



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 78 on 02/12/2021. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTEyMDIxMDIwNDBfMTAwOTQ%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.

Table of Contents

1. Introduction
2. Properties
3. Genome-wide overview
4. Most significant pathways
5. Pathways details
6. Identifiers found
7. Identifiers not found

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:

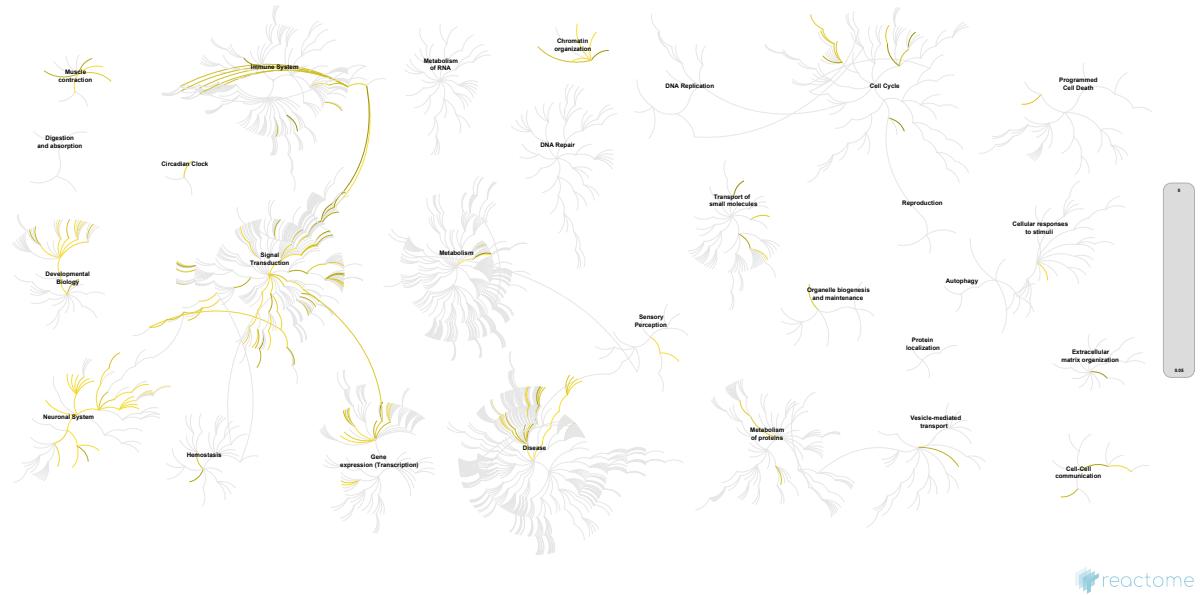
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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 Benjamani-Hochberg method. ↗
- 762 out of 1019 identifiers in the sample were found in Reactome, where 1740 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMTEyMDIxMDIwNDBfMTAwOTQ%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



This figure shows a genome-wide overview of the results of your pathway analysis. Reactome pathways are arranged in a hierarchy. The center of each of the circular "bursts" is the root of one top-level pathway, for example "DNA Repair". Each step away from the center represents the next level lower in the pathway hierarchy. The color code denotes over-representation of that pathway in your input dataset. Light grey signifies pathways which are not significantly over-represented.

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
Neuronal System	120 / 489	0.034	1.11e-16	2.10e-13	174 / 216	0.016
Protein-protein interactions at synapses	39 / 93	0.007	2.55e-15	2.41e-12	29 / 33	0.002
Neurexins and neuroligins	31 / 60	0.004	8.66e-15	5.46e-12	19 / 19	0.001
Transmission across Chemical Synapses	79 / 343	0.024	1.54e-14	7.28e-12	138 / 163	0.012
Chromatin modifying enzymes	58 / 256	0.018	9.47e-11	2.98e-08	51 / 85	0.006
Chromatin organization	58 / 256	0.018	9.47e-11	2.98e-08	51 / 85	0.006
L1CAM interactions	37 / 130	0.009	7.50e-10	2.02e-07	30 / 54	0.004
Neurotransmitter receptors and postsynaptic signal transmission	51 / 232	0.016	3.41e-09	8.04e-07	106 / 109	0.008
Axon guidance	95 / 585	0.041	6.58e-09	1.38e-06	215 / 298	0.022
Nervous system development	98 / 621	0.044	1.49e-08	2.82e-06	223 / 324	0.024
Regulation of MECP2 expression and activity	16 / 39	0.003	5.26e-07	8.99e-05	13 / 14	0.001
Cardiac conduction	32 / 138	0.01	9.11e-07	1.43e-04	20 / 27	0.002
Dopamine Neurotransmitter Release Cycle	13 / 28	0.002	1.59e-06	2.31e-04	4 / 5	3.68e-04
Interaction between L1 and Ankyrins	14 / 33	0.002	1.81e-06	2.44e-04	4 / 4	2.95e-04
Phase 0 - rapid depolarisation	14 / 34	0.002	2.54e-06	3.20e-04	2 / 2	1.47e-04
Unblocking of NMDA receptors, glutamate binding and activation	12 / 27	0.002	6.12e-06	7.22e-04	5 / 5	3.68e-04
Serotonin Neurotransmitter Release Cycle	11 / 23	0.002	7.54e-06	8.37e-04	3 / 4	2.95e-04
Transcriptional Regulation by MECP2	24 / 100	0.007	1.16e-05	0.001	76 / 77	0.006
Long-term potentiation	12 / 31	0.002	2.35e-05	0.002	7 / 7	5.16e-04
Glutamate Neurotransmitter Release Cycle	12 / 32	0.002	3.19e-05	0.003	5 / 8	5.89e-04
Negative regulation of NMDA receptor-mediated neuronal transmission	11 / 27	0.002	3.23e-05	0.003	4 / 4	2.95e-04
Muscle contraction	38 / 213	0.015	3.54e-05	0.003	30 / 42	0.003
Diseases of signal transduction by growth factor receptors and second messengers	71 / 498	0.035	4.05e-05	0.003	298 / 484	0.036
Disorders of Developmental Biology	8 / 16	0.001	9.57e-05	0.007	5 / 5	3.68e-04

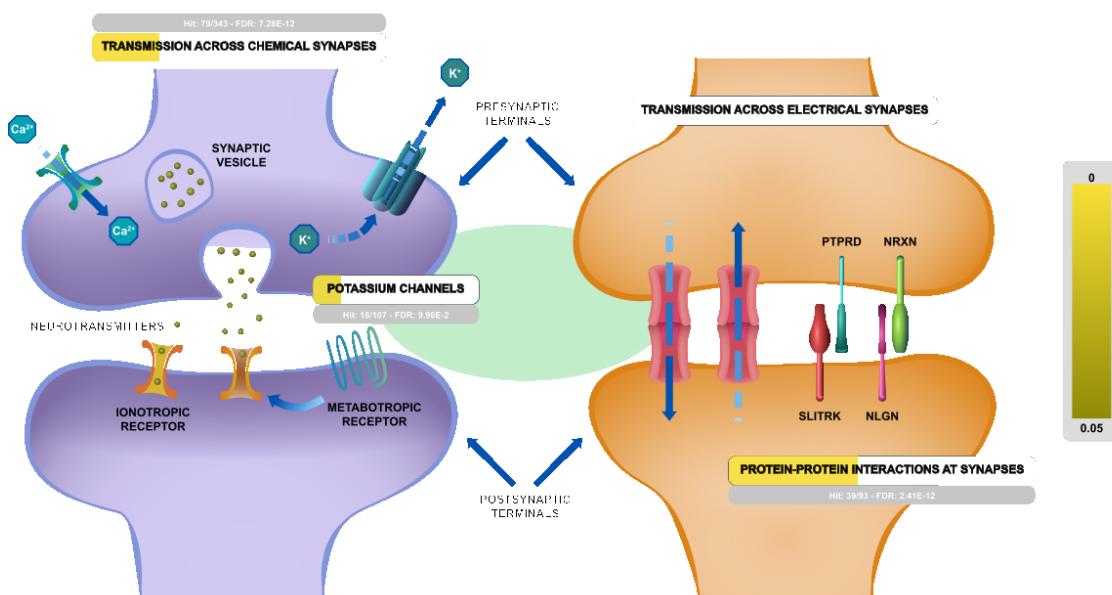
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Disorders of Nervous System Development	8 / 16	0.001	9.57e-05	0.007	5 / 5	3.68e-04

