



# Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 79 on 26/02/2022. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMjAyMjYwMTE1MTlfMTcyODM%3D>

Please keep in mind that analysis results are temporarily stored on our server. The storage period depends on usage of the service but is at least 7 days. As a result, please note that this URL is only valid for a limited time period and it might have expired.

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# 1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for *Homo sapiens* are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and *Arabidopsis*. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

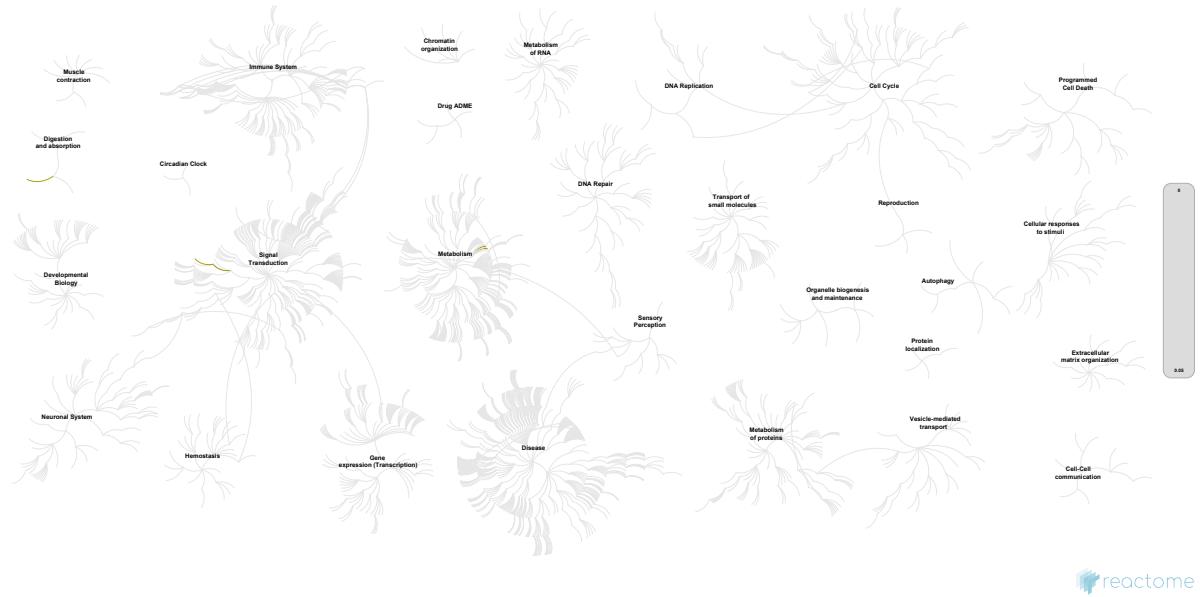
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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

## 2. Properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamini-Hochberg method. ↗
- 23 out of 27 identifiers in the sample were found in Reactome, where 1100 pathways were hit by at least one of them.
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjAyMjYwMTE1MTlfMTcyODM%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

### 3. Genome-wide overview



## 4. Most significant pathways

The following table shows the 25 most relevant pathways sorted by p-value.

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Intestinal lipid absorption	1 / 6	2.69e-04	0.035	0.826	3 / 3	2.20e-04
Glucagon-type ligand receptors	2 / 50	0.002	0.036	0.826	4 / 8	5.86e-04
PKA-mediated phosphorylation of key metabolic factors	1 / 7	3.14e-04	0.041	0.826	4 / 5	3.66e-04
Class B/2 (Secretin family receptors)	3 / 130	0.006	0.044	0.826	5 / 20	0.001
Glucagon signaling in metabolic regulation	2 / 59	0.003	0.049	0.826	2 / 6	4.40e-04
PP2A-mediated dephosphorylation of key metabolic factors	1 / 9	4.04e-04	0.052	0.826	3 / 4	2.93e-04
Glucagon-like Peptide-1 (GLP1) regulates insulin secretion	2 / 69	0.003	0.065	0.826	3 / 11	8.06e-04
Sensory processing of sound by outer hair cells of the cochlea	2 / 73	0.003	0.071	0.826	1 / 8	5.86e-04
Activation of AMPA receptors	1 / 16	7.18e-04	0.091	0.826	5 / 5	3.66e-04
Defective EXT1 causes exostoses 1, TRPS2 and CHDS	1 / 16	7.18e-04	0.091	0.826	4 / 4	2.93e-04
Defective EXT2 causes exostoses 2	1 / 16	7.18e-04	0.091	0.826	4 / 4	2.93e-04
Defective B4GALT7 causes EDS, progeroid type	1 / 21	9.43e-04	0.118	0.826	1 / 1	7.33e-05
Defective B3GALT6 causes EDSP2 and SEMDJL1	1 / 21	9.43e-04	0.118	0.826	1 / 1	7.33e-05
Defective B3GAT3 causes JDSSDHD	1 / 22	9.87e-04	0.123	0.826	1 / 1	7.33e-05
ChREBP activates metabolic gene expression	1 / 23	0.001	0.128	0.826	6 / 6	4.40e-04
Presynaptic function of Kainate receptors	1 / 23	0.001	0.128	0.826	1 / 2	1.47e-04
G-protein activation	1 / 26	0.001	0.144	0.826	5 / 6	4.40e-04
ADP signalling through P2Y purinoceptor 12	1 / 26	0.001	0.144	0.826	3 / 4	2.93e-04
AMPK inhibits chREBP transcriptional activation activity	1 / 26	0.001	0.144	0.826	1 / 4	2.93e-04
Intestinal absorption	1 / 27	0.001	0.149	0.826	3 / 6	4.40e-04
Negative regulation of TCF-dependent signaling by WNT ligand antagonists	1 / 27	0.001	0.149	0.826	1 / 5	3.66e-04
HDL clearance	1 / 28	0.001	0.154	0.826	2 / 5	3.66e-04
VxPx cargo-targeting to cilium	1 / 29	0.001	0.159	0.826	9 / 10	7.33e-04

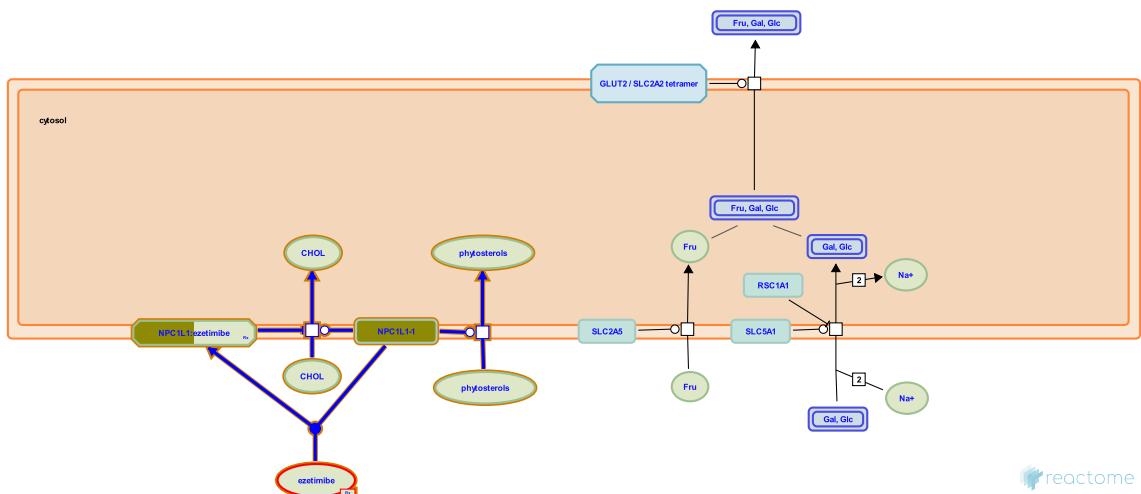
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Prostacyclin signalling through prostacyclin receptor	1 / 30	0.001	0.164	0.826	3 / 4	2.93e-04
Sensory processing of sound by inner hair cells of the cochlea	2 / 123	0.006	0.168	0.826	1 / 7	5.13e-04

\* False Discovery Rate

## 5. Pathways details

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

### 1. Intestinal lipid absorption (R-HSA-8963678)



Niemann-Pick C1 Like 1 (NPC1L1) protein in enterocytes is critical for intestinal cholesterol and phytosterol absorption, and is the target of the drug ezetimibe (Davis et al. 2004).

### References

Iyer SP, Altmann SW, Detmers PA, Lam MH, Maguire M, Yao X, ... Zhu LJ (2004). Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. *J. Biol. Chem.*, 279, 33586-92. [View](#)

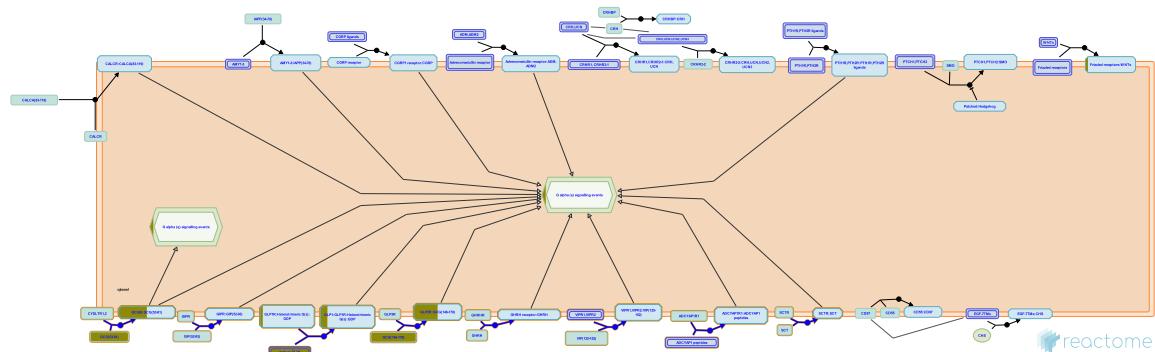
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Date	Action	Author
2008-05-12	Authored	D'Eustachio P
2008-06-13	Reviewed	Jassal B
2017-02-10	Edited	D'Eustachio P
2017-02-10	Created	D'Eustachio P
2021-11-28	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
NPC1L1	Q9UHC9-2

## 2. Glucagon-type ligand receptors (R-HSA-420092)



The glucagon hormone family regulates the activity of GPCRs from the secretin receptor subfamily in Class II/B (Mayo KE et al, 2003).

## References

Miller LJ, Thorens B, Drucker DJ, Giese B, Mayo KE, Dalle S & Bataille D (2003). International Union of Pharmacology. XXXV. The glucagon receptor family. *Pharmacol Rev*, 55, 167-94. 

