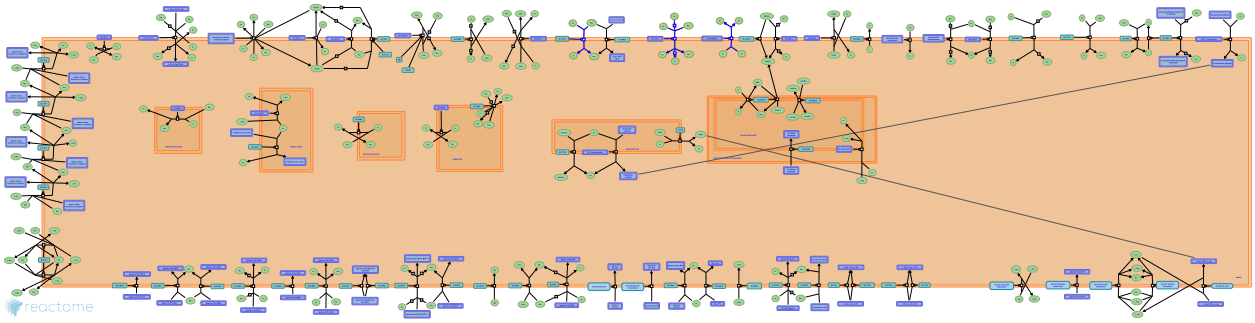
Cation-coupled Chloride cotransporters



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

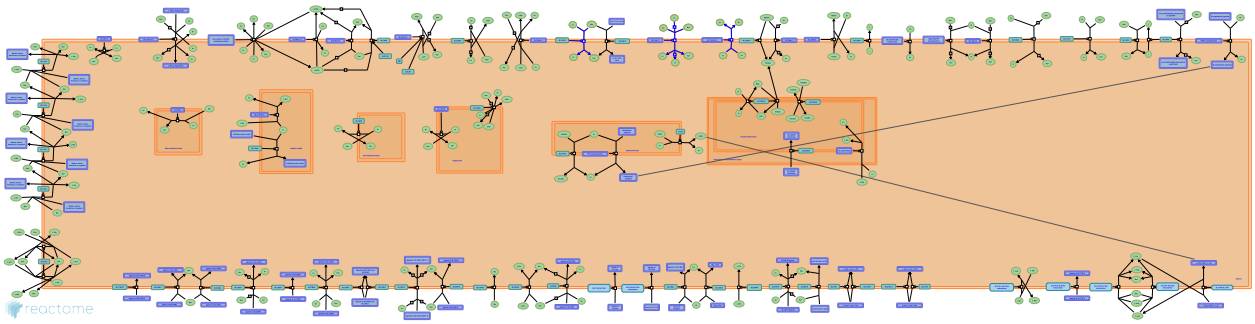
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Cation-coupled Chloride cotransporters ↗

Stable identifier: R-HSA-426117



The cation-chloride cotransporter family (SLC12 gene family) are membrane proteins that cotranslocate chloride (Cl-) with either Na+, K+, or both cations electroneutrally. The general topology of these proteins feature 12 transmembrane domains flanked by hydrophilic NH2 and COOH-terminal domains. They are secondary transporters and movement of these cations is determined by gradients established by primary transporters such as Na+-K+-ATPase. Cotransporters that use Na+ as the driving force move Cl- into the cell because Na+ concentration is higher in the extracellular region. Conversely, cotransporters that use K+ as the driving force move Cl- out of the cell because K+ concentration is higher inside the cell.

The SLC12 gene family contains nine members, of which seven are clearly characterized genes and two are orphans. They encode cotransporter proteins which are 1) involved in Cl- homeostasis, 2) regulate cell volume, 3) involved in transepithelial ion movement (salt reabsorption in the kidney) and 4) involved in response to neurotransmitters such as GABA.

Three different cotransporter subtypes are expressed by the seven characterized genes; one thiazide-sensitive Na+/Cl- cotransporter, two loop diuretic-sensitive Na+, K+/2Cl- cotransporters and four K+/Cl- cotransporters (Gamba G, 2005; Hebert SC et al, 2004).