* 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. Neuronal System (R-HSA-112316)



The human brain contains at least 100 billion neurons, each with the ability to influence many other cells. Clearly, highly sophisticated and efficient mechanisms are needed to enable communication among this astronomical number of elements. This communication occurs across synapses, the functional connection between neurons. Synapses can be divided into two general classes: electrical synapses and chemical synapses. Electrical synapses permit direct, passive flow of electrical current from one neuron to another. The current flows through gap junctions, specialized membrane channels that connect the two cells. Chemical synapses enable cell-to-cell communication using neurotransmitter release. Neurotransmitters are chemical agents released by presynaptic neurons that trigger a secondary current flow in postsynaptic neurons by activating specific receptor molecules. Neurotransmitter secretion is triggered by the influx of Ca²⁺ through voltage-gated channels, which gives rise to a transient increase in Ca²⁺ concentration within the presynaptic terminal. The rise in Ca²⁺ concentration causes synaptic vesicles (the presynaptic organelles that store neurotransmitters) to fuse with the presynaptic plasma membrane and release their contents into the space between the pre- and postsynaptic cells.

References

Fitzpatrick D, Augustine DJ, Katz LC, Williams JM, Purves D, McNamara JO & LaMantia AS (2001). *Neuroscience 2nd Edition*.

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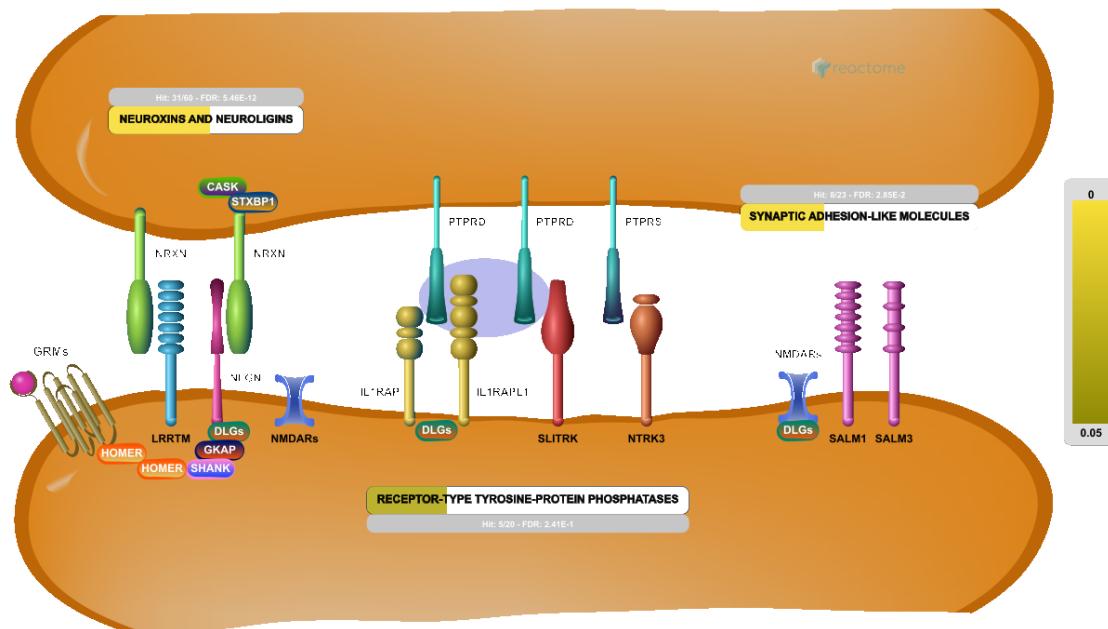
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2004-04-22	Created	Joshi-Tope G
2005-11-10	Edited	Gillespie ME

Date	Action	Author
2005-11-10	Authored	Gillespie ME
2021-09-10	Modified	Weiser JD

122 submitted entities found in this pathway, mapping to 130 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1007	Q9P2U7	10089	Q9Y2U2	1012	Q05940
109	O60266	111	O95622	11141	Q9NZN1
1139	P36544	1142	Q05901	1175	P53680-1
170572	Q8WXA8	1739	Q12959	1740	Q15700
1742	P78352	18	P80404	2258	P0DP23
2259	P0DP23	22829	Q8NFZ3	22871	Q8N2Q7
22941	Q9UPX8	22999	Q86UR5	23229	O43307
23236	Q9NQ66	2556	P34903	2557	P48169
2561	P47870	2562	P28472	2567	Q99928
26050	O94991	26122	O43307	26173	Q16558
26280	Q9NP60	26960	Q8NFP9	27328	Q15825
2739	Q14957	2742	P23416, Q13255	2770	P63096
2890	P42261	2891	O94925, P42262	2898	Q13002
2899	Q13003	2900	Q16099	2901	Q16478
2902	Q05586	2903	Q12879	2904	Q13224
2915	P41594	29998	P46098	321	Q99767
3265	P01112	3359	P46098	348980	O60741
373	P46098	3745	Q14721	3746	P48547
3751	Q9NZV8	3752	Q9UK17	3766	P78508
3772	Q99712	3778	Q12791	3785	O43526, P61764
3786	O43525, Q09428	3790	Q9BQ31	3949	P63027
4128	P21397	4137	P10636-8	43	P22303
438	P78508	473	Q05901	476	Q07001
4916	Q16288	50944	Q9Y566	54413	Q9NZ94
546	Q14721	547	Q92953	552	Q9NSA2
553	Q9NZV8	5575	P31321	5578	P17252
5579	P05771	55799	Q8IZS8	5595	P27361
563	P56696	57497	Q9ULH4	57502	Q8N0W4
57555	Q8NFZ4	58512	O95886	5879	P63000
6196	Q15349	6197	P51812	64130	Q9HAP6
6505	P43005	6506	P43004	6529	P30531
6531	Q01959	6532	P31645	6616	P60880
6804	Q16623	6812	P61764, P61764-1	6844	P63027
6853	P17600	6854	Q92777	6857	P21579
7102	P41732	773	O00555	774	Q00975
777	Q15878	782	Q02641	783	Q08289
7915	P51649	814	Q16566	815	Q9UQM7
816	Q13554	8500	Q13136	8573	O14936
9228	Q9P1A6	9229	O14490	9256	O95153
9369	Q9HDB5, Q9Y4C0	9378	P58400, Q9ULB1	9379	P58401, Q9P2S2
9456	Q86YM7	9568	O75899		

2. Protein-protein interactions at synapses (R-HSA-6794362)



Cellular compartments: plasma membrane, cytosol.

Synapses constitute highly specialized sites of asymmetric cell-cell adhesion and intercellular communication. Its formation involves the recruitment of presynaptic and postsynaptic molecules at newly formed contacts. Synapse assembly and maintenance invokes heterophilic presynaptic and postsynaptic transmembrane proteins that bind each other in the extracellular space and recruit additional proteins via their intracellular domains. Members of the cadherin and immunoglobulin (Ig) superfamilies are thought to mediate this function. Several molecules, including synaptic cell-adhesion molecule (SynCAM), N-cadherin, neural cell-adhesion molecule (NCAM), Eph receptor tyrosine kinases, and neuroligins and neurexins, have been implicated in synapse formation and maintenance (Dean & Dresbach 2006, Craig et al. 2006, Craig & Kang 2007, Sudhof 2008).