## Edit history

Date	Action	Author
2009-05-11	Edited	Jassal B
2009-05-11	Authored	Jassal B
2009-05-11	Created	Jassal B
2009-05-29	Reviewed	D'Eustachio P
2021-11-26	Modified	Weiser ID

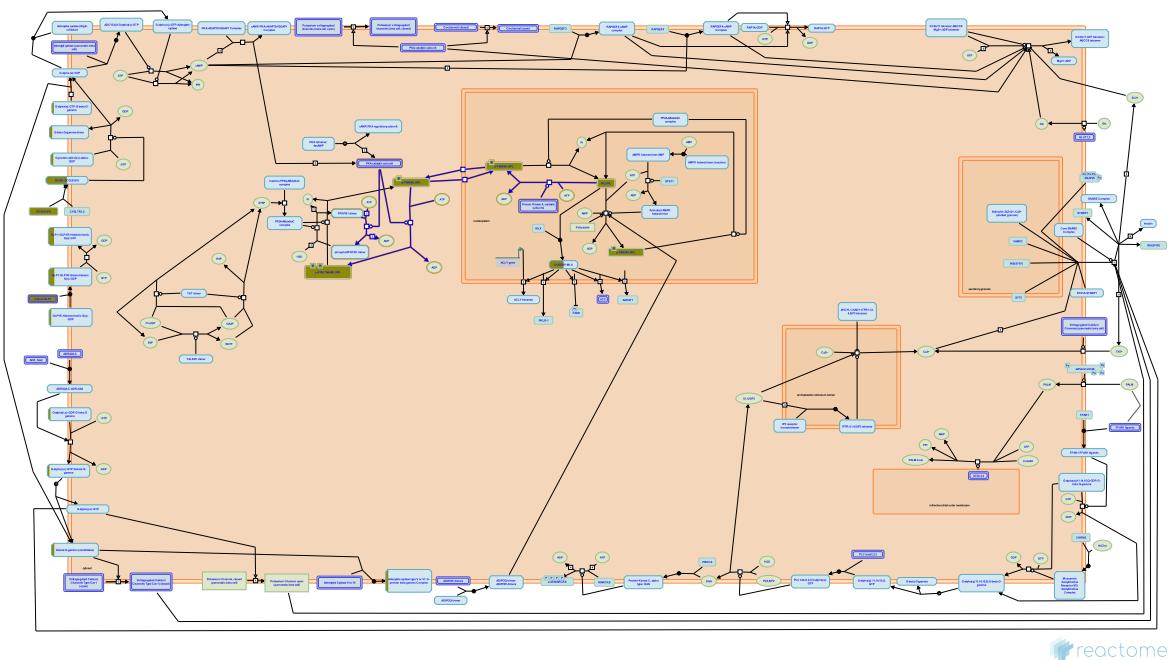
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Input	UniProt Id	Input	UniProt Id
GCG	P01275	GNB2	P62879

## Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
GCG	P01275	P01275, P48546			

### 3. PKA-mediated phosphorylation of key metabolic factors (R-HSA-163358)



**Cellular compartments:** nucleoplasm, cytosol.

Upon dissociation of protein kinase A (PKA) tetramers in the presence of cAMP, the released PKA catalytic monomers phosphorylate specific serine and threonine residues of several metabolic enzymes. These target enzymes include glycogen phosphorylase kinase, glycogen synthase and PF2K-Pase. PKA also phosphorylates ChREBP (Carbohydrate Response Element Binding Protein), preventing its movement into the nucleus and thus its function as a positive transcription factor for genes involved in glycolytic and lipogenic reactions.

## References

Veech RL (2003). A humble hexose monophosphate pathway metabolite regulates short- and long-term control of lipogenesis. Proc Natl Acad Sci U S A, 100, 5578-80. [View](#)

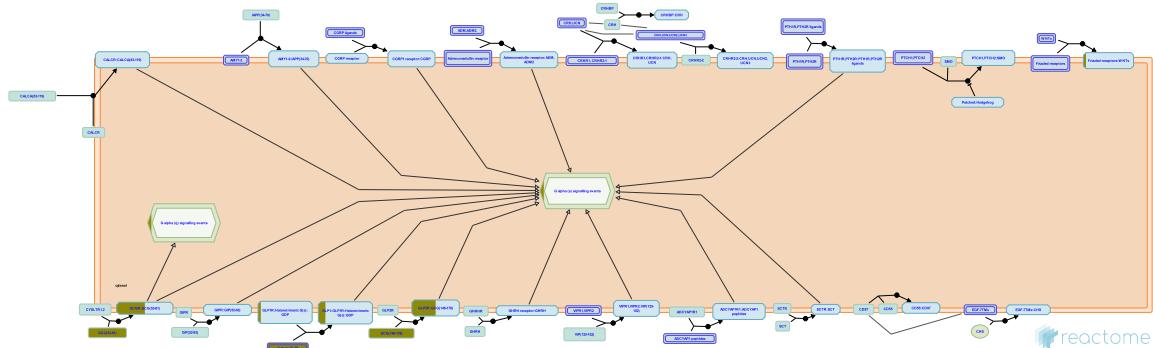
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2005-05-13	Authored	Gopinathrao G
2021-11-27	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
MLXIPL	Q9NP71

#### 4. Class B/2 (Secretin family receptors) (R-HSA-373080)



This family is known as Family B (secretin-receptor family, family 2) G-protein-coupled receptors. Family B GPCRs include secretin, calcitonin, parathyroid hormone/parathyroid hormone-related peptides and vasoactive intestinal peptide receptors; all of which activate adenylyl cyclase and the phosphatidyl-inositol-calcium pathway (Harmar AJ, 2001).

#### References

Harmar AJ (2001). Family-B G-protein-coupled receptors. *Genome Biol*, 2, REVIEWS3013. [View](#)

#### Edit history

Date	Action	Author
2008-07-14	Edited	Jassal B
2008-07-14	Authored	Jassal B
2008-07-14	Created	Jassal B
2009-05-29	Reviewed	D'Eustachio P
2021-11-27	Modified	Weiser JD

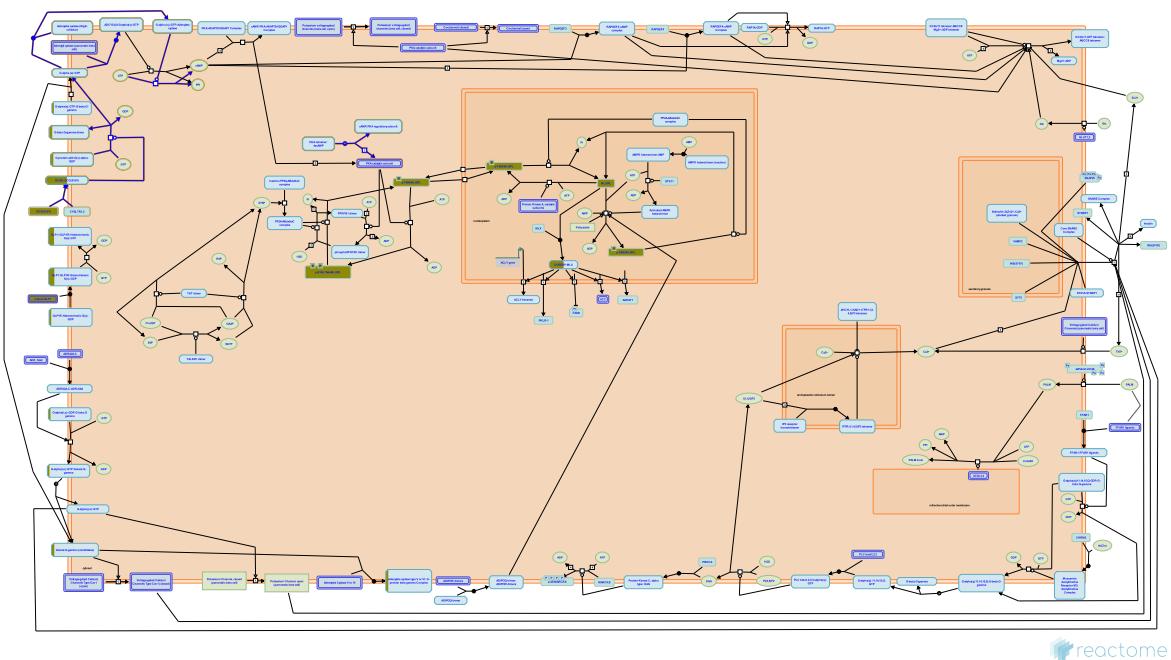
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#### Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
GCG	P01275	P01275, P48546			

## 5. Glucagon signaling in metabolic regulation (R-HSA-163359)



Glucagon and insulin are peptide hormones released from the pancreas into the blood, that normally act in complementary fashion to stabilize blood glucose concentration. When blood glucose levels rise, insulin release stimulates glucose uptake from the blood, glucose breakdown (glycolysis), and glucose storage as glycogen. When blood glucose levels fall, glucagon release stimulates glycogen breakdown and de novo glucose synthesis (gluconeogenesis), while inhibiting glycolysis and glycogen synthesis.

At a molecular level, the binding of glucagon to the extracellular face of its receptor causes conformational changes in the receptor that allow the dissociation and activation of subunits Gs and Gq. The activation of Gq leads to the activation of phospholipase C, production of inositol 1,4,5-triphosphate, and subsequent release of intracellular calcium. The activation of Gs leads to activation of adenylate cyclase, an increase in intracellular cAMP levels, and activation of protein kinase A (PKA). Active PKA phosphorylates key enzymes of glycogenolysis, glycogenesis, gluconeogenesis, and glycolysis, modifying their activities. These signal transduction events, and some of their downstream consequences, are illustrated below (adapted from Jiang and Zhang, 2003).

### References

Zhang BB & Jiang G (2003). Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab, 284, E671-8. [View](#)

### Edit history

Date	Action	Author
2005-04-28	Authored	Gopinathrao G
2005-04-28	Created	Gopinathrao G
2021-11-28	Modified	Weiser JD

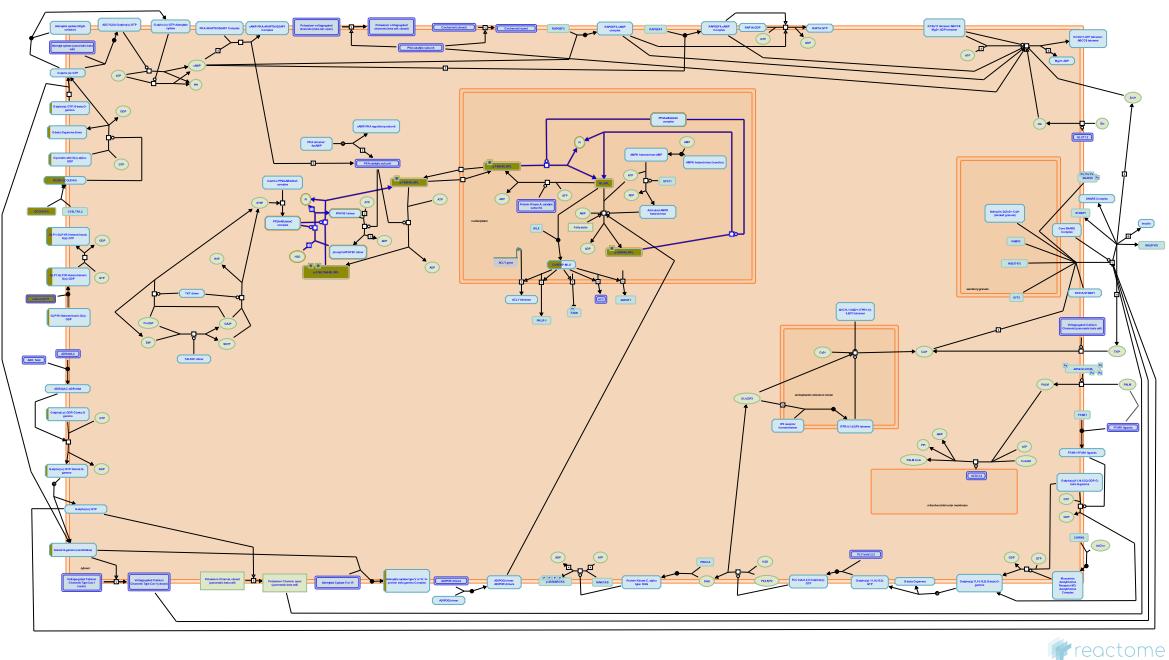
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GCG	P01275	GNB2	P62879

### Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
GCG	P01275	P01275			

## 6. PP2A-mediated dephosphorylation of key metabolic factors (R-HSA-163767)



**Cellular compartments:** nucleoplasm, cytosol.

A member of the PP2A family of phosphatases dephosphorylates both cytosolic and nuclear forms of ChREBP (Carbohydrate Response Element Binding Protein). In the nucleus, dephosphorylated ChREBP complexes with MLX protein and binds to ChRE sequence elements in chromosomal DNA, activating transcription of genes involved in glycolysis and lipogenesis. The phosphatase is activated by Xylulose-5-phosphate, an intermediate of the pentose phosphate pathway (Kabashima et al. 2003). The rat enzyme has been purified to homogeneity and shown by partial amino acid sequence analysis to differ from previously described PP2A phosphatases (Nishimura and Uyeda 1995) - the human enzyme has not been characterized.

### References

Veech RL (2003). A humble hexose monophosphate pathway metabolite regulates short- and long-term control of lipogenesis. Proc Natl Acad Sci U S A, 100, 5578-80. [View](#)

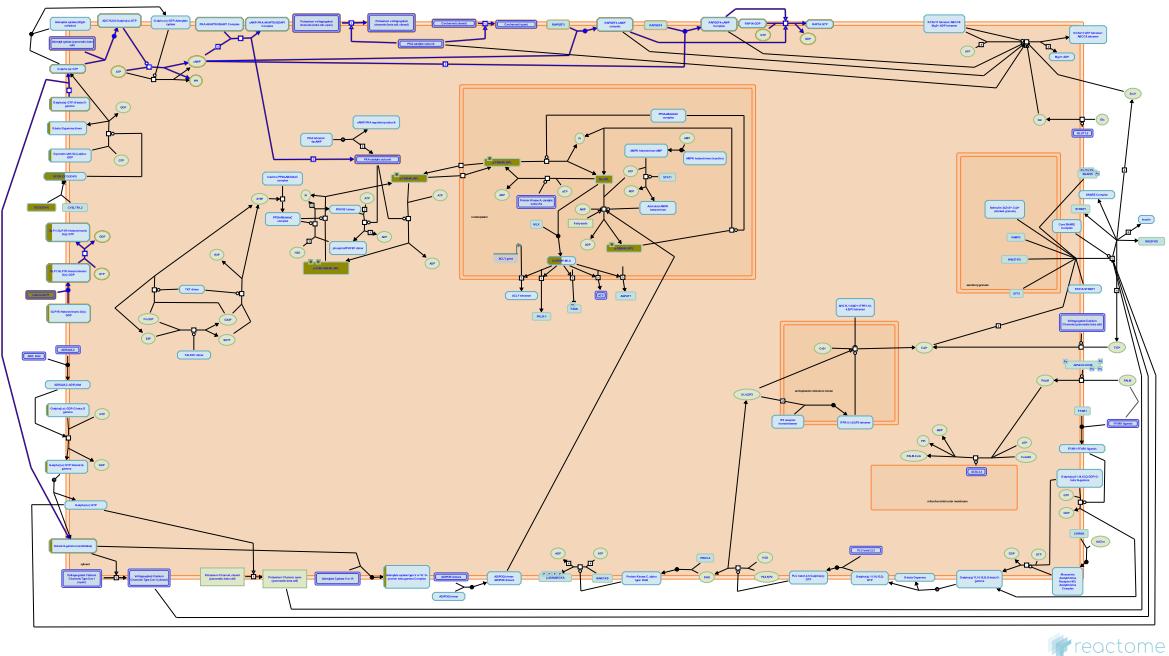
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Date	Action	Author
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2005-05-13	Authored	Gopinathrao G
2020-11-10	Modified	D'Eustachio P

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
MLXIPL	Q9NP71

## 7. Glucagon-like Peptide-1 (GLP1) regulates insulin secretion ([R-HSA-381676](#))



 reactome

**Cellular compartments:** plasma membrane, cytosol.

Glucagon-like Peptide-1 (GLP-1) is secreted by L-cells in the intestine in response to glucose and fatty acids. GLP-1 circulates to the beta cells of the pancreas where it binds a G-protein coupled receptor, GLP-1R, on the plasma membrane. The binding activates the heterotrimeric G-protein G(s), causing the alpha subunit of G(s) to exchange GDP for GTP and dissociate from the beta and gamma subunits.

The activated G(s) alpha subunit interacts with Adenylyl Cyclase VIII (Adenylate Cyclase VIII, AC VIII) and activates AC VIII to produce cyclic AMP (cAMP). cAMP then has two effects: 1) cAMP activates Protein Kinase A (PKA), and 2) cAMP activates Epac1 and Epac2, two guanyl nucleotide exchange factors.

Binding of cAMP to PKA causes the catalytic subunits of PKA to dissociate from the regulatory subunits and become an active kinase. PKA is known to enhance insulin secretion by closing ATP-sensitive potassium channels, closing voltage-gated potassium channels, releasing calcium from the endoplasmic reticulum, and affecting insulin secretory granules. The exact mechanisms for PKA's action are not fully known. After prolonged increases in cAMP, PKA translocates to the nucleus where it regulates the PDX-1 and CREB transcription factors, activating transcription of the insulin gene.

cAMP produced by AC VIII also activates Epac1 and Epac2, which catalyze the exchange of GTP for GDP on G-proteins, notably Rap1A.. Rap1A regulates insulin secretory granules and is believed to activate the Raf/MEK/ERK mitogenic pathway leading to proliferation of beta cells. The Epac proteins also interact with RYR calcium channels on the endoplasmic reticulum, the SUR1 subunits of ATP-sensitive potassium channels, and the Piccolo:Rim2 calcium sensor at the plasma membrane.

## References

- Gromada J & Rorsman P (1996). Molecular mechanism underlying glucagon-like peptide 1 induced calcium mobilization from internal stores in insulin-secreting beta TC3 cells. *Acta Physiol Scand*, 157, 349-51. [🔗](#)
- Brock B, Gromada J, Rorsman P & Schmitz O (2004). Glucagon-like peptide-1: regulation of insulin secretion and therapeutic potential. *Basic Clin Pharmacol Toxicol*, 95, 252-62. [🔗](#)
- Riedel MJ, Wheeler MB, MacDonald PE, Light PE, Salapatek AM & El-Kholy W (2002). The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. *Diabetes*, 51, S434-42. [🔗](#)
- Ahren B & Winzell MS (2007). G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes. *Pharmacol Ther*, 116, 437-48. [🔗](#)
- Lang J (1999). Molecular mechanisms and regulation of insulin exocytosis as a paradigm of endocrine secretion. *Eur J Biochem*, 259, 3-17. [🔗](#)

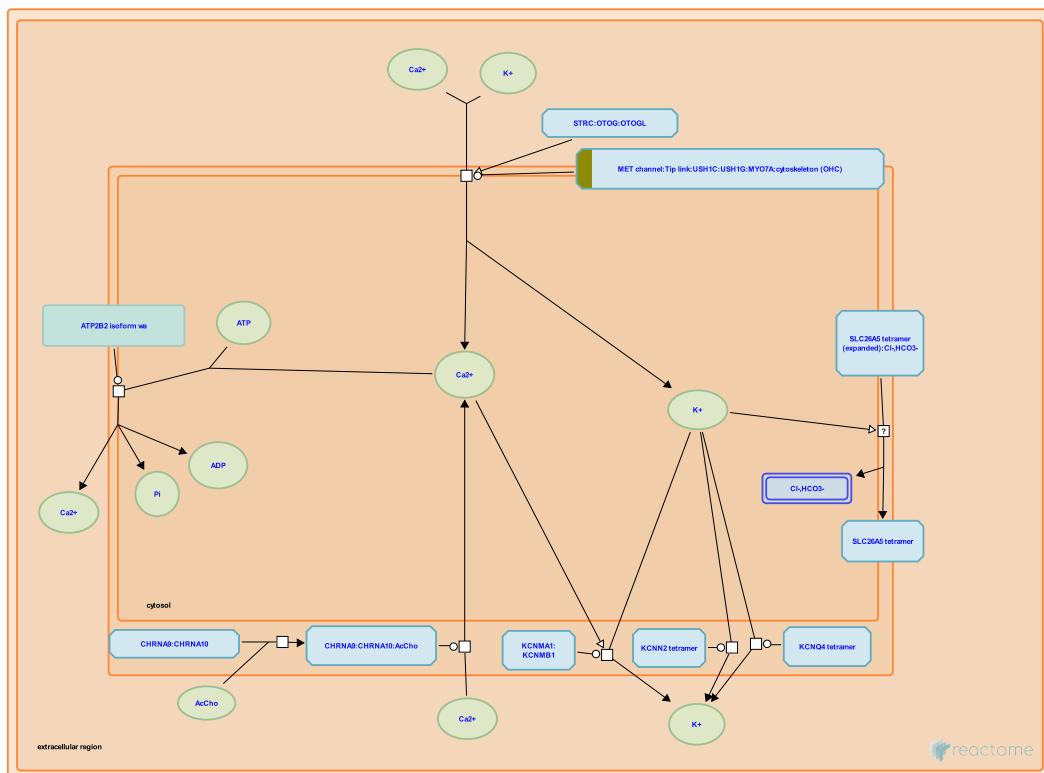
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2008-11-20	Created	May B
2009-05-28	Edited	May B
2009-05-28	Authored	May B
2009-06-02	Reviewed	Gillespie ME
2021-11-28	Modified	Weiser JD

## 2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
GCG	P01275	GNB2	P62879

## 8. Sensory processing of sound by outer hair cells of the cochlea (R-HSA-9662361 )



Outer hair cells (OHCs) produce amplification of sound waves in the cochlea by shortening and lengthening in response to sound, a phenomenon called electromotility (reviewed in Kim and Fettiplace 2014, Fettiplace 2016, Fettiplace 2017, Fritzsch et al. 2017, Ashmore 2019). Like inner hair cells, OHCs possess apical stereocilia arranged in rows of ascending height. A taller stereocilium is connected to a shorter stereocilium by a tip link comprising a CDH23 dimer on the side of the taller stereocilium and a PCDH15 dimer on the apex of the shorter stereocilium. PCDH15 interacts with LHFPL5, a subunit of the mechanoelectrical transduction channel complex (MET channel, also called the mechanotransduction channel), which contains TMC1 or TMC2, TMIE, CIB2, and LHFPL5 (reviewed in Fettiplace 2016). Deflection of the stereocilia in one direction produces tension on the tip link that increases the open probability of the MET channel, resulting in depolarization of the OHC. Deflection of the stereocilia in the opposite direction produces compression on the tip link that decreases the open probability of the MET channel, resulting in hyperpolarization of the OHC.

Sound causes micromechanical motions of the organ of Corti that result in alternating tension and compression in the tip link that produce excitatory-inhibitory cycles of MET channel openings and closings relative to the MET channel's resting open probability. This causes directionally alternating fluxes of K<sup>+</sup> and Ca<sup>2+</sup>, yielding depolarization-hyperpolarization cycles that cause conformational changes in prestin (SLC26A5). These cycles are asymmetrical, with contraction caused by depolarization dominating elongation caused by hyperpolarization due to the asymmetry of the open probability of MET channels. Stereociliary ATP2B2 (PMCA2) extrudes calcium ions and basally located KCNQ4 extrudes potassium ions to repolarize the OHC.

Depolarization of the OHC causes a decrease in length of the OHC due to a very rapid, voltage-sensitive change in conformation of the membrane protein prestin (SLC26A5), an unusual member of the anion transporter family located in the lateral membrane (Mahendrasingam et al, 2010) that appears to respond to cytosolic chloride by altering its conformation in the plane of the plasma membrane (reviewed in Dallos et al. 2006, Dallos 2008, Hudspeth 2014, Reichenbach and Hudspeth 2014, Ashmore 2019, Santos-Sacchi 2019). Prestin also appears to act as a weak chloride-bicarbonate antiporter (Mistrik et al. 2012). Changes in length of the OHCs cause movement of the reticular lamina toward and away from the basilar membrane.

## References

- Santos-Sacchi J (2019). The speed limit of outer hair cell electromechanical activity. *HNO*, 67, 159-164. [🔗](#)
- Fritzsch B & Elliott KL (2017). Evolution and Development of the Inner Ear Efferent System: Transforming a Motor Neuron Population to Connect to the Most Unusual Motor Protein via Ancient Nicotinic Receptors. *Front Cell Neurosci*, 11, 114. [🔗](#)
- Fettiplace R (2016). Is TMC1 the Hair Cell Mechanotransducer Channel?. *Biophys. J.*, 111, 3-9. [🔗](#)
- Ashmore JF, Mistrák P, Morandell K & Daudet N (2012). Mammalian prestin is a weak Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> electrogenic antiporter. *J. Physiol. (Lond.)*, 590, 5597-610. [🔗](#)
- Kim KX & Fettiplace R (2014). The physiology of mechanoelectrical transduction channels in hearing. *Physiol. Rev.*, 94, 951-86. [🔗](#)

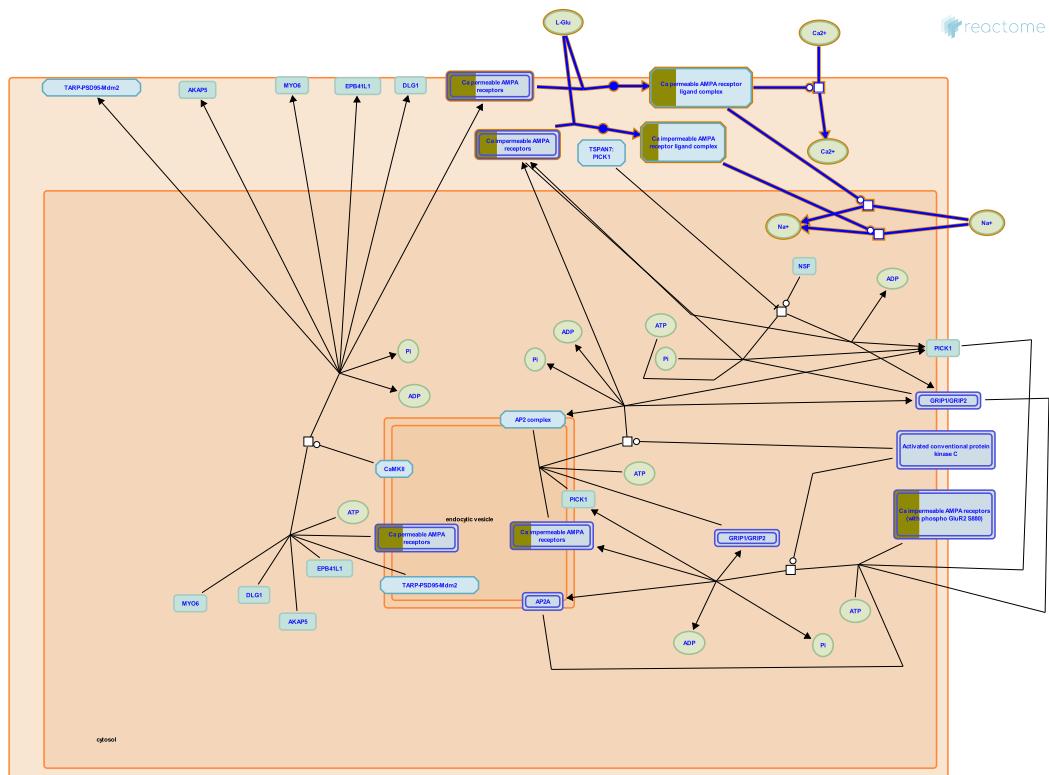
## Edit history

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2019-09-23	Edited	May B
2019-09-23	Authored	May B
2019-09-23	Created	May B
2020-09-14	Reviewed	Furness DN, Dallos P
2020-12-12	Modified	May B

## 2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
EPB41L3	Q9Y2J2	USH1C	Q9Y6N9

## 9. Activation of AMPA receptors (R-HSA-399710)



**Cellular compartments:** plasma membrane, extracellular region.

AMPA receptors are functionally either Ca permeable or Ca impermeable based on the subunit composition. Ca permeability is determined by GluR2 subunit which undergoes post-transcriptional RNA editing that changes glutamine (Q) at the pore to arginine (R). Incorporation of even a single subunit in the AMPA receptor confers Ca-limiting properties. Ca permeable AMPA receptors permit Ca and Na whereas Ca impermeable AMPA receptors permit only Na. In general, glutamatergic neurons contain Ca impermeable AMPA receptors and GABAergic interneurons contain Ca permeable AMPA receptors. However, some synapses do contain a mixture of Ca permeable and Ca impermeable AMPA receptors. GluR1-4 are encoded by four genes however, alternative splicing generates several functional subunits namely long and short forms of GluR1 and GluR2. GluR4 has long tail only and GluR3 has short tail only. Besides the differences in the tail length, flip/flop isoforms are generated by an interchangeable exon that codes the fourth membranous domain towards the C terminus. The flip/flop isoforms determine rate of desensitization/resensitization and the rate of channel closing. Receptors homomers or heteromers assembled from the combination of GluR1-4 subunits that vary in C tail length and flip/flop versions generates a whole battery of functionally distinct AMPA receptors.

## References

- Niu L, Huang Z & Pei W (2007). GluR3 flip and flop: differences in channel opening kinetics. *Biochemistry*, 46, 2027-36. [🔗](#)
- Burnashev N, Schoepfer R, Mosbacher J, Ruppersberg JP, Seuberg PH & Monyer H (1994). A molecular determinant for submillisecond desensitization in glutamate receptors. *Science*, 266, 1059-62. [🔗](#)
- Schuman EM & Seuberg PH (2006). Signalling mechanisms. *Curr Opin Neurobiol*, 16, 247-50. [🔗](#)

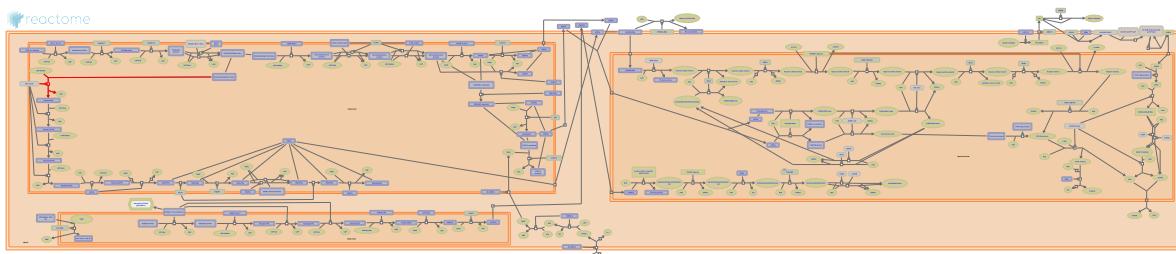
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Date	Action	Author
2008-01-14	Edited	Mahajan SS
2008-01-14	Authored	Mahajan SS
2009-03-19	Created	Mahajan SS
2009-05-15	Reviewed	Ziff EB
2022-01-09	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
GRIA3	P42263

## 10. Defective EXT1 causes exostoses 1, TRPS2 and CHDS (R-HSA-3656253)



**Diseases:** hereditary multiple exostoses.

Heparan sulfate (HS) is involved in regulating various body functions during development, homeostasis and pathology including blood clotting, angiogenesis and metastasis of cancer cells. Exostosin 1 and 2 (EXT1 and 2) glycosyltransferases are required to form HS. They are able to transfer N-acetylgalactosamine (GlcNAc) and glucuronate (GlcA) to HS during its synthesis. The functional form of these enzymes appears to be a complex of the two located on the Golgi membrane. Defects in either EXT1 or EXT2 can cause hereditary multiple exostoses 1 (Petersen 1989) and 2 (McGaughran et al. 1995) respectively (MIM:133700 and MIM:133701), autosomal dominant disorders characterized by multiple projections of bone capped by cartilage resulting in deformed legs, forearms and hands. Trichorhinophalangeal syndrome, type II (TRPS2 aka Langer-Giedion syndrome, LGS) is a disorder that combines the clinical features of trichorhinophalangeal syndrome type I (TRPS1, MIM:190350) and multiple exostoses type I, caused by mutations in the TRPS1 and EXT1 genes, respectively (Langer et al. 1984, Ludecke et al. 1995). Defects in EXT1 may also be responsible for chondrosarcoma (CHDS; MIM:215300) (Schajowicz & Bessone 1967, Hecht et al. 1995).

## References

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## Edit history

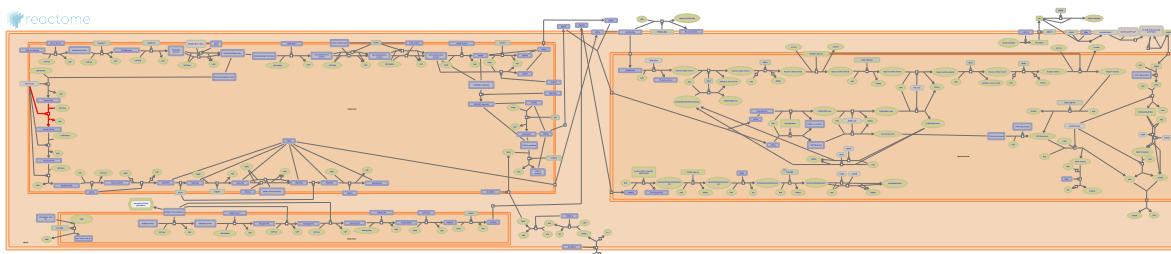
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2013-05-31	Created	Jassal B
2014-07-09	Reviewed	Spillmann D

Date	Action	Author
2018-01-31	Modified	Jassal B

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
GPC6	Q9Y625

## 11. Defective EXT2 causes exostoses 2 (R-HSA-3656237)



**Diseases:** hereditary multiple exostoses.

Heparan sulfate (HS) is involved in regulating various body functions during development, homeostasis and pathology including blood clotting, angiogenesis and metastasis of cancer cells. Exostosin 1 and 2 (EXT1 and 2) glycosyltransferases are required to form HS. They are able to transfer N-acetylgalactosamine (GlcNAc) and glucuronic acid (GlcA) to HS during its synthesis. The functional form of these enzymes appears to be a complex of the two located on the Golgi membrane. Defects in either EXT1 or EXT2 can cause hereditary multiple exostoses 1 (Petersen 1989) and 2 (McGaughran et al. 1995) respectively (MIM:133700 and MIM:133701), autosomal dominant disorders characterised by multiple projections of bone capped by cartilage resulting in deformed legs, forearms and hands.

## References

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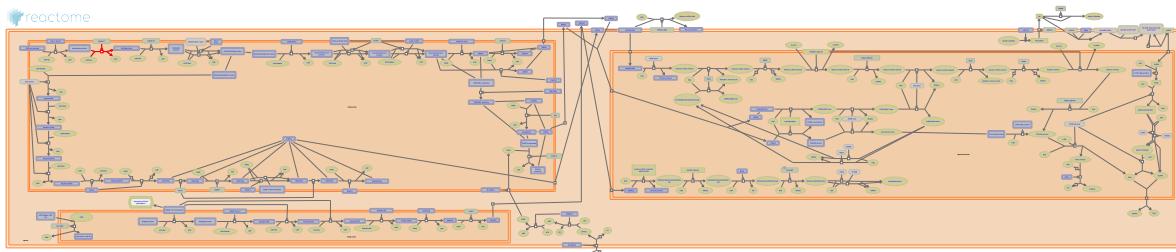
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2013-05-31	Authored	Jassal B
2013-05-31	Created	Jassal B
2014-07-09	Reviewed	Spillmann D
2018-01-31	Modified	Jassal B

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
GPC6	Q9Y625

## 12. Defective B4GALT7 causes EDS, progeroid type (R-HSA-3560783)



**Diseases:** Ehlers-Danlos syndrome.

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders, caused by a defect in the synthesis of collagen types I or III. Abnormal collagen renders connective tissues more elastic. The severity of the mutation can vary from mild to life-threatening. There is no cure and treatment is supportive, including close monitoring of the digestive, excretory and particularly the cardiovascular systems. Defective B4GALT7, a galactosyltransferase important in proteoglycan synthesis, causes the progeroid variant of EDS (MIM:130070). Features include an aged appearance, developmental delay, short stature, generalized osteopenia, defective wound healing, hypermobile joints, hypotonic muscles, and loose but elastic skin (Okajima et al. 1999).

### References

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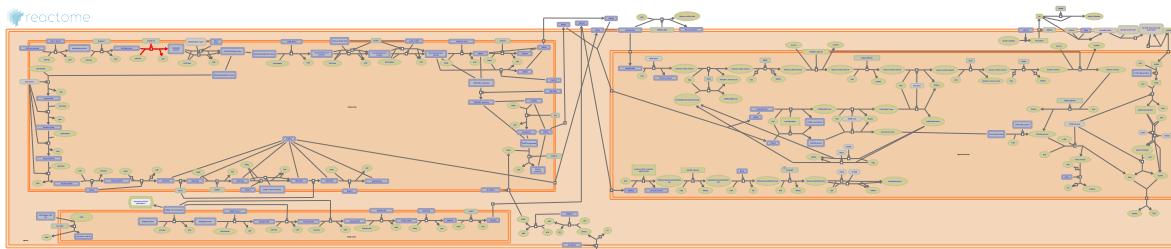
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2013-05-21	Authored	Jassal B
2013-05-21	Created	Jassal B
2014-07-09	Reviewed	Spillmann D
2015-02-09	Modified	Wu G

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
GPC6	Q9Y625

### 13. Defective B3GALT6 causes EDSP2 and SEMDJL1 (R-HSA-4420332)



**Diseases:** Ehlers-Danlos syndrome, spondyloepimetaphyseal dysplasia.

The biosynthesis of dermatan sulfate/chondroitin sulfate and heparin/heparan sulfate glycosaminoglycans (GAGs) starts with the formation of a tetrasaccharide linker sequence attached to the core protein. Beta-1,3-galactosyltransferase 6 (B3GALT6) is one of the critical enzymes involved in the formation of this linker sequence. Defects in B3GALT6 cause Ehlers-Danlos syndrome progeroid type 2 (EDSP2; MIM:615349), a severe disorder resulting in a broad spectrum of skeletal, connective tissue and wound healing problems. Defects in B3GALT6 can also cause spondyloepimetaphyseal dysplasia with joint laxity type 1 (SEMDJL1; MIM:271640), characterised by spinal deformity and lax joints, especially of the hands and respiratory compromise resulting in early death (Nakajima et al. 2013, Malfait et al. 2013).

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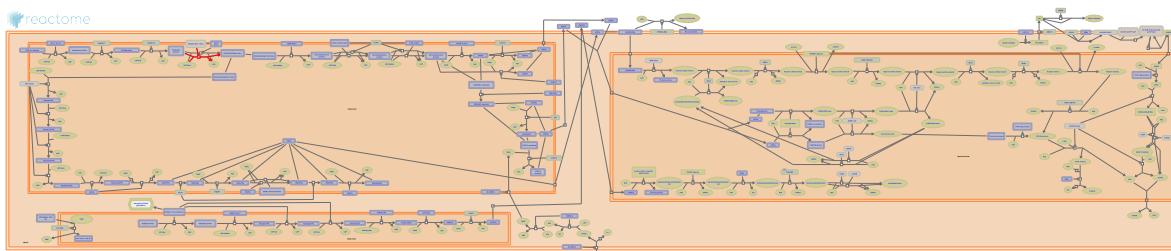
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2013-09-03	Created	Jassal B
2014-07-09	Reviewed	Spillmann D
2015-09-01	Modified	Jassal B

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
GPC6	Q9Y625

## 14. Defective B3GAT3 causes JDSSDHD (R-HSA-3560801)



**Diseases:** Larsen syndrome, congenital heart defect.

Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferases1, 2 and 3 (B3GAT1-3) are involved in forming the linker tetrasaccharide present in heparan sulfate and chondroitin sulfate. Defects in B3GAT3 cause multiple joint dislocations, short stature, craniofacial dysmorphism, and congenital heart defects (JDSSDHD; MIM:245600). This is an autosomal recessive disease characterized by dysmorphic facies, elbow, hip and knee dislocations, clubfeet, short stature and cardiovascular defects (Steel & Kohl 1972, Bonaventure et al. 1992, Baasanjav et al. 2011). JDSSDHD has phenotypic similarities to Larsen syndrome (Larsen et al. 1950).

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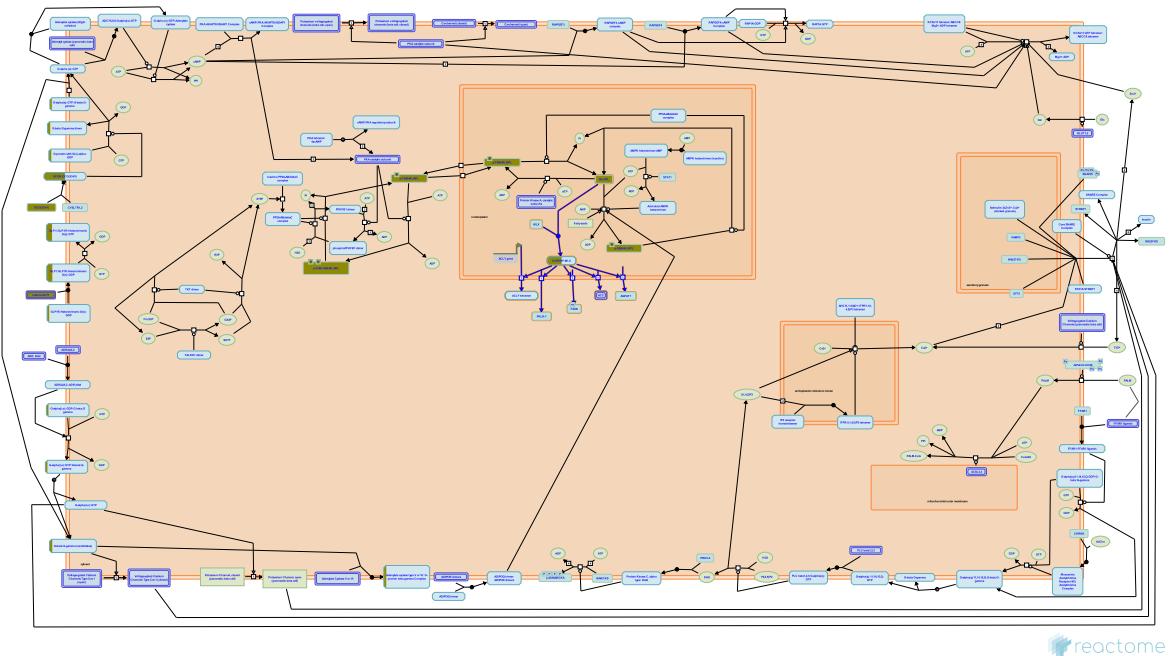
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2013-05-21	Authored	Jassal B
2013-05-21	Created	Jassal B
2014-07-09	Reviewed	Spillmann D
2015-02-09	Modified	Wu G

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
GPC6	Q9Y625

## 15. ChREBP activates metabolic gene expression (R-HSA-163765)



 reactome

**Cellular compartments:** endoplasmic reticulum membrane, nucleoplasm, cytosol.

ChREBP (Carbohydrate Response Element Binding Protein) is a large multidomain protein containing a nuclear localization signal near its amino terminus, polyproline domains, a basic helix-loop-helix-leucine zipper domain, and a leucine-zipper-like domain (Uyeda et al., 2002). Its dephosphorylation in response to molecular signals associated with the well-fed state allows it to enter the nucleus, interact with MLX protein, and bind to ChRE DNA sequence motifs near Acetyl-CoA carboxylase, Fatty acid synthase, and Pyruvate kinase (L isoform) genes (Ishi et al. 2004). This sequence of events is outlined schematically in the picture below (adapted from Kawaguchi et al. (2001) - copyright (2001) National Academy of Sciences, U.S.A.).

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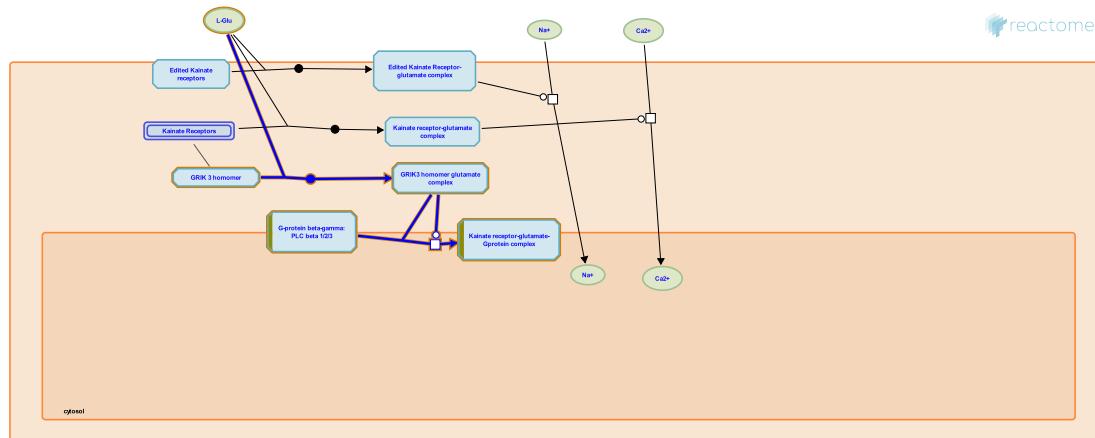
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Date	Action	Author
2005-05-06	Created	Gopinathrao G
2005-05-13	Authored	Gopinathrao G
2021-11-28	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
MLXIPL	Q9NP71

## 16. Presynaptic function of Kainate receptors ([R-HSA-500657](#))



**Cellular compartments:** plasma membrane, extracellular region, cytosol.

Kainate receptors in the presynaptic neuron are involved in modulating the release of neurotransmitters like glutamate and gamma amino butyric acid (GABA). This activity of Kainate receptors is independent of ionic fluxes through the channel. Homomeric kainate receptors containing GRIK3 are shown to be involved in this process. Kainate receptors in these neurons bind G-protein coupled receptors that activate phospholipase C which eventually triggers the release of Ca<sup>2+</sup> from the intracellular stores. The released Ca<sup>2+</sup> further initiates the fusion and release of vesicles containing the neurotransmitter.

## References

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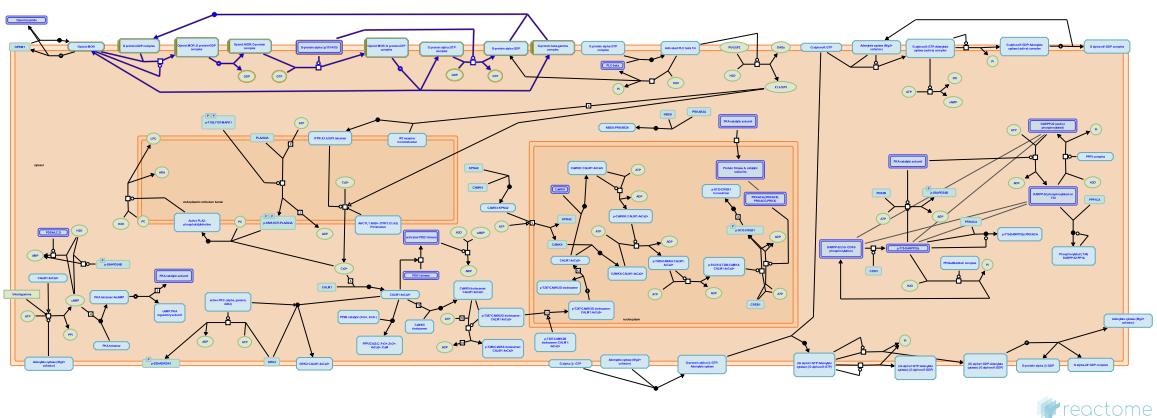
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Date	Action	Author
2009-11-18	Reviewed	Tukey D
2010-01-15	Authored	Mahajan SS
2010-02-05	Created	Mahajan SS
2010-02-06	Edited	Gillespie ME
2021-11-26	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
GNB2	P62879

## 17. G-protein activation (R-HSA-202040)



Receptor activated heterotrimeric G proteins consist of the G $\alpha$  and the tightly associated G $\beta$ -gamma subunits. When a ligand binds to a G protein-coupled receptor, it stabilizes a conformation with a high affinity for the G-protein bound to GDP. GDP is then exchanged for GTP on the G $\alpha$  subunit. This exchange triggers the dissociation of the G $\alpha$  subunit from the G $\beta$ -gamma dimer and the receptor. G $\alpha$ -GTP and G $\beta$ -gamma, can then modulate different signalling cascades and effector proteins, while the receptor is able to activate another G protein, resulting in an amplification cascade. The G $\alpha$  subunit will eventually hydrolyze the attached GTP to GDP by its inherent enzymatic activity, allowing it to reassociate with G $\beta$ -gamma and start a new cycle.

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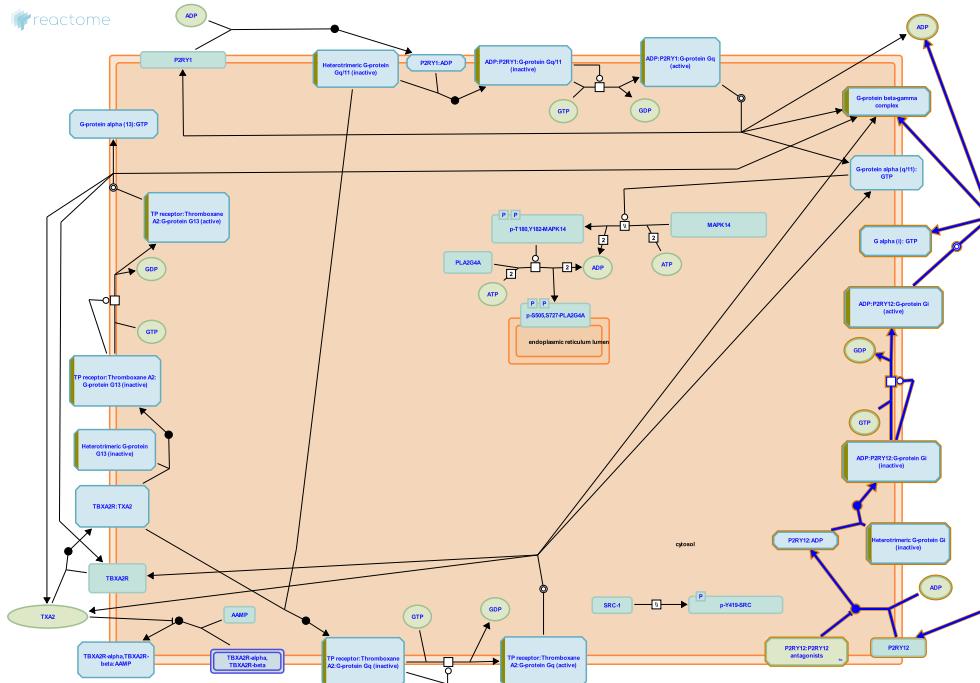
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2007-10-11	Created	Jassal B
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2022-01-09	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
GNB2	P62879

## 18. ADP signalling through P2Y purinoceptor 12 (R-HSA-392170)



**Cellular compartments:** plasma membrane.

Co-activation of P2Y1 and P2Y12 is necessary for complete platelet activation. P2Y1 is coupled to G<sub>q</sub> and helps trigger the release of calcium from internal stores, leading to weak and reversible platelet aggregation. P2Y12 is G<sub>i</sub> coupled, inhibiting adenylate cyclase, leading to decreased cAMP, a consequent decrease in cAMP-dependent protein kinase activity which increases cytoplasmic [Ca<sub>2+</sub>], necessary for activation (Woulfe et al. 2001).

In activated platelets, P2Y12 signaling is required for the amplification of aggregation induced by all platelet agonists including collagen, thrombin, thromboxane, adrenaline and serotonin. P2Y12 activation causes potentiation of thromboxane generation, secretion leading to irreversible platelet aggregation and thrombus stabilization.

## References

Vincent D, Conley PB, Yang RB, Jantzen HM, England L, Li G, ... Hollopeter G (2001). Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature*, 409, 202-7. [🔗](#)

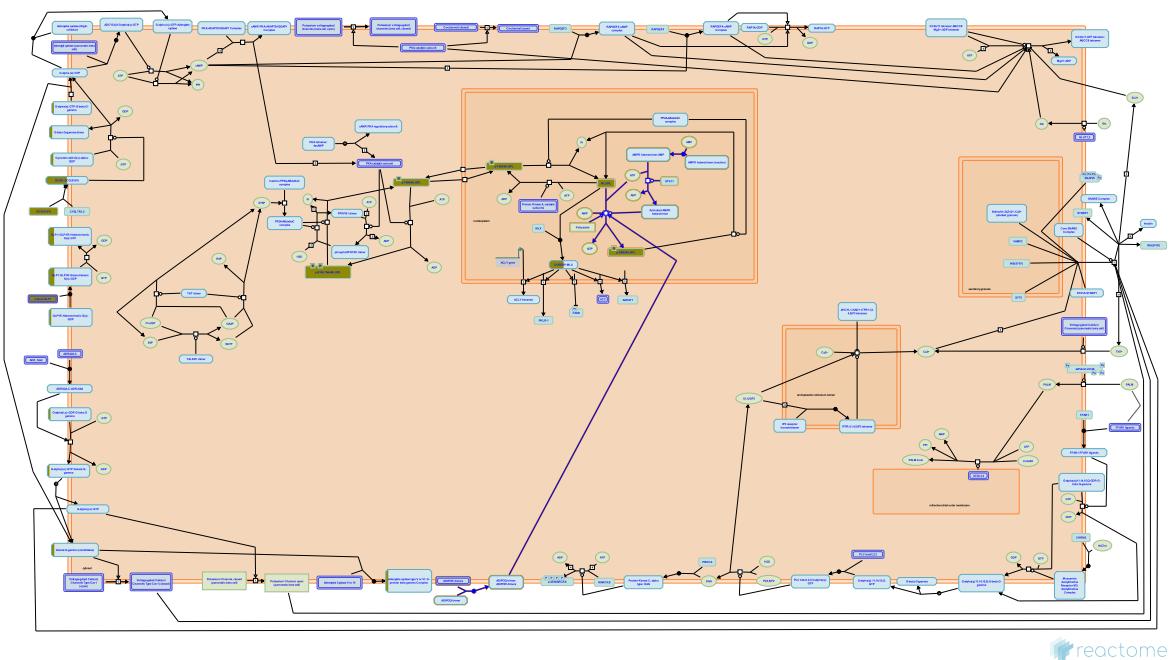
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2009-02-27	Created	Jupe S
2009-09-04	Reviewed	Akkerman JW
2009-09-10	Edited	Jupe S
2022-01-09	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
GNB2	P62879

## 19. AMPK inhibits chREBP transcriptional activation activity (R-HSA-163680)



**Cellular compartments:** nucleoplasm.

AMP-activated protein kinase (AMPK) is a sensor of cellular energy levels. A high cellular ratio of AMP:ATP triggers the phosphorylation and activation of AMPK. Activated AMPK in turn phosphorylates a wide array of target proteins, as shown in the figure below (reproduced from (Hardie et al. 2003), with the permission of D.G. Hardie). These targets include ChREBP (Carbohydrate Response Element Binding Protein), whose inactivation by phosphorylation reduces transcription of key enzymes of the glycolytic and lipogenic pathways.

### References

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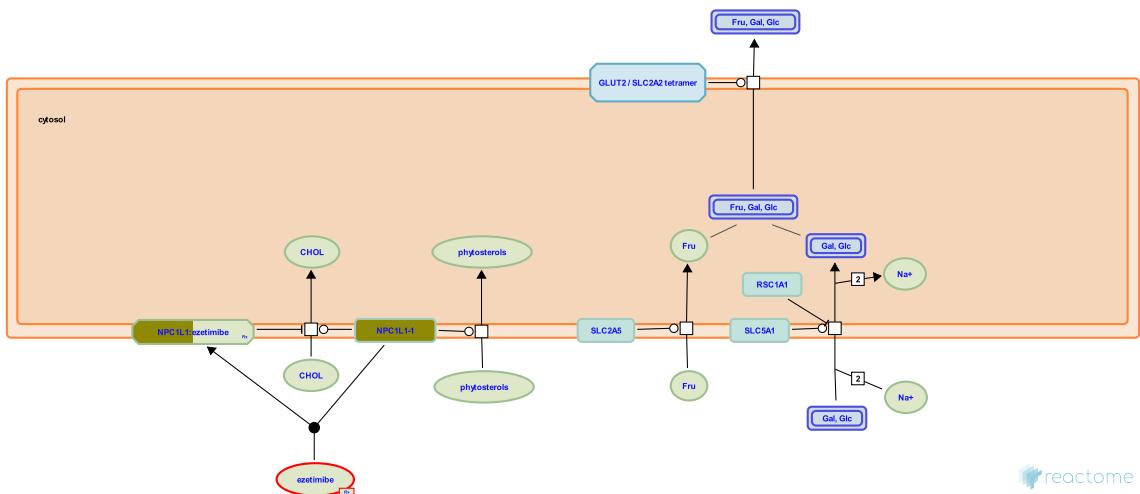
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2005-05-13	Authored	Gopinathrao G
2021-11-28	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
MLXIPL	Q9NP71

## 20. Intestinal absorption (R-HSA-8963676)



reactome

Nutrient absorption occurs mostly in the small intestine. Processes annotated here include the uptake of dietary cholesterol and phytosterols, and of monosaccharides. Movement of the final products of digestion out of the intestinal lumen is mediated by arrays of transporters associated with the apical and basolateral surfaces of enterocytes (Yamada 2015).

## References

Yamada T (2015). *Yamada's Textbook of Gastroenterology*, 3440.

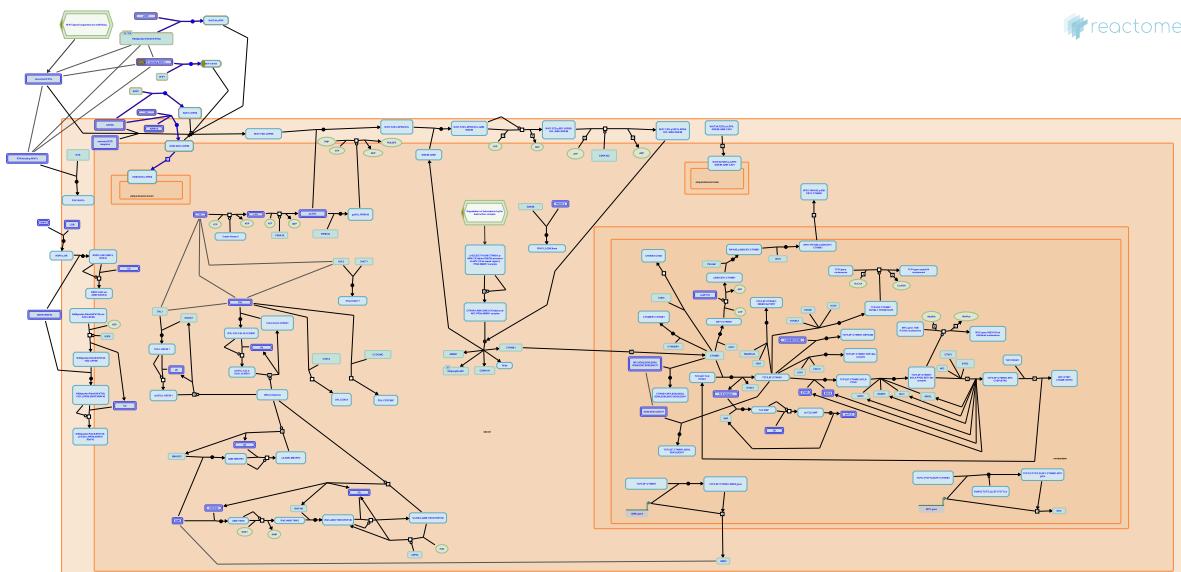
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2017-02-10	Edited	D'Eustachio P
2017-02-10	Created	D'Eustachio P
2021-11-28	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
NPC1L1	Q9UHC9-2

## 21. Negative regulation of TCF-dependent signaling by WNT ligand antagonists (R-HSA-3772470)



**Cellular compartments:** extracellular region.

Several unrelated families of secreted proteins antagonize WNT signaling. Secreted frizzled-related proteins (sFRPs) have a cysteine rich domain (CRD) that is also found in FZD and ROR receptors, while WNT inhibitory factor (WIF) proteins contain a WIF domain also present in the WNT-receptor RYK. Both these classes of secreted WNT antagonists inhibit signaling by binding to WNTs and preventing their interaction with the FZD receptors. sFRPs may also able to bind the receptors, blocking ligand binding (Bafico et al, 1999; reviewed in Kawano and Kypta, 2003). The interaction of WIF and sFRPs with WNT ligand may also play a role in regulating WNT diffusion and gradient formation (reviewed in Bovolenta et al, 2008).

Dickkopf (DKK) and Sclerostin (SOST) family members, in contrast, antagonize WNT signaling by binding to LRP5/6. There are four DKK family members in vertebrates; the closely related DKK1, 2 and 4 proteins have been shown to have roles in WNT signaling, while the more divergent DKK3 appears not to (Glinka et al, 1998; Fedi et al, 1999; Mao et al, 2001; Semenov et al, 2001; reviewed in Niehrs, 2006). Secreted DKK proteins bind to LRP6 in conjunction with the single-pass transmembrane proteins Kremen 1 and 2, and this interaction is thought to disrupt the WNT-induced FZD-LRP5/6 complex. In some cases, DKK2 has also been shown to function as a WNT agonist (reviewed in N (reviewed in Niehrs, 2006).

Like DKK proteins, SOST binds LRP5/6 and disrupts WNT-dependent receptor activation (Semenov et al, 2005).

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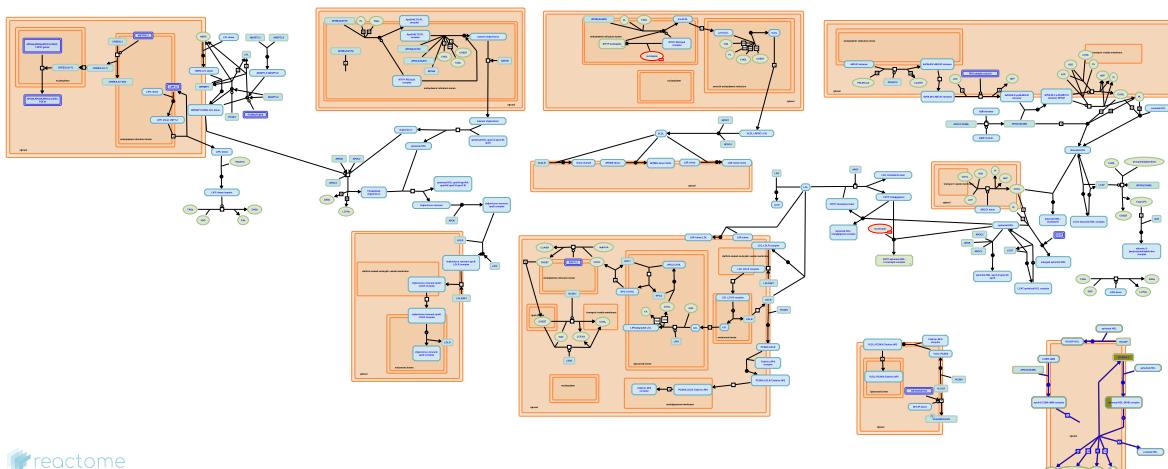
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2013-05-30	Authored	Rothfels K
2013-06-25	Created	Rothfels K
2013-10-03	Edited	Gillespie ME
2014-01-22	Reviewed	Rajakulendran N
2014-02-15	Reviewed	van Amerongen R
2014-04-22	Reviewed	Kikuchi A
2021-11-26	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
WNT4	P56705

## 22. HDL clearance (R-HSA-8964011)



Clearance of circulating HDL particles involves particle binding to cell-surface SR-BI receptors, particle disassembly with release of pre-beta HDL (Silver & Tall 2001), and uptake of the latter mediated by cell-surface CUBN:AMN complex (Kozyraki et al. 1999).

## References

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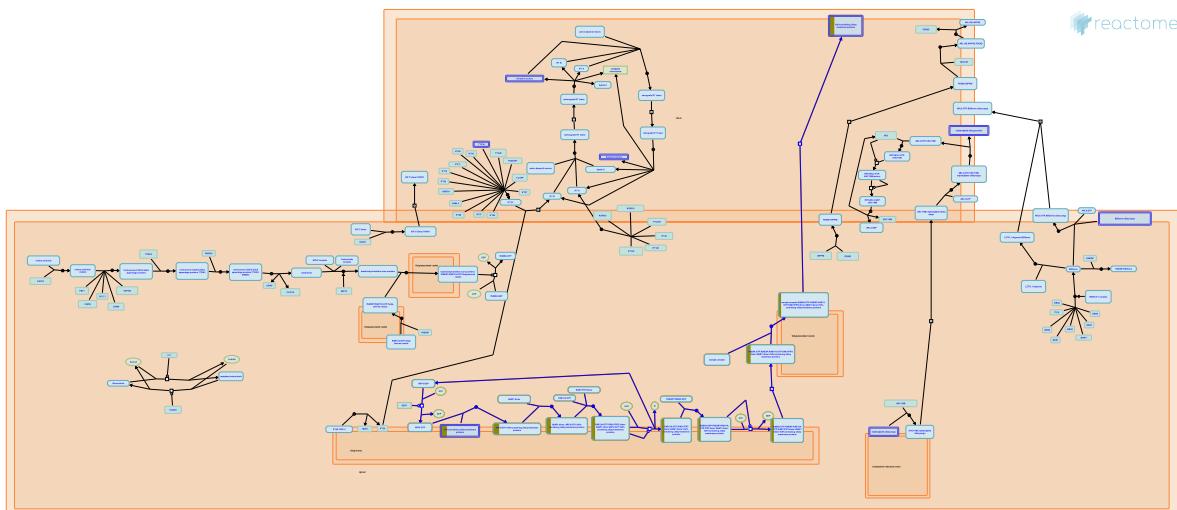
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Date	Action	Author
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2008-05-12	Authored	D'Eustachio P
2016-02-18	Reviewed	Jassal B
2017-02-15	Created	D'Eustachio P
2022-01-09	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
SCARB1	Q8WTV0-2

## 23. VxPx cargo-targeting to cilium (R-HSA-5620916)



A number of membrane proteins destined for the ciliary membrane are recognized by ARF4 in the trans-Golgi network, initiating the formation of a ciliary targeting complex that directs the passage of these cargo to the cilium (Mazelova et al, 2009; Geng et al, 2006; Jenkins et al, 2006; Ward et al, 2011; reviewed in Deretic, 2013). Although there is some support for the presence of a VxPx or related motif in the C-terminal tail of cargo destined for ARF4-mediated transport to the cilium, the details of this have not been definitively established and other ciliary targeting sequences have also been identified (reviewed in Deretic, 2013; Bhogaraju et al, 2013).

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- Deretic D (2013). Crosstalk of Arf and Rab GTPases en route to cilia. *Small GTPases*, 4, 70-7. [🔗](#)

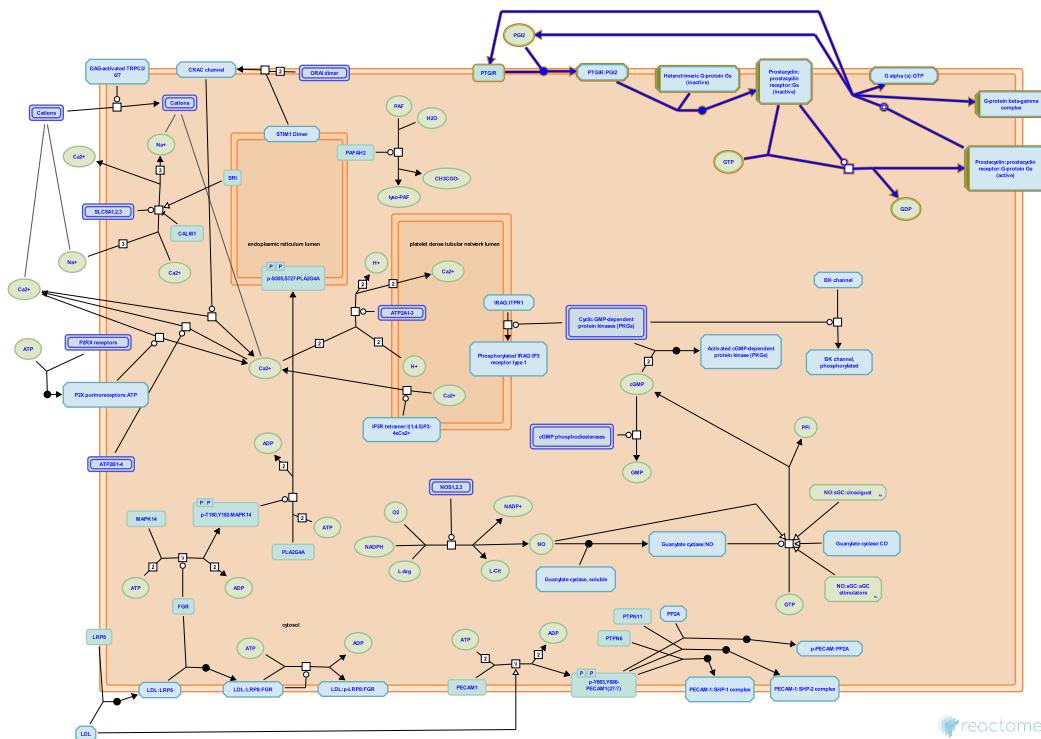
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2014-08-28	Created	Rothfels K
2014-10-13	Edited	Jassal B
2014-11-10	Reviewed	Lorentzen E
2014-11-14	Reviewed	Goncalves J
2021-11-28	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
PKD1	P98161

## 24. Prostacyclin signalling through prostacyclin receptor (R-HSA-392851)



**Cellular compartments:** plasma membrane.

Prostacyclin (PGI<sub>2</sub>) is continuously produced by healthy vascular endothelial cells. It inhibits platelet activation through interaction with the Gs-coupled receptor PTGIR, leading to increased cAMP, a consequent increase in cAMP-dependent protein kinase activity which prevents increases of cytoplasmic [Ca<sup>2+</sup>] necessary for activation (Woulfe et al. 2001). PGI<sub>2</sub> is also an effective vasodilator. These effects oppose the effects of thromboxane (TXA<sub>2</sub>), another eicosanoid, creating a balance of blood circulation and platelet activation.

## References

Douville KL, Stitham J, Arehart EJ, Hwa J & Gleim SR (2007). Human prostacyclin receptor structure and function from naturally-occurring and synthetic mutations. *Prostaglandins Other Lipid Mediat*, 82, 95-108. [View](#)

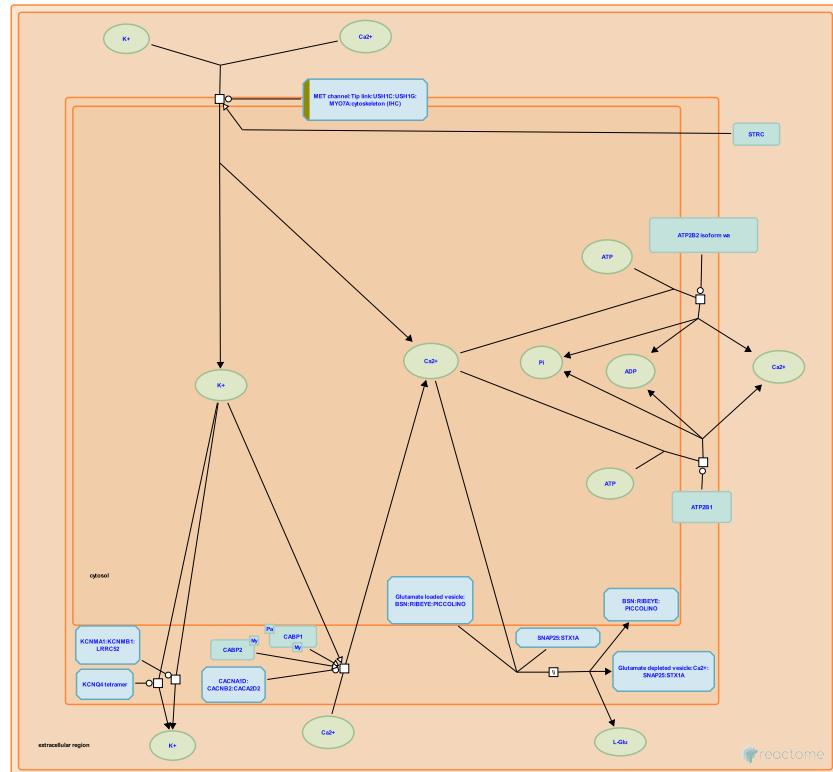
## Edit history

Date	Action	Author
2009-03-09	Created	Jupe S
2009-06-03	Authored	Akkerman JW
2010-06-07	Edited	Jupe S
2010-06-07	Reviewed	Kunapuli SP
2022-01-09	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
GNB2	P62879

## 25. Sensory processing of sound by inner hair cells of the cochlea (R-HSA-9662360)



Inner hair cells (IHCs) of the cochlea transduce sound waves into an ionic (mainly potassium) current that leads to exocytosis of glutamate from the IHC and activation of postsynaptic type I afferent fibers of the radial ganglion (reviewed in Meyer and Moser 2010, Moser and Vogl 2016, Fettiplace 2017). IHCs have stereocilia on their apical surface that are arranged in rows of increasing height, a "staircase" arrangement. Stereocilia of different rows are connected by a tip link comprising a CDH23 dimer on the taller stereocilium bound to a PCDH15 dimer on the shorter stereocilium. PCDH15 interacts with LHFPL5, an auxiliary subunit of the mechanoelectrical transduction channel (MET channel, also called the mechanotransduction channel), which contains at least TMC1 (adults) or TMC2 (newborns), TMIE, and the auxiliary subunits LHFPL5 and CIB2 (reviewed in Fettiplace and Kim 2014, Fettiplace 2016).

Deflection of the stereocilia by sound waves creates tension on the tip link that increases the open probability of the MET channel, which then transports calcium and potassium ions from the scala media into the IHC, depolarizing the IHC (reviewed in Fettiplace 2017). The potassium channel KCNQ4 located in the neck region of the cell may also participate in depolarization. The depolarization of the IHC opens voltage-gated Cav1.3 channels (CACNA1D:CACA2D2:CACNB2) located in stripes near ribbon synapses on the basolateral surface of the IHC. The resulting localized influx of calcium ions activates exocytosis of glutamate into the synapse by an interaction between calcium and Otoferlin (OTOF) on glutamate-loaded vesicles in the IHC (reviewed in Wichmann 2015).

Ribbon synapses are characterized by a multiprotein complex, the ribbon, that contains at least BASSOON, RIBEYE (an isoform of CTBP2), and PICCOLINO (a small isoform of PICCOLO) and appears to act to transiently tether vesicles near the synapse and thereby increase the pool of readily releasable vesicles (reviewed in Safieddine et al. 2012, Wichman and Moser 2015, Pangrsic and Vogl 2018, Moser et al. 2020).

ATP2B1 calcium channels, ATP2B2 calcium channels, KCNMA1:KCNMB1:LRRC52 potassium channels, and basolateral KCNQ4 potassium channels transport cations out of the IHC and thereby act to repolarize the cell and limit the duration of the synaptic potentials (reviewed in Patuzzi 2011, Oak and Yi 2014).

## References

- Wichmann C (2015). Molecularly and structurally distinct synapses mediate reliable encoding and processing of auditory information. *Hear. Res.*, 330, 178-90. [🔗](#)
- Moser T & Vogl C (2016). New insights into cochlear sound encoding. *F1000Res*, 5. [🔗](#)
- Fettiplace R (2016). Is TMC1 the Hair Cell Mechanotransducer Channel?. *Biophys. J.*, 111, 3-9. [🔗](#)
- Oak MH & Yi E (2014). Voltage-gated K(+) channels contributing to temporal precision at the inner hair cell-auditory afferent nerve fiber synapses in the mammalian cochlea. *Arch. Pharm. Res.*, 37, 821-33. [🔗](#)
- Kim KX & Fettiplace R (2014). The physiology of mechanoelectrical transduction channels in hearing. *Physiol. Rev.*, 94, 951-86. [🔗](#)

## Edit history

Date	Action	Author
2019-09-23	Edited	May B
2019-09-23	Authored	May B
2019-09-23	Created	May B
2020-09-14	Reviewed	Furness DN
2020-12-12	Modified	May B

## 2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
EPB41L3	Q9Y2J2	USH1C	Q9Y6N9

## 6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

**23 of the submitted entities were found, mapping to 124 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CAPNS1	A0A5S6GT88, P04574	CBX6	O95503	CECR1	A0A3Q2ULP3
EPB41L3	Q9Y2J2	FBXW4	P57775	GCG	P01275
GNB2	P62879	GPC6	Q9Y625	GRIA3	P42263
LSAMP	Q13449	MLXIPL	Q99MZ3	NPC1L1	Q6T3U4
PCSK2	P16519	PDK4	Q16654	PI4KA	F1PMC5
PKD1	P98161	RPS4Y1	P22090	SCARB1	Q61009
SMPD1	P17405	TXNIP	Q2HY40	USH1C	Q9Y6N9
WDR59	Q6PJI9	WNT4	P56705		

Input	Ensembl Id	Input	Ensembl Id
GCG	ENSG00000115263	WNT4	ENSG00000162552

### Interactors (16)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
C19orf63	Q5UCC4	Q8N4V1	CAPNS1	P04632	P20936
CBX6	O95503	P11940	EPB41L3	Q9Y2J2	P49841
FBXW4	P57775	P63208	GCG	P01275	P01275, P48546
GNB2	P62879	P61081	GRIA3	P19492	Q9EP80
KIAA1324	Q6UXG2-3	P07196	LSAMP	Q13449	Q13352
PI4KA	P42356	P19320	PKD1	Q15139	P02795
SCARB1	Q8WTV0-2	P02649	TXNIP	Q9H3M7	P10599
USH1C	Q9Y6N9-4	P54646	WDR59	Q6PJI9	P55735

## 7. Identifiers not found

These 4 identifiers were not found neither mapped to any entity in Reactome.

FEV

GPR64

KIAA1244

SNX29