Literature references

Gamba, G. (2005). Molecular physiology and pathophysiology of electroneutral cation-chloride cotransporters. *Physiol Rev, 85*, 423-93. ↗

Hebert, SC., Mount, DB., Gamba, G. (2004). Molecular physiology of cation-coupled Cl- cotransport: the SLC12 family . *Pflugers Arch, 447*, 580-93. ↗

Editions

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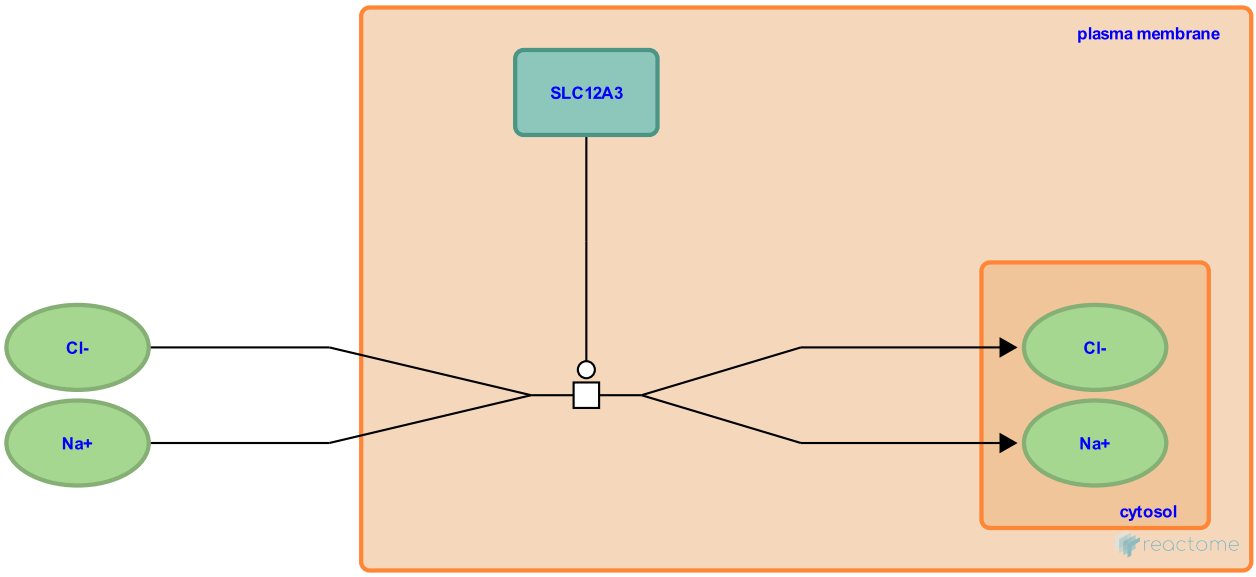
SLC12A3 cotransports Cl-, Na+ from extracellular region to cytosol ↗

Location: Cation-coupled Chloride cotransporters

Stable identifier: R-HSA-426130

Type: transition

Compartments: plasma membrane



The SLC12A3 gene encodes for the Thiazide-sensitive sodium-chloride cotransporter (TSC). TSC mediates sodium and chloride removal from the distal convoluted tubule of the kidney (Mastroianni N et al, 1996). Defects in SLC12A3 are the cause of Gitelman syndrome (GS). GS is an autosomal recessive disorder that allows the kidneys to pass sodium, magnesium, chloride, and potassium into the urine, rather than being reabsorbed into the bloodstream (Simon et al. 1996). This cotransporter is the major target for thiazide-type diuretics, used in the treatment of hypertension, extracellular fluid overload and renal stone disease.

Literature references

Mastroianni, N., De Fusco, M., Zollo, M., Arrigo, G., Zuffardi, O., Bettinelli, A. et al. (1996). Molecular cloning, expression pattern, and chromosomal localization of the human Na-Cl thiazide-sensitive cotransporter (SLC12A3). *Genomics, 35*, 486-93. ↗

Simon, DB., Nelson-Williams, C., Bia, MJ., Ellison, D., Karet, FE., Molina, AM. et al. (1996). Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. *Nat Genet, 12*, 24-30. ↗