References

- McClelland AC, Dalva MB & Kayser MS (2007). Cell adhesion molecules: signalling functions at the synapse. *Nat. Rev. Neurosci.*, 8, 206-20. [🔗](#)
- Dresbach T & Dean C (2006). Neuroligins and neurexins: linking cell adhesion, synapse formation and cognitive function. *Trends Neurosci.*, 29, 21-9. [🔗](#)
- Südhof TC (2008). Neuroligins and neurexins link synaptic function to cognitive disease. *Nature*, 455, 903-11. [🔗](#)

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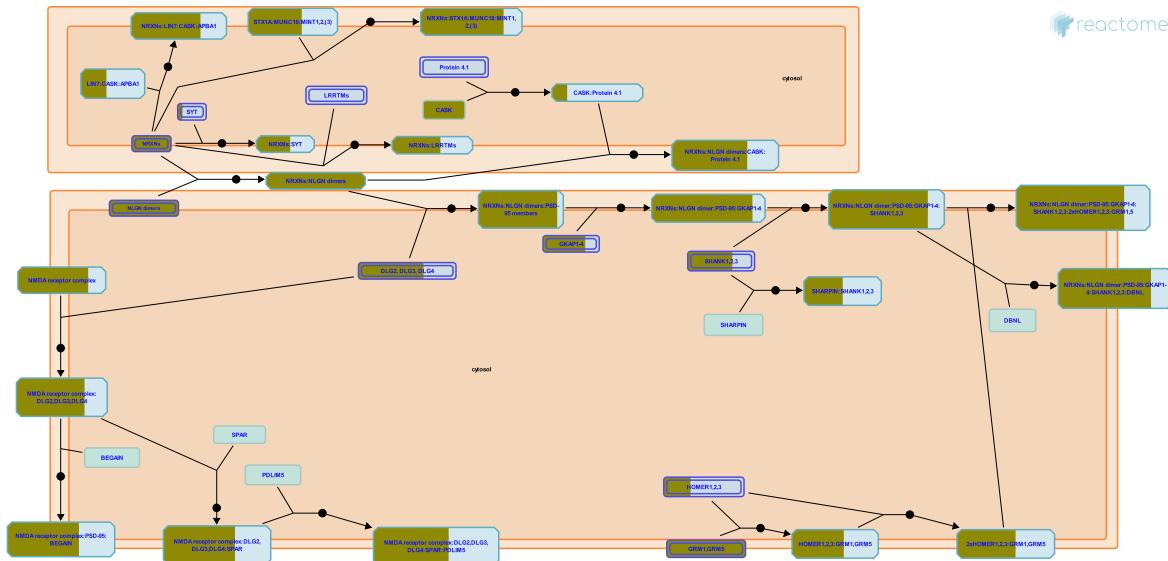
Date	Action	Author
2015-09-04	Edited	Garapati P V
2015-09-04	Authored	Garapati P V
2015-09-04	Created	Garapati P V
2015-11-09	Reviewed	Washbourne P

Date	Action	Author
2021-09-10	Modified	Weiser JD

37 submitted entities found in this pathway, mapping to 40 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
11141	Q9NZN1	1739	Q12959	1740	Q15700
1742	P78352	22829	Q8NFZ3	22871	Q8N2Q7
22941	Q9UPX8	26050	O94991	26280	Q9NP60
2739	Q14957	2742	Q13255	2890	P42261
2902	Q05586	2903	Q12879	2904	Q13224
2915	P41594	321	Q99767	3785	P61764
4916	Q16288	50944	Q9Y566	54413	Q9NZ94
57497	Q9ULH4	57502	Q8N0W4	57555	Q8NFZ4
58512	O95886	64130	Q9HAP6	6804	Q16623
6812	P61764	6857	P21579	8500	Q13136
8573	O14936	9228	Q9P1A6	9229	O14490
9369	Q9HDB5, Q9Y4C0	9378	P58400, Q9ULB1	9379	P58401, Q9P2S2
9456	Q86YM7				

3. Neurexins and neuroligins (R-HSA-6794361)



Neurexins (NRXNs) and neuroligins (NLGNs) are best characterized synaptic cell-adhesion molecules. They are part of excitatory glutamatergic and inhibitory GABAergic synapses in mammalian brain, mediate trans-synaptic signaling, and shape neural network properties by specifying synaptic functions. As cell-adhesion molecules, NRXNs and NLGNs probably function by binding to each other and by interacting with intracellular PDZ-domain proteins, but the precise mechanisms involved and their relation to synaptic transmission remain unclear. The binding of NRXNs and NLGNs to their partners, helps to align the pre-synaptic release machinery and post-synaptic receptors. The importance of neurexins and neuroligins for synaptic function is evident from the dramatic deficits in synaptic transmission in mice lacking Nrxns or Nlgn. In humans, alterations in NRXNs or NLGNs genes are implicated in autism and other cognitive diseases, connecting synaptic cell adhesion to cognition and its disorders (Sudhof 2008, Craig et al. 2006, Craig & Kang 2007).

References

- Bang ML & Owczarek S (2013). A matter of balance: role of neurexin and neuroligin at the synapse. *Neurochem. Res.*, 38, 1174-89. [View](#)
- Papadopoulos T, Brose N, Tuffy LP & Krueger DD (2012). The role of neurexins and neuroligins in the formation, maturation, and function of vertebrate synapses. *Curr. Opin. Neurobiol.*, 22, 412-22. [View](#)
- Craig AM & Kang Y (2007). Neurexin-neuroligin signaling in synapse development. *Curr. Opin. Neurobiol.*, 17, 43-52. [View](#)
- Wright GJ & Washbourne P (2011). Neurexins, neuroligins and LRRM: synaptic adhesion getting fishy. *J. Neurochem.*, 117, 765-78. [View](#)
- McClelland AC, Dalva MB & Kayser MS (2007). Cell adhesion molecules: signalling functions at the synapse. *Nat. Rev. Neurosci.*, 8, 206-20. [View](#)

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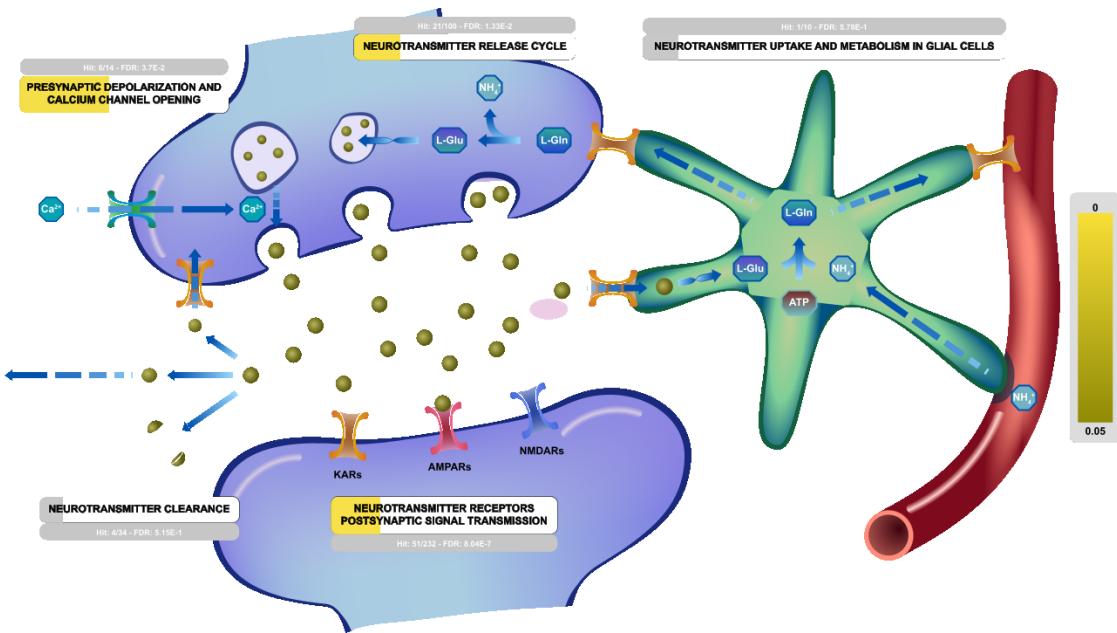
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2015-09-04	Edited	Garapati P V

Date	Action	Author
2015-09-04	Authored	Garapati P V
2015-09-04	Created	Garapati P V
2015-11-09	Reviewed	Washbourne P
2021-09-10	Modified	Weiser JD

29 submitted entities found in this pathway, mapping to 32 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1740	Q15700	1742	P78352	22829	Q8NFZ3
22871	Q8N2Q7	22941	Q9UPX8	2739	Q14957
2742	Q13255	2902	Q05586	2903	Q12879
2904	Q13224	2915	P41594	321	Q99767
3785	P61764	50944	Q9Y566	54413	Q9NZ94
57502	Q8N0W4	57555	Q8NFZ4	58512	O95886
64130	Q9HAP6	6804	Q16623	6812	P61764
6857	P21579	8573	O14936	9228	Q9P1A6
9229	O14490	9369	Q9HDB5, Q9Y4C0	9378	P58400, Q9ULB1
9379	P58401, Q9P2S2	9456	Q86YM7		

4. Transmission across Chemical Synapses (R-HSA-112315)



Chemical synapses are specialized junctions that are used for communication between neurons, neurons and muscle or gland cells. The synapse involves a presynaptic neuron and a postsynaptic neuron, muscle cell or glad cell. The pre and the postsynaptic cell are separated by a gap (space) of 20 to 40 nm called the synaptic cleft. The signals pass in a single direction from the presynaptic to postsynaptic neuron (cell). The presynaptic neuron communicates via the release of neurotransmitter which bind the receptors on the postsynaptic cell. The process is initiated when an action potential invades the terminal membrane of the presynaptic neuron.

Action potentials occur in electrically excitable cells such as neurons and muscles and endocrine cells. They are initiated by the transient opening of voltage dependent sodium channels, causing a rapid, large depolarization of membrane potentials that spread along the axon membrane.

When action potentials arrive at the synaptic terminals, depolarization in membrane potential leads to the opening of voltage gated calcium channels located on the presynaptic membrane. The external Ca^{2+} concentration is approximately 10-3 M while the internal Ca^{2+} concentration is approximately 10-7 M. Opening of calcium channels causes a rapid influx of Ca^{2+} into the presynaptic terminal. The elevated presynaptic Ca^{2+} concentration allows synaptic vesicles to fuse with the plasma membrane of the presynaptic neuron and release their contents, neurotransmitters, into the synaptic cleft. These diffuse across the synaptic cleft and bind to specific receptors on the membrane of the postsynaptic cells. Activation of postsynaptic receptors upon neurotransmitter binding can lead to a multitude of effects in the postsynaptic cell, such as changing the membrane potential and excitability, and triggering intracellular signaling cascades.

References

Fitzpatrick D, Augustine DJ, Katz LC, Williams JM, Purves D, McNamara JO & LaMantia AS (2001). *Neuroscience 2nd Edition*.

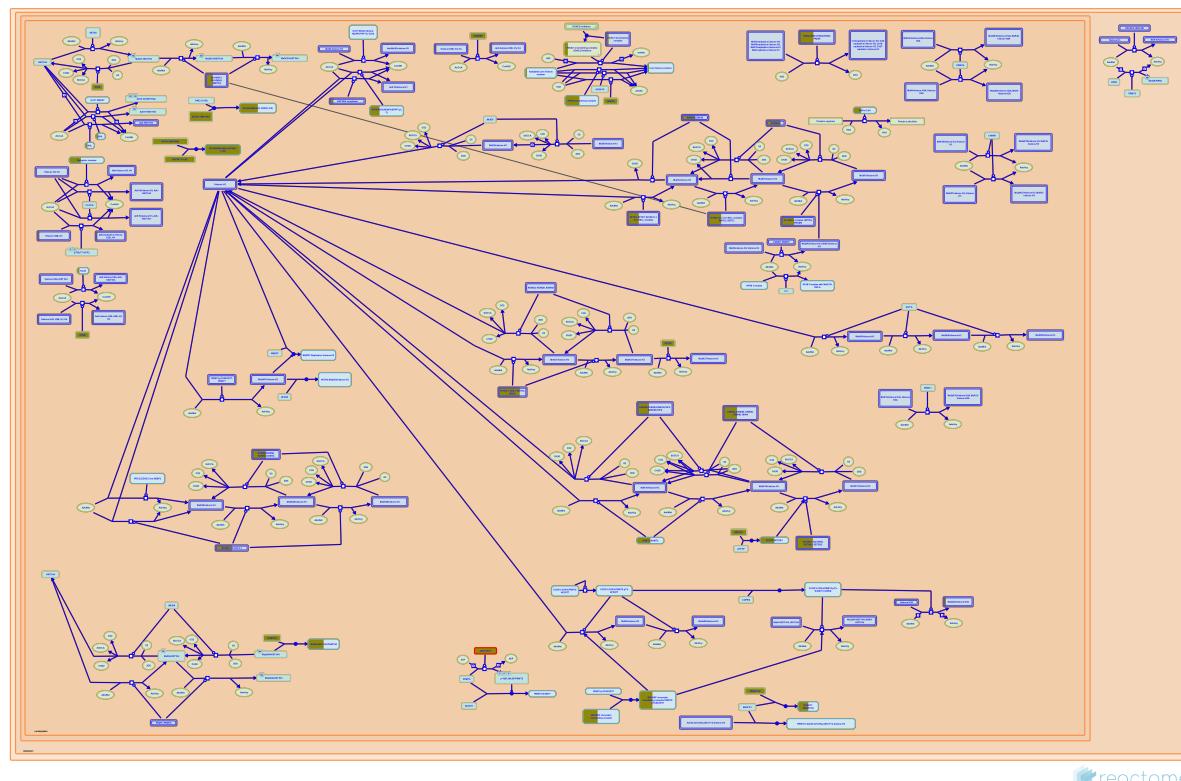
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Date	Action	Author
2004-04-22	Created	Joshi-Tope G
2008-01-14	Edited	Mahajan SS
2008-01-14	Authored	Mahajan SS
2008-12-02	Reviewed	Restituito S, Kavalali E
2020-01-24	Reviewed	Wen H
2021-09-10	Modified	Weiser JD

85 submitted entities found in this pathway, mapping to 86 Reactome entities

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1007	Q9P2U7	1012	Q05940	109	O60266
111	O95622	1139	P36544	1142	Q05901
1175	P53680-1	170572	Q8WXA8	1739	Q12959
1740	Q15700	1742	P78352	18	P80404
2258	P0DP23	2259	P0DP23	22999	Q86UR5
23229	O43307	23236	Q9NQ66	2556	P34903
2557	P48169	2561	P47870	2562	P28472
2567	Q99928	26122	O43307	26960	Q8NFP9
27328	Q15825	2739	Q14957	2742	P23416
2770	P63096	2890	P42261	2891	O94925, P42262
2898	Q13002	2899	Q13003	2900	Q16099
2901	Q16478	2902	Q05586	2903	Q12879
2904	Q13224	29998	P46098	3265	P01112
3359	P46098	373	P46098	3766	P78508
3772	Q99712	3949	P63027	4128	P21397
4137	P10636-8	43	P22303	438	P78508
473	Q05901	476	Q07001	5575	P31321
5578	P17252	5579	P05771	55799	Q8IZS8
5595	P27361	5879	P63000	6196	Q15349
6197	P51812	64130	Q9HAP6	6505	P43005
6506	P43004	6529	P30531	6531	Q01959
6532	P31645	6616	P60880	6804	Q16623
6812	P61764-1	6844	P63027	6853	P17600
6854	Q92777	6857	P21579	7102	P41732
773	O00555	774	Q00975	777	Q15878
782	Q02641	783	Q08289	7915	P51649
814	Q16566	815	Q9UQM7	816	Q13554
8500	Q13136	8573	O14936	9256	O95153
9568	O75899				

5. Chromatin modifying enzymes (R-HSA-3247509)



reactome

Eukaryotic DNA is associated with histone proteins and organized into a complex nucleoprotein structure called chromatin. This structure decreases the accessibility of DNA but also helps to protect it from damage. Access to DNA is achieved by highly regulated local chromatin decondensation.

The 'building block' of chromatin is the nucleosome. This contains ~150 bp of DNA wrapped around a histone octamer which consists of two each of the core histones H2A, H2B, H3 and H4 in a 1.65 left-handed superhelical turn (Luger et al. 1997, Andrews & Luger 2011).

Most organisms have multiple genes encoding the major histone proteins. The replication-dependent genes for the five histone proteins are clustered together in the genome in all metazoans. Human replication-dependent histones occur in a large cluster on chromosome 6 termed HIST1, a smaller cluster HIST2 on chromosome 1q21, and a third small cluster HIST3 on chromosome 1q42 (Marzluff et al. 2002). Histone genes are named systematically according to their cluster and location within the cluster.

The 'major' histone genes are expressed primarily during the S phase of the cell cycle and code for the bulk of cellular histones. Histone variants are usually present as single-copy genes that are not restricted in their expression to S phase, contain introns and are often polyadenylated (Old & Woodland 1984). Some variants have significant differences in primary sequence and distinct biophysical characteristics that are thought to alter the properties of nucleosomes. Others localize to specific regions of the genome. Some variants can exchange with pre-existing major histones during development and differentiation, referred to as replacement histones (Kamakaka & Biggins 2005). These variants can become the predominant species in differentiated cells (Pina & Suau 1987, Wunsch et al. 1991). Histone variants may have specialized functions in regulating chromatin dynamics.

The H2A histone family has the highest sequence divergence and largest number of variants. H2A.Z and H2A.XH2A are considered 'universal variants', found in almost all organisms (Talbert & Henikoff 2010). Variants differ mostly in the C-terminus, including the docking domain, implicated in interactions with the (H3-H4)x2 tetramer within the nucleosome, and in the L1 loop, which is the interaction interface of H2A-H2B dimers (Bonisch & Hake 2012). Canonical H2A proteins are expressed almost exclusively during S-phase. There are several nearly identical variants (Marzluff et al. 2002). No functional specialization of these canonical H2A isoforms has been demonstrated (Bonisch & Hake 2012). Reversible histone modifications such as acetylation and methylation regulate transcription from genomic DNA, defining the 'readability' of genes in specific tissues (Kouzarides 2007, Marmorstein & Trievel 2009, Butler et al. 2012).

N.B. The coordinates of post-translational modifications represented here follow Reactome standardized naming, which includes the UniProt standard practice whereby coordinates refer to the translated protein before any further processing. Histone literature typically refers to coordinates of the protein after the initiating methionine has been removed; therefore the coordinates of post-translated histone residues described here are frequently +1 when compared with the literature. For more information on Reactome's standards for naming pathway events, the molecules that participate in them and representation of post-translational modifications, please refer to Naming Conventions on the Reactome Wiki or Jupe et al. 2014.

References

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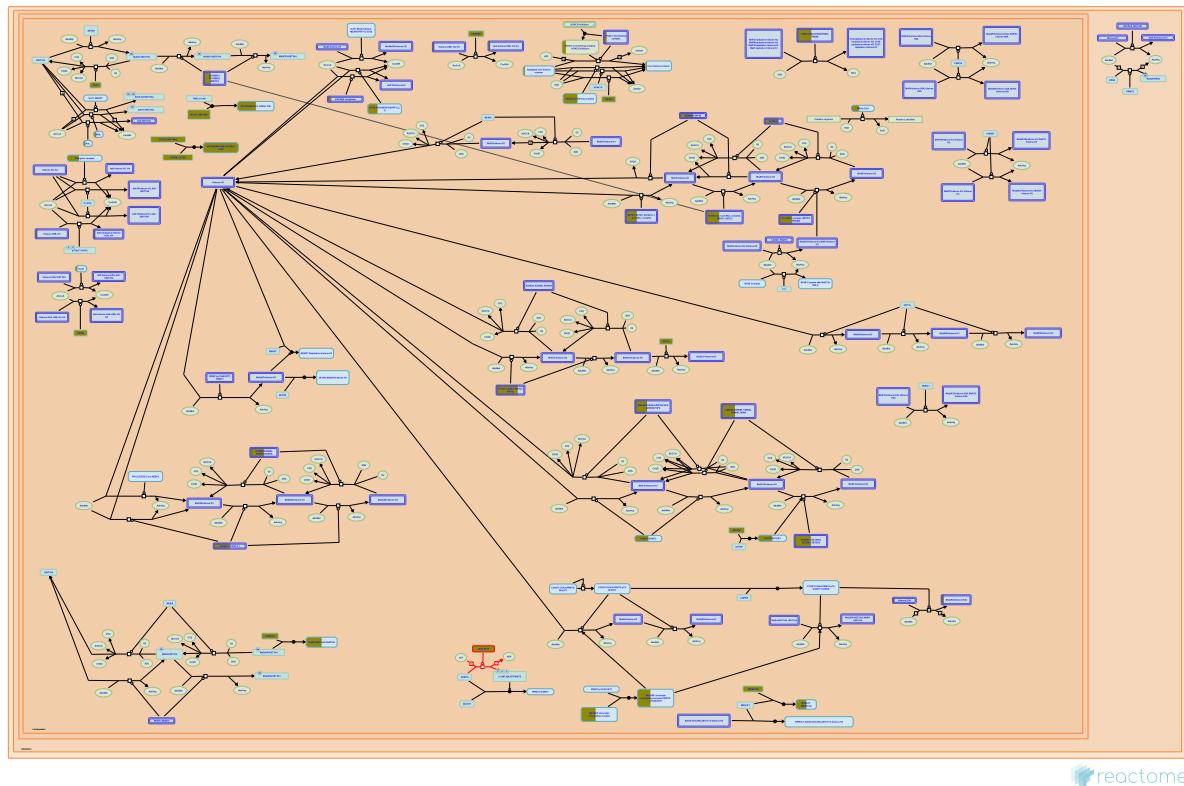
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2013-04-04	Created	Jupe S
2013-11-18	Edited	Jupe S
2013-11-18	Reviewed	Karagiannis T
2021-09-10	Modified	Weiser JD

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10499	Q15596	10765	Q9UGL1	10943	Q8N5Y2
1107	Q12873	1387	Q92793	1788	Q9Y6K1
196528	Q68CP9	2033	Q09472	2048	O60674
221656	Q8NB78	23030	O94953	23067	Q9UPS6
23081	Q9H3R0	23133	Q9UPP1	23135	O15054
23522	Q8WYB5	26610	Q96EB1	2670	Q8NB78
2739	P51531	284058	Q7Z3B3	2894	Q9ULC6
29072	Q9BYW2	3054	P51610	3290	Q9UM07
4297	Q03164	51111	Q4FZB7	51317	Q96BD5
51412	O94805	51780	Q7LBC6	53615	O95983
55250	Q6IA86	55689	Q9ULM3	55869	Q9BY41
55870	Q9NR48	55904	Q8IZD2	57492	Q8NFD5
57634	Q96L91	58508	Q8NEZ4	5927	P29375
60	P60709	64324	Q96L73	6595	P51531
6597	P51532	6601	Q8TAQ2	6907	O60907

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
7403	O15550	7468	O96028	79718	Q9BZK7
79813	Q9H9B1	7994	Q92794	8242	P41229
8295	Q9Y4A5	83696	P0C0S5	83852	Q96T68
8648	Q15788	8850	Q92831	8970	P06899
9611	O75376	9739	O15047	9869	Q15047

6. Chromatin organization (R-HSA-4839726)



Cellular compartments: nucleoplasm.

Chromatin organization refers to the composition and conformation of complexes between DNA, protein and RNA. It is determined by processes that result in the specification, formation or maintenance of the physical structure of eukaryotic chromatin. These processes include histone modification, DNA modification, and transcription. The modifications are bound by specific proteins that alter the conformation of chromatin.

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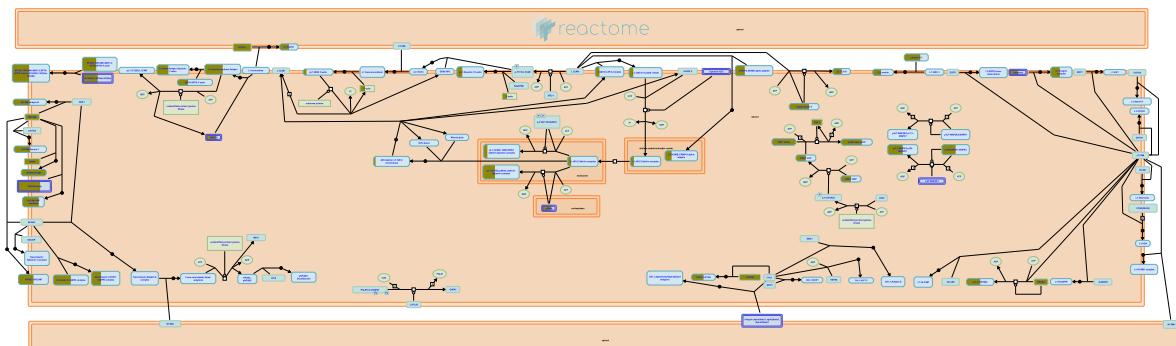
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Date	Action	Author
2013-11-02	Edited	May B
2013-11-02	Authored	May B
2013-11-02	Created	May B
2013-11-18	Reviewed	Karagiannis T
2021-09-10	Modified	Weiser JD

60 submitted entities found in this pathway, mapping to 60 Reactome entities

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1107	Q12873	1387	Q92793	1788	Q9Y6K1
196528	Q68CP9	2033	Q09472	2048	O60674
221656	Q8NB78	23030	O94953	23067	Q9UPS6
23081	Q9H3R0	23133	Q9UPP1	23135	O15054
23522	Q8WYB5	26610	Q96EB1	2670	Q8NB78
2739	P51531	284058	Q7Z3B3	2894	Q9ULC6
29072	Q9BYW2	3054	P51610	3290	Q9UM07
4297	Q03164	51111	Q4FZB7	51317	Q96BD5
51412	O94805	51780	Q7LBC6	53615	O95983
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55870	Q9NR48	55904	Q8IZD2	57492	Q8NFD5
57634	Q96L91	58508	Q8NEZ4	5927	P29375
60	P60709	64324	Q96L73	6595	P51531
6597	P51532	6601	Q8TAQ2	6907	O60907
7403	O15550	7468	O96028	79718	Q9BZK7
79813	Q9H9B1	7994	Q92794	8242	P41229
8295	Q9Y4A5	83696	P0C0S5	83852	Q96T68
8648	Q15788	8850	Q92831	8970	P06899
9611	O75376	9739	O15047	9869	Q15047

7. L1CAM interactions (R-HSA-373760)



The L1 family of cell adhesion molecules (L1CAMs) are a subfamily of the immunoglobulin superfamily of transmembrane receptors, comprised of four structurally related proteins: L1, Close Homolog of L1 (CHL1), NrCAM, and Neurofascin. These CAMs contain six Ig like domains, five or six fibronectin like repeats, a transmembrane region and a cytoplasmic domain. The L1CAM family has been implicated in processes integral to nervous system development, including neurite outgrowth, neurite fasciculation and inter neuronal adhesion.

L1CAM members are predominately expressed by neuronal, as well as some nonneuronal cells, during development. Except CHL1 all the other members of L1 family contain an alternatively spliced 12-nucleotide exon, encoding the amino acid residues RSLE in the neuronal splice forms but missing in the non-neuronal cells. The extracellular regions of L1CAM members are divergent and differ in their abilities to interact with extracellular, heterophilic ligands. The L1 ligands include other Ig-domain CAMs (such as NCAM, TAG-1/axonin and F11), proteoglycans type molecules (neurocan), beta1 integrins, and extra cellular matrix protein laminin, Neuropilin-1, FGF and EGF receptors. Some of these L1-interacting proteins also bind to other L1CAM members. For example TAG-1/axonin interact with L1 and NrCAM; L1, neurofascin and CHL1 binds to contactin family members. The cytoplasmic domains of L1CAM members are most highly conserved. Nevertheless, they have different cytoplasmic binding partners, and even those with similar binding partners may be involved in different signaling complexes and mechanisms. The most conserved feature of L1CAMs is their ability to interact with the actin cytoskeletal adapter protein ankyrin. The cytoplasmic ankyrin-binding domain, exhibits the highest degree of amino acid conservation throughout the L1 family.

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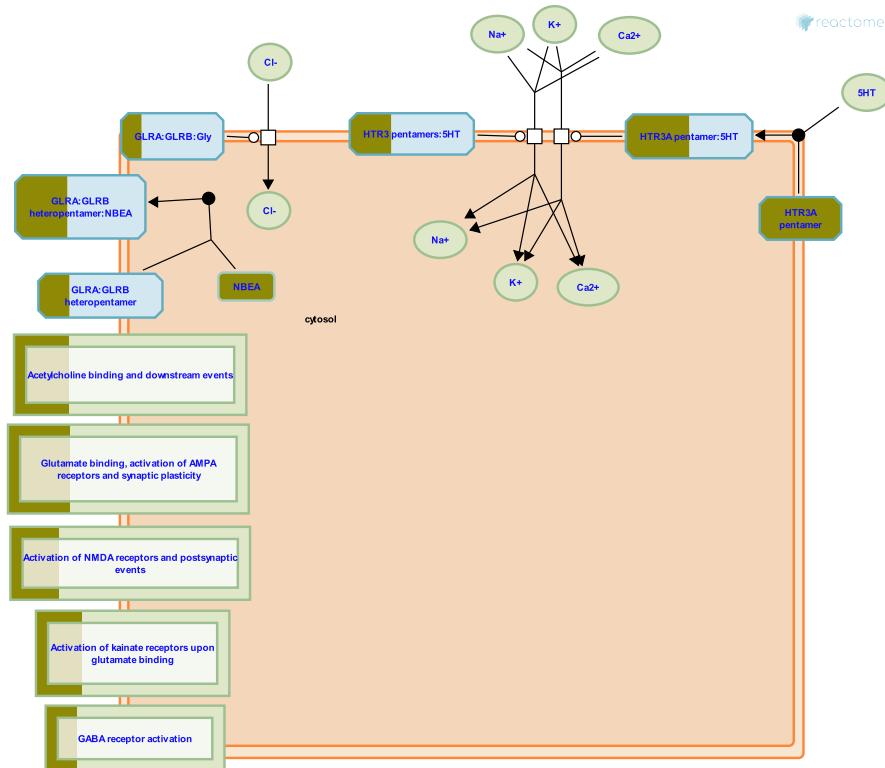
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2008-07-16	Created	Garapati P V
2008-07-30	Edited	Garapati P V
2008-07-30	Authored	Garapati P V
2010-02-16	Reviewed	Maness PF
2021-09-10	Modified	Weiser JD

38 submitted entities found in this pathway, mapping to 39 Reactome entities

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1742	P78352	1808	P11362-1, Q16555	2048	P29323
2260	P11362-1	22907	P78357	23001	P25391
2444	P08648	26470	Q13797	27255	Q9UQ52
284217	P25391	287	Q01484	288	Q12955
3690	P05106	3751	O15020	3785	O43526
3786	O43525	3912	P07942	4897	Q92823
5058	Q13153	5595	P27361	585	Q9Y5Y9
5879	P63000	60	P60709	6196	Q15349
6197	P51812	6323	P35498	6326	Q99250
6329	P35499	6334	Q9UQD0	6335	Q15858
6711	Q01082	8828	O60462		

8. Neurotransmitter receptors and postsynaptic signal transmission (R-HSA-112314)



The neurotransmitter in the synaptic cleft released by the pre-synaptic neuron binds specific receptors located on the post-synaptic terminal. These receptors are either ion channels or G protein coupled receptors that function to transmit the signals from the post-synaptic membrane to the cell body.

References

Edit history

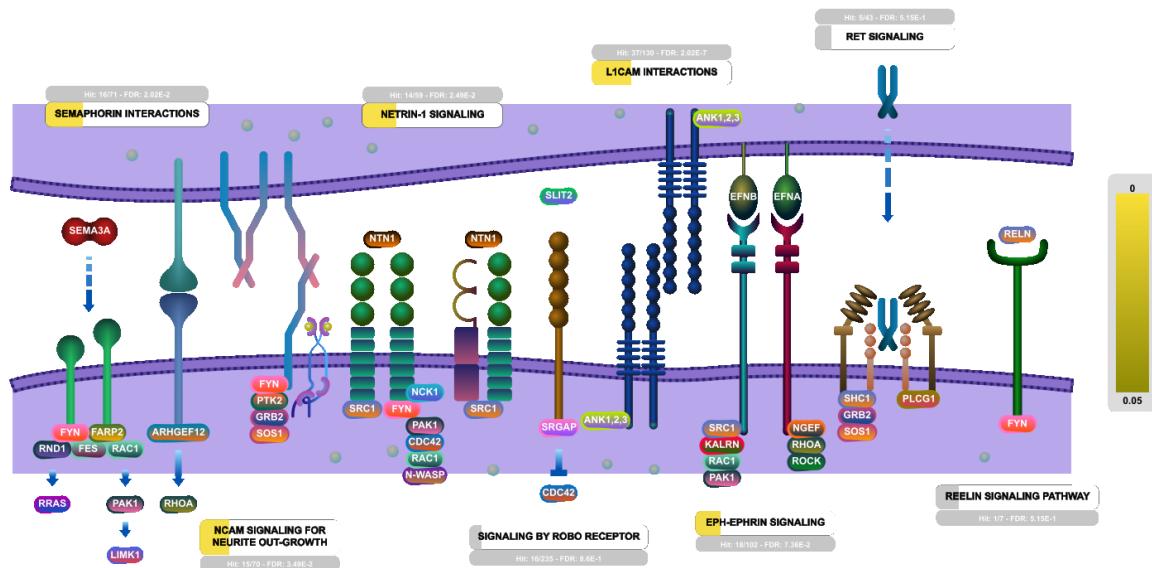
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2004-04-22	Created	Joshi-Tope G
2008-01-14	Authored	Mahajan SS
2008-12-02	Reviewed	Restituito S, Kavalali E
2021-09-10	Modified	Weiser JD

57 submitted entities found in this pathway, mapping to 57 Reactome entities

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109	O60266	111	O95622	1139	P36544
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2258	P0DP23	2259	P0DP23	23229	O43307
23236	Q9NQ66	2556	P34903	2557	P48169
2561	P47870	2562	P28472	2567	Q99928
26122	O43307	26960	Q8NFP9	27328	Q15825

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
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2899	Q13003	2900	Q16099	2901	Q16478
2902	Q05586	2903	Q12879	2904	Q13224
29998	P46098	3265	P01112	3359	P46098
373	P46098	3766	P78508	3772	Q99712
4137	P10636-8	438	P78508	473	Q05901
476	Q07001	5575	P31321	5578	P17252
5579	P05771	5595	P27361	5879	P63000
6196	Q15349	6197	P51812	64130	Q9HAP6
7102	P41732	814	Q16566	815	Q9UQM7
816	Q13554	8573	O14936	9568	O75899

9. Axon guidance (R-HSA-422475)



Axon guidance / axon pathfinding is the process by which neurons send out axons to reach the correct targets. Growing axons have a highly motile structure at the growing tip called the growth cone, which senses the guidance cues in the environment through guidance cue receptors and responds by undergoing cytoskeletal changes that determine the direction of axon growth.

Guidance cues present in the surrounding environment provide the necessary directional information for the trip. These extrinsic cues have been divided into attractive or repulsive signals that tell the growth cone where and where not to grow.

Genetic and biochemical studies have led to the identification of highly conserved families of guidance molecules and their receptors that guide axons. These include netrins, Slits, semaphorins, and ephrins, and their cognate receptors, DCC and or uncoordinated-5 (UNC5), roundabouts (Robo), neuropilin and Eph. In addition, many other classes of adhesion molecules are also used by growth cones to navigate properly which include NCAM and L1CAM.

For review of axon guidance, please refer to Russel and Bashaw 2018, Chedotal 2019, Suter and Jaworski 2019).

Axon guidance cues and their receptors are implicated in cancer progression (Biankin et al. 2012), where they likely contribute to cell migration and angiogenesis (reviewed by Mehlen et al. 2011).

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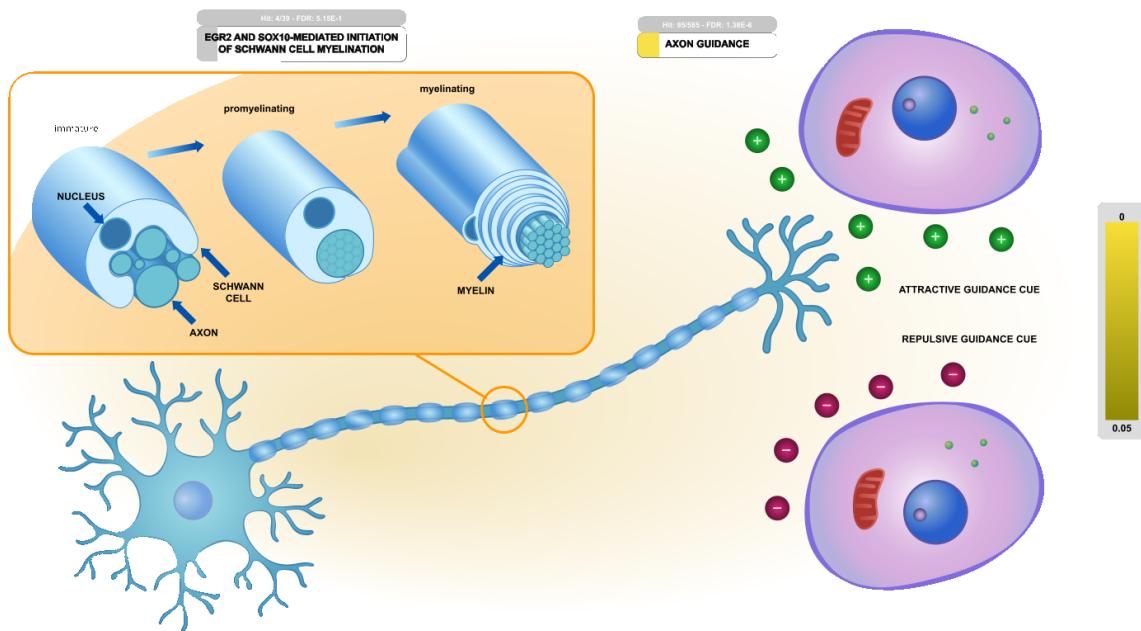
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2009-05-29	Edited	Garapati P V
2009-05-29	Authored	Garapati P V
2009-05-31	Created	Garapati P V
2021-09-10	Modified	Weiser JD

94 submitted entities found in this pathway, mapping to 97 Reactome entities

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1499	Q16539	1501	P53778	1523	O75582
1524	O75676	1630	P43146	1739	Q12959
1742	P78352	1746	Q9GZZ7	1793	Q14185
1808	P11362-1, Q16555	1809	Q14195	1826	O60469, Q9UF33
1977	Q00535	1981	Q04637	2048	P29323
2055	P53671	2260	P11362-1	22907	P78357
23001	P25391	23332	Q7Z460	23380	O75044
2444	P08648	2556	P54762	26019	Q9HAU5
26470	Q13797	27255	Q9UQ52	284217	P25391
287	Q01484	288	Q12955	2902	Q05586
2904	Q13224	3265	P01112	3690	P05106
3751	O15020	3785	O43526	3786	O43525
3912	P07942	4233	P08581	4627	P35579
4628	P35580	4650	Q13459	4756	Q92859
4897	Q92823	5058	Q13153	5062	Q13177
51107	Q96BI3	5290	P42336	5296	O00459
5364	O43157	55558	P51805	5578	P17252
5595	P27361	56141	P61513	5649	P78509
5718	O00232	5781	Q06124	5788	P08575
585	Q9Y5Y9	5879	P63000	60	P60709
6092	Q9HCK4	6134	P27635	6196	Q15349
6197	P51812	6323	P35498	6326	Q99250
6329	P35499	6334	Q9UQD0	6335	Q15858
6383	P34741	6453	Q15811	65109	Q9BZI7
6711	Q01082	7204	O75962	7225	Q9Y210
775	Q13936	776	Q01668	782	Q02641
783	Q08289	8128	Q92186	8218	P53675
8828	O60462	8861	Q86U70	8911	Q9P0X4
8912	O95180	8913	O43497	9037	Q13591
91584	O60486, Q9HCM2				

10. Nervous system development (R-HSA-9675108)



Neurogenesis is the process by which neural stem cells give rise to neurons, and occurs both during embryonic and perinatal development as well as in specific brain lineages during adult life (reviewed in Gotz and Huttner, 2005; Yao et al, 2016; Kriegstein and Alvarez-Buylla, 2009).

References

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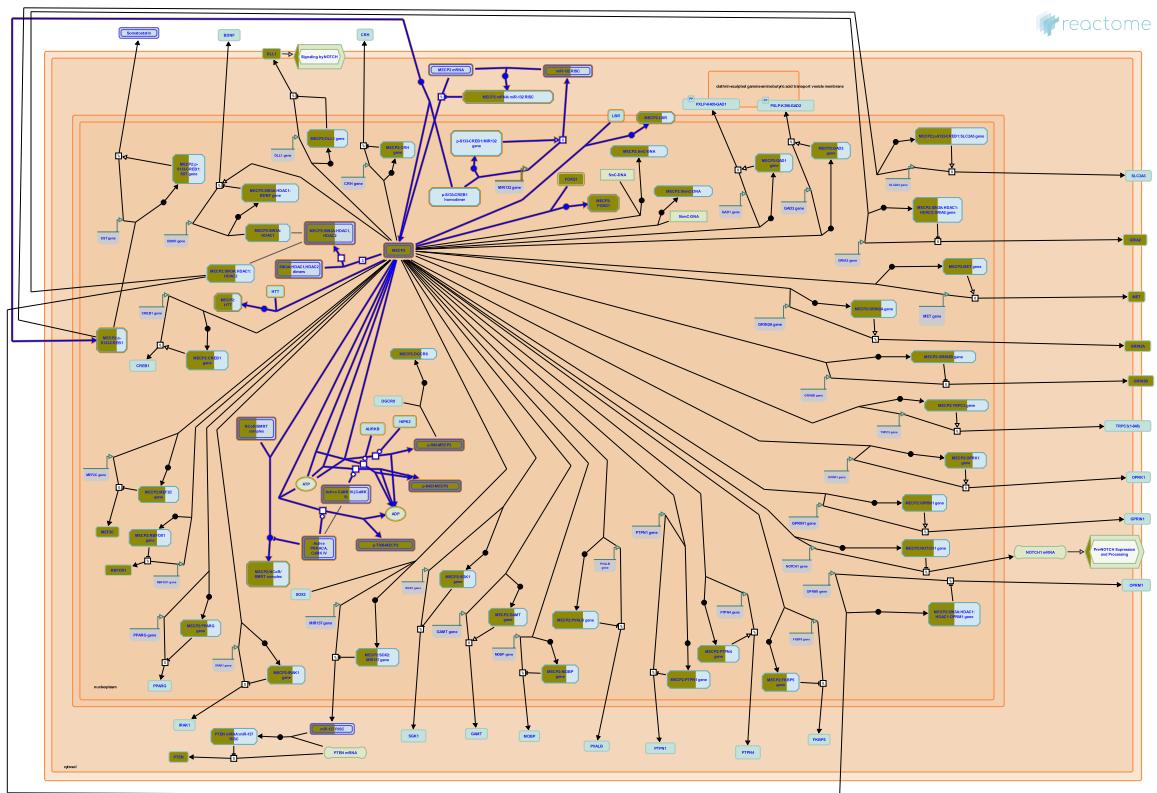
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2020-01-31	Edited	Rothfels K
2020-01-31	Authored	Rothfels K
2020-01-31	Created	Rothfels K
2021-09-10	Modified	Weiser JD

97 submitted entities found in this pathway, mapping to 100 Reactome entities

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1524	O75676	1630	P43146	1739	Q12959

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1977	Q00535	1981	Q04637	2048	P29323
2055	P53671	2260	P11362-1	22907	P78357
23001	P25391	23229	Q9GZV5	23332	Q7Z460
23380	O75044	2444	P08648	2556	P54762
26019	Q9HAU5	26470	Q13797	27255	Q9UQ52
284217	P25391	287	Q01484	288	Q12955
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3786	O43525	3912	P07942	4233	P08581
4359	P25189	4627	P35579	4628	P35580
4650	Q13459	4756	Q92859	4897	Q92823
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55558	P51805	5578	P17252	5595	P27361
56141	P61513	5649	P78509	5718	O00232
5781	Q06124	5788	P08575	585	Q9Y5Y9
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6134	P27635	6196	Q15349	6197	P51812
6323	P35498	6326	Q99250	6329	P35499
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6711	Q01082	7204	O75962	7225	Q9Y210
775	Q13936	776	Q01668	782	Q02641
783	Q08289	8128	Q92186	8218	P53675
8828	O60462	8861	Q86U70	8911	Q9P0X4
8912	O95180	8913	O43497	9037	Q13591
91584	O60486, Q9HCM2				

11. Regulation of MECP2 expression and activity (R-HSA-9022692)



Transcription of the MECP2 gene is known to be regulated by methylation of the promoter and the first intron, but the responsible methyltransferases are not known (Nagarajan et al. 2008, Franklin et al. 2010, Liyanage et al. 2013).

Translation of MECP2 mRNA is negatively regulated by the microRNA miR-132. Transcription of miR-132 is regulated by BDNF signaling, through an unknown mechanism (Klein et al. 2007, Su et al. 2015).

Binding of MECP2 to other proteins and to DNA is regulated by posttranslational modifications, of which phosphorylation has been best studied. Calcium dependent protein kinases, PKA and CaMK IV, activated by neuronal membrane depolarization, phosphorylate MECP2 at threonine residue T308 (corresponding to T320 in the longer MECP2 splicing isoform, MECP2_e1). Phosphorylation at T308 correlates with neuronal activity and inhibits binding of MECP2 to the nuclear receptor co-repressor complex (NCoR/SMRT) (Ebert et al. 2013). In resting neurons, MECP2 is phosphorylated at serine residue S80, which results in a decreased association of MECP2 with chromatin. Nuclear serine/threonine protein kinase HIPK2 phosphorylates MECP2 on serine residue S80 (Bracaglia et al. 2009). In activity-induced neurons, upon neuronal membrane depolarization, MECP2 S80 becomes dephosphorylated, and MECP2 acquires phosphorylation on serine S423 (corresponding to mouse Mecp2 serine S421). CaMK IV is one of the kinases that can phosphorylate MECP2 on S423. Phosphorylation of MECP2 at S423 increases MECP2 binding to chromatin (Zhou et al. 2006, Tao et al. 2009, Qiu et al. 2012). AURKB phosphorylates MECP2 at serine residue S423 in dividing adult neuronal progenitor cells (Li et al. 2014).

Besides binding to the NCoR/SMRT co-repressor complex (Lyst et al. 2013, Ebert et al. 2013), MECP2 binds the SIN3A co-repressor complex. This interaction involves the transcriptional repressor domain of MECP2 and the amino terminal part of the HDAC interaction domain (HID) of SIN3A. HDAC1 and HDAC2 are part of the SIN3A co-repressor complex that co-immunoprecipitates with MECP2 (Nan et al. 1998). While binding of MECP2 to SIN3A at target genes is associated with transcriptional repression, binding to CREB1 at target genes is associated with transcriptional activation (Chahrour et al. 2008, Chen et al. 2013). Function of MECP2 can be affected by binding to FOXG1, another gene mutated in Rett syndrome besides MECP2 and CDKL5 (Dastidