC41A1 as a distinct band (Wabakken et al., 2003). SLC41A1 was initially implicated in vertebrate Mg^{2+} transport when mice that were kept on low magnesium versus normal magnesium diet for 5 days were shown to have increased *Slc41a1* mRNA expression in the kidney, colon and heart, suggesting its involvement in Mg^{2+} homeostasis (Goytain and Quamme, 2005a).

SLC41A1 protein appears to exist primarily in intracellular compartments and on the plasma membrane. An N-terminal FLAG-tagged version of the protein can be detected at the plasma membrane of HEK293 cells by confocal microscopy, an observation that has been further confirmed biochemically (Kolisek et al., 2008). Flow cytometric analysis of SLC41A1 tagged at both N and C-termini with epitope tags also demonstrates plasma membrane expression (Mandt et al., 2011).

3.2 Characterization and topology

The protein encoded by human *SLC41A1* has a predicted molecular weight of ~56kDa, and this has been well established by a number of studies (Kolisek et al., 2008; Mandt et al., 2011; Wabakken et al., 2003). Although initial studies proposed that the protein had 10 transmembrane (TM) spans, epitope tagging studies indicate that the transporter has an odd number of TM spans, most likely 11, with an N-terminus in/C-terminus out topology. In addition, our lab has shown that intracellular transport serves as a regulatory mechanism for expression of SLC41A1 on the cell surface (Mandt et al., 2011). Protein-protein interaction resulting in formation of large Multiprotein functional complexes (MPCs) have been shown to play a role in cellular signaling processes, and biochemical analysis of SLC41A1 indicates that it might be part of such a MPC in HEK293 cells (Kolisek et al., 2008). The nature of the MPC's which may contain SLC41A1 remain obscure, as although increasing concentrations of detergent are able to dissociate SLC41A1 from its associated MPC, it has yet to be determined what proteins are interacting with SLC41A1 and constitute the MPC (Kolisek et al., 2008).

3.3 Functional studies

An initial study suggested that SLC41A1 functions as a nonspecific divalent cation channel, since expression of the mouse *Slc41a1* in *Xenopus* oocytes led to the generation of Mg^{2+} specific currents as well as mediated transport of Fe^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+} and Cd^{2+}(Goytain and Quamme, 2005a). In contrast, whole cell patch clamp analysis by our group following expression of SLC41A1 in TRPM7-deficient DT40 cells was not able to detect any currents associated with SLC41A1 expression (J. Sahni and A. M. Scharenberg, unpublished

observations), and Kolisek and colleagues observed that overexpression of the human SLC41A1 in HEK293 cells resulted in development of endogenous Cl^- currents, which were repressed by DIDS (4,4′ Diisothiocyanatostilbene-2, 2′-disulfonic acid), a broad-spectrum inhibitor of chloride transport (Kolisek et al., 2008). These observations raise the question as to why development of prominent Mg^{2+} specific currents was observed in the first study, especially as the mouse and human sequences display a high degree of homology (98% identity). One explanation could be that SLC41A1's interaction with a larger multi-protein complex in the HEK-293 system results in activation or regulation of associated Cl^- channels, whereas the absence of its partner proteins in the DT40 or *Xenopus* oocytes contexts results in alternative modes of function.

Using the TRPM7-deficient DT40 B-cell model system previously characterized in our lab (Schmitz et al., 2003), we have used functional complementation of cell growth to infer that SLC41A1 is capable of trans-plasma membrane Mg^{2+} transport. Furthermore, we identified the N-terminus of SLC41A1 as a defined protein domain of SLC41A1 that is required for regulation of its intracellular transport, suggesting that it was involved in the sensing or receipt by SLC41A1 of information regarding the status of intracellular Mg^{2+} homeostasis (Mandt et al., 2011). Our findings suggest a model wherein under Mg^{2+}-replete conditions, SLC41A1 is internalized and predominantly shuttled to the lysosomes for degradation. However, under low or Mg^{2+}-deficient conditions, the transporter either avoids internalization or is internalized, but does not undergo lysosomal degradation and is instead recycled back to the cell surface. Such a model is similar to that proposed for the regulation of the Alr family of Mg^{2+} transporters in yeast by Graschopf and colleagues (Graschopf et al., 2001).

Kolisek and colleagues recently found that the expression of human SLC41A1 in HEK293 cells leads to Mg^{2+} efflux, on the basis of which they proposed that SLC41A1 may function as a Na^+/ Mg^{2+} exchanger (Kolisek et al., 2008; Kolisek et al., 2012). The disparate observation of enhanced Mg^{2+} uptake in TRPM7-deficient cells vs. enhanced Mg^{2+} export in HEK293 cells likely reflects differences in the presence of protein interaction partners, or regulation of Mg^{2+} transport in the two systems used in the studies, and suggests the presence of a deeper level of coordination of Mg^{2+} transport among transporters of the various families. These results emphasize that understanding the coordination of Mg^{2+} transport among the various families of Mg^{2+} transporters, and defining specific functions or roles for Mg^{2+} transport mediated by each family member, are an important priority for the field.

3.4 Implications in disease

The PARK16 (Parkinson disease 16) locus has been shown to carry mutations in patients of both European and Asian ancestries (Pankratz et al., 2009; Satake et al., 2009). Sequencing analysis of this locus recently revealed novel mutations in the *SLC41A1* gene - A350V (Tucci et al., 2010), A436G and A1440G (Yan et al., 2011). However, it's still unclear how SLC41A1 impacts this neurodegenerative disease at a biochemical level.

4. SLC41A2

4.1 Expression and localization

The second member of the SLC41 transporter family, SLC41A2, is expressed in normal human tissues with lymph nodes, stomach, lungs, testis and skin with the highest expression followed by spleen, intestine, heart, breast and kidneys exhibiting moderate expression. Respiratory epithelia, liver, pancreas, thyroid, uterine glands and glial cells show weak or negative expression (expression data obtained from - http://www.proteinatlas.org/ENSG00000136052/normal). Real-time RT-PCR analysis of Mouse Distal Convoluted

Tubule (MDCT) cells cultured in low Mg^{2+} media (1mM) or Mg^{2+} free media for 16h indicated no change in *Slc41a2* expression and the same was found to be the case with kidney cortical tissue harvested from mice kept on normal or low Mg^{2+} diet for 5 days (Goytain and Quamme, 2005b).

The subcellular localization of SLC41A2 remains unclear - although heterologously expressed epitope tagged protein showed detectable plasma membrane localization in TRPM7-deficient DT40 cells by flow cytometry, its orientation appeared to be the opposite of that predicted by the structure of prokaryotic MgtE proteins or SLC41A1 (see discussion below), raising the possibility that the protein detected on the plasma membrane localization may have reflected aberrant cell surface transport due to overexpression (Sahni et al., 2007). The N-terminal out orientation observed in these studies would be consistent with a role for SLC41A2 in Mg^{2+} transport across organellar membranes, where the N-terminal domain of SLC41A2 would be involved in regulation of the internal Mg^{2+} content of the organelle

4.2 Characterization and topology

SLC41A2 has now been identified in a large number of vertebrate species. The initial characterization of the human SLC41A2 in the NCBI database (accession# AAI06873) indicated that it comprised of 490 amino acid residues with a molecular weight of ~53.2kDa and was shorter than the reported mouse SLC41A2 protein (573 aa residues; MW=62.1kDa) (Goytain and Quamme, 2005b). Interestingly, upon ORF analysis of the human *SLC41A2*, we found presence of 83 extra amino acid residues in-frame at 5′ of the reported N-terminus (J. Sahni and A.M.Scharenberg, unpublished observation), which displayed close homology to the mouse SLC41A2 present in the database. Subsequently, the originally reported shorter sequence (referred to as SS in this review) was replaced by an updated full-length (FL) SLC41A2 sequence in the NCBI database (accession# NP_115524.3). The predicted molecular weight of the full-length protein is ~62.3kDa (573 aa residues) and sequence analysis of its long N-terminus indicated absence of any signal peptide and/or conserved domains. Although existing data unambiguously shows that the extended N-terminal region of SLC41A2 is highly conserved amongst vertebrates (Figure 2), it's exact role remains undefined.

Goytain and Quamme characterized the mouse SLC41A2 and their hydophobicity analysis suggested that it consisted of 12 TM spans (Goytain and Quamme, 2005b). However, heterologous expression of the epitope-tagged SS human SLC41A2 in DT40 TRPM7-deficient cells revealed the presence of N and C-terminal epitopes on opposite sides of the plasma membrane, most consistent with SLC41A2 possessing 11 TM spans in an unexpected N-terminus-outside/C-terminus inside topology (Sahni et al., 2007). As noted above, because this orientation is the reverse of that observed for the *B. subtilis* MgtE homologue, SLC41A1, one possibility is that SLC41A2 is normally involved in organellar Mg^{2+} transport (where its topology would place its N-terminus inside an intracellular organelle), and that SLC41A2 transporters may have aberrantly accumulated on the plasma membrane in our initial study due to overexpression.

4.3 Functional studies

Expression of the mouse *Slc41a2* in *Xenopus* oocytes was shown to mediate Mg^{2+} currents as well as the transport of a variety of divalent cations including Ba^{2+}, Ni^{2+}, Co^{2+} and Fe^{2+}, suggesting that it might be associated with cellular Mg^{2+} transport (Goytain and Quamme, 2005b). Confirmation that SLC41A2 (SS) could indeed function as a plasma membrane Mg^{2+} transporter upon overexpression in TRPM7-deficient DT40 cells was provided when these cells were able to grow and proliferate in regular cell culture media without supplemental Mg^{2+} upon induction of the protein. However, similar to our results with

SLC41A1, investigation of SLC41A2 expressing cells by whole cell patch clamp did not reveal any novel currents associated with its expression (Goytain and Quamme, 2005b; Sahni et al., 2007). Our inability to detect any apparent currents, despite the capacity of SLC41A2 to complement the Mg^{2+} uptake and growth defects of TRPM7-deficient cells, suggests that the regulation or function of SLC41A2 in the DT40 context differs from that in the *Xenopus* oocyte system. It will be interesting to resolve the differences in the behavior of SLC41A2 in order to generate a clearer understanding of both its regulatory and Mg^{2+}-transport functions.

Consistent with our observations, a recent study carried out by Liu et al in which the authors analyzed the role of TRPM7 in vertebrate embryogenesis, found that SLC41A2 (SS) was able to rescue the phenotype caused by depletion of TRPM7 (Liu et al., 2011). Additional findings by the same group further reported that expression of SLC41A2 in fibroblasts with knocked down TRPM7 could restore both cell morphology as well as cell motility (Su et al., 2011). Taken together, the above studies provide further support for the concept that SLC41A2 is involved in maintenance of cellular Mg^{2+} homeostasis in vertebrates, and that Mg^{2+} transport mediated by SLC41 transporters may have some functional overlap with that mediated by TRPM7. Moreover, in-depth functional analysis of both the SS and full-length SLC41A2 in TRPM7-deficient cells showed that inducible expression of only the SS version was able to restore their cell growth and proliferative defects (J. Sahni and A.M.Scharenberg, unpublished observations). This alludes to a likelihood of the shorter form of the protein functioning as a potential splice variant of the full-length protein. However, it's also conceivable the epitope-tagged full-length SLC41A2 does not fold properly or has intracellular trafficking issues due to the presence of epitope tags, which might hinder its transport and localization at the plasma membrane (e.g. see (Yewdell et al., 2011) , (Snapp, 2009)).

Despite the abundant evidence that links SLC41A2 to Mg^{2+} transport, a plethora of questions regarding SLC41A2 remain unanswered: the functional role, if any, for its N-terminus that is analogous to what has been observed for SLC41A1; identification of signals or metabolic cues that regulate its expression and activity; and determination of its specific role in maintenance of Mg^{2+} homeostasis in intracellular or organellar milieus.

4.4 Implications in disease

There is no current evidence to indicate association of SLC41A2 or its mutated forms with any specific disease, although *SLC41A2* is reported as either over or under expressed in 75 disease states including a number of carcinomas and lymphomas according to the database on European Bioinformatics Institute (EBI) website (ref-http://www.ebi.ac.uk/gxa/gene/ENST00000258538).

5. SLC41A3

As both SLC41A1 and SLC41A2 have been shown to function as magnesium transporters, it's quite likely that SLC41A3 plays a similar functional role in vertebrates. However, in contrast to SLC41A1 and SLC41A2, no studies have yet been published regarding the third member of this family, to date. Unpublished data from our lab using recombinant SLC41A3 constructs have not been able to consistently detect protein expression or capacity to complement TRPM7-deficient DT40 cell lines, suggesting that SLC41A3 may be more dependent on partner proteins, or possess specialized functions. This may in part be because five splice isoforms of SLC41A3 have been reported, and their explicit biochemical role(s) may need to be individually characterized in the specific cell or tissue context where they are normally expressed. As bioinformatics data on EBI suggests that *SLC41A3* is differentially expressed in a number of human organs including cerebellum, testis, prostate,

etc. as well as in some cell lines - SW480, MOLT4, MCF-7, etc, it seems likely that role(s) for the various SLC41A3 isoforms in Mg^{2+} transport will eventually be defined.

6. Pharmaceutical aspects

Currently, no small molecule drugs have been reported that specifically target the SLC41 family of transporters.

7. Coordination with other vertebrate Mg^{2+} transporters

Given emerging evidence that multiple vertebrate Mg^{2+} transporters are expressed in many vertebrate cell types and collectively contribute to Mg^{2+} homeostasis, the existence of a dynamic interplay between the various individual transporters seems likely. One example of such functional overlap or linkage is Mg^{2+} transport mediated by SLC41 Mg^{2+} transporters and TRPM7, as suggested by the observation that SLC41A1 is upregulated in a Mg^{2+} concentration-dependent manner in TRPM7-deficient DT40 cells (Mandt et al., 2011). As the expression pattern and functions of each family become more clearly defined, it is likely that similar interactions will be identified, both with respect to Mg^{2+} transport, as well as the regulatory mechanisms that govern the function of each type of protein.

8. Summary

That SLC41 family members play an important role in the maintenance of cellular Mg^{2+} homeostasis is now well supported, but the mechanisms through which Mg^{2+} transport mediated by these proteins is regulated, and how their functions are coordinated with Mg^{2+} transport mediated by other transporters, remain largely obscure. Future studies focused on a mechanistic understanding of these questions promise to provide important insights into how Mg^{2+} transport mediated by SLC41 family proteins, as well as that mediated by members of other Mg^{2+} transporter families, is coordinated with myriad aspects of cell biology.

Acknowledgments

We would like to acknowledge past and present members of the Ion Channel group in the Scharenberg lab for helpful discussions.

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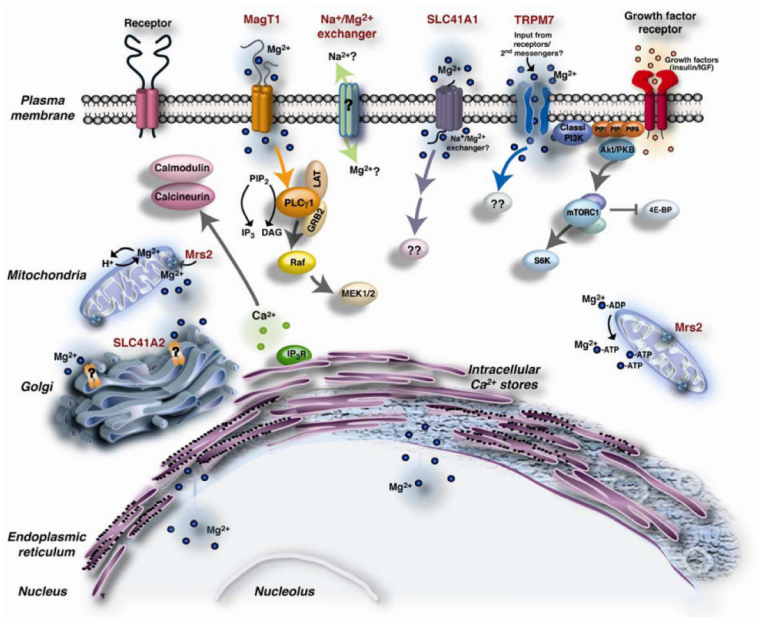

Figure 1. Mg^{2+} transporters in vertebrate cells

Pictured are various proposed transporters and their predicted transport mechanisms: **SLC41A1/A2** (channel transport mechanism based on structural homology with prokaryotic MgtE transporters); **Mrs2**, a mitochondrial Mg^{2+} uptake system that transports Mg^{2+} with $\Delta\Psi$ (channel transport mechanism based on similarity with yeast Alr family); **TRPM7** channel kinase (channel transport mechanism), and **MagT1** (thought to be a plasma membrane Mg^{2+} transporter with an ion channel transport mechanism). Overexpression of either TRPM7 or SLC41A1 in TRPM7-deficient cells allows them to grow and proliferate due to Mg^{2+} transport via the respective overexpressed transporters, suggesting they may have some overlap in function. **TRPM7** has been implicated to regulate lymphocyte growth via rapid onset of PI3K activation and its downstream signaling events. **MagT1** has been proposed to regulate the PLCγ1 signaling pathway in T-lymphocytes, based on studies of human patients with mutations in MagT1. Note that Mg^{2+} transport into both the endoplasmic reticulum and nucleus are very poorly characterized and hence are pictured simply as passive exchange mechanisms. Although the gene for **Na^+/Mg^{2+} exchanger** (**?**) has not been cloned, such an exchange mechanism has been proposed to exist and mediate Mg^{2+} efflux in vertebrate cells.

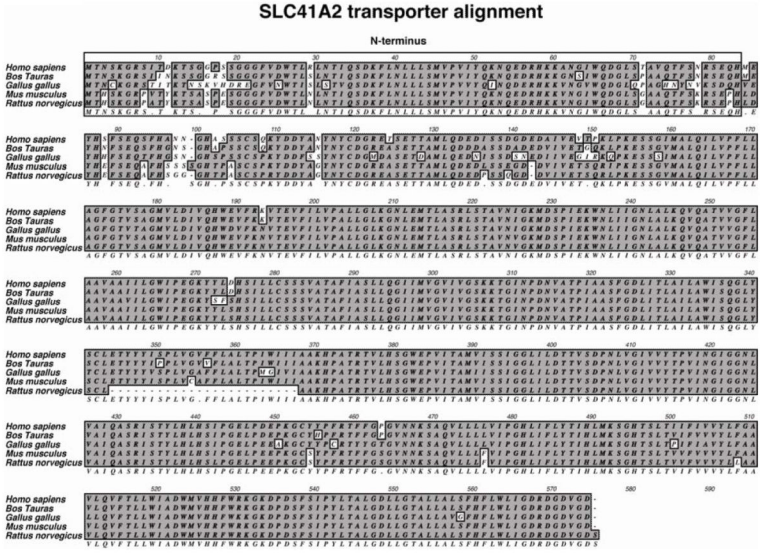

Figure 2. ClustalW alignment of the full-length human SLC41A2 with other identified homologues in the NCBI database

Sequence comparison of the full-length human SLC41A2 showed that the long N-terminus (outlined box) is highly conserved amongst most of its homologous sequences, although its precise function is unclear.

Table 1

SLC41-MgtE-like magnesium transporter family

Human gene name	Protein name	Aliases	Predominant substrates	Transport type*)/ coupling ions	Tissue distribution & cellular/subcellular expression	Link to disease	Human gene locus	Sequence accession ID	Splice variants
SLC41A1	MgtE		Mg^{2+}(Sr^{2+},Zn^{2+},Cu^{2+}, Fe^{2+},Co^{2+},Ba^{2+},Cd^{2+})	Ch	Kidney,heart, testis, skeletal muscle, prostate, adrenal gland and thyrold	Mutations in PARK 16 locus	1q32.1	NM_173854	
SLC41A2		SLC1A1-L1 SLC41A1-like 1	Mg^{2+}(Ba^{2+},Ni^{2+},Co^{2+} Fe^{2+},Mn^{2+})	Ch	Highest expression in cerebellum, lymph nodes, stomach, lungs, testis and skin		12q23.3	NM_032148.3	2 potential splice variants
SLC41A3		SLC41A1-L2 SLC41A1-like 2 FLJ20473		Ch? (predicted based on homology with the other 2 members/MgtE transporter)			3q21.2	NM_001008485.1 NM_017836.3 NM_001008486.1 NM_001008487.1 NM_001164475.1	5 splice variants

*)C:Cotransporter; E:Exchanger; F:Facilitated transporter; O:Orphan transporter; Ch: channel