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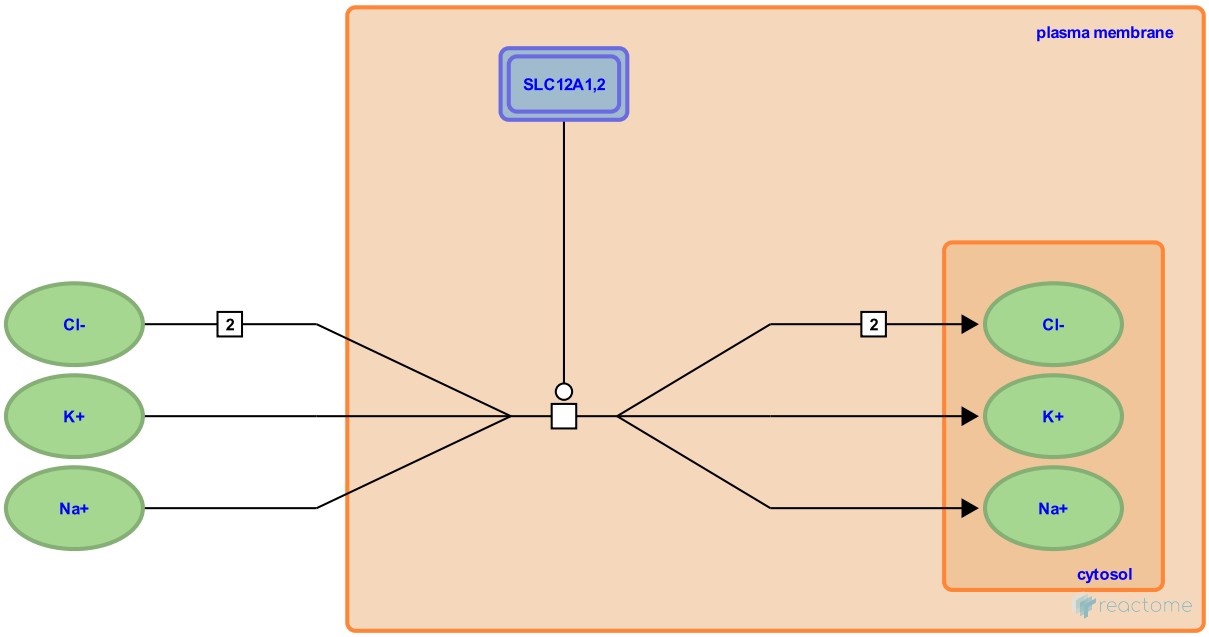
SLC12A1,2 cotransports Na+, K+, 2Cl- from extracellular region to cytosol ↗

Location: Cation-coupled Chloride cotransporters

Stable identifier: R-HSA-426086

Type: transition

Compartments: plasma membrane



Two genes (SLC12A1 and SLC12A2) encode Na+,K+/2Cl- cotransporters (NKCC2 and NKCC1 respectively). SLC12A1 (Simon DB et al, 1996) is kidney-specific whilst SLC12A2 (Payne JA et al, 1995) is ubiquitously expressed. Two Cl- ions are electroneutrally transported into cells with a Na+ ion and a K+ ion.

Literature references

Payne, JA., Xu, JC., Haas, M., Lytle, CY., Ward, D., Forbush B, 3rd. (1995). Primary structure, functional expression, and chromosomal localization of the bumetanide-sensitive Na-K-Cl cotransporter in human colon. *J Biol Chem, 270*, 17977-85. ↗

Simon, DB., Karet, FE., Hamdan, JM., DiPietro, A., Sanjad, SA., Lifton, RP. (1996). Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat Genet, 13*, 183-8. ↗

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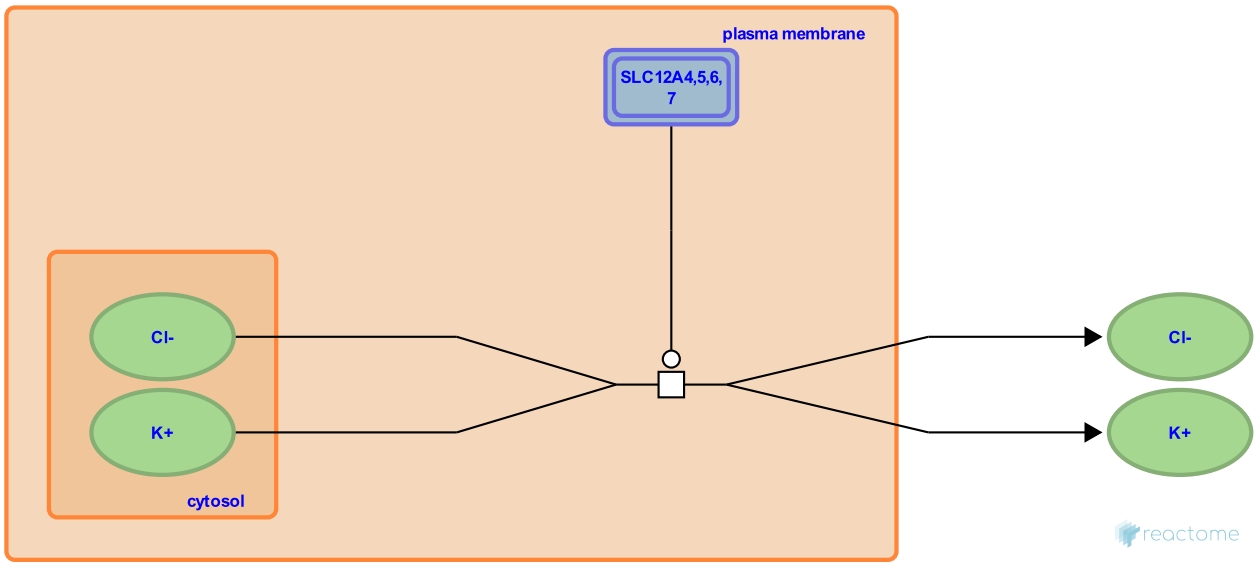
SLC12A4,5,6,7 cotransport K+, Cl- from cytosol to extracellular region ↗

Location: Cation-coupled Chloride cotransporters

Stable identifier: R-HSA-426155

Type: transition

Compartments: plasma membrane



K+/Cl- cotransport is implicated not only in regulatory volume decrease, but also in transepithelial salt absorption, renal K+ secretion, myocardial K+ loss during ischemia and regulation of neuronal Cl- concentration. Four genes (SLC12A4-7) encode the K+/Cl- cotransporters KCC1-4 respectively. Cotransport of K+ and Cl- is electroneutral with a 1:1 stoichiometry. These cotransporters function as homomultimers or heteromultimers with other K+/Cl- cotransporters.

SLC12A4 encodes KCC1 (Gillen CM et al, 1996). KCC1 is ubiquitously expressed, suggesting a housekeeping role in the regulation of cell volume. SLC12A5 encodes KCC2 (Song L et al, 2002). KCC2's expression is restricted to neurons in the CNS and retina. It is thought KCC2 is important for Cl- homeostasis in neurons. SLC12A6 encodes KCC3 (Race JE et al, 1999; Mount DB et al, 1999). KCC3 is highly expressed in heart, brain, spinal cord, kidney, muscle, pancreas and placenta. Defects in SLC12A6 are a cause of agenesis of the corpus callosum with peripheral neuropathy (ACCPN) (Howard HC et al, 2002). SLC12A7 encodes KCC4 (Mount DB et al, 1999) which is widely expressed, especially in the kidney. It is thought to play a role in transepithelial transport of Cl- by the proximal tubule.

Literature references

Gillen, CM., Brill, S., Payne, JA., Forbush B, 3rd. (1996). Molecular cloning and functional expression of the K-Cl cotransporter from rabbit, rat, and human. A new member of the cation-chloride cotransporter family. *J Biol Chem, 271*, 16237-44. ↗

Song, L., Mercado, A., Vázquez, N., Xie, Q., Desai, R., George AL, Jr. et al. (2002). Molecular, functional, and genomic characterization of human KCC2, the neuronal K-Cl cotransporter. *Brain Res Mol Brain Res, 103*, 91-105. ↗

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Howard, HC., Mount, DB., Rochefort, D., Byun, N., Dupré, N., Lu, J. et al. (2002). The K-Cl cotransporter KCC3 is mutant in a severe peripheral neuropathy associated with agenesis of the corpus callosum. *Nat Genet, 32*, 384-92. ↗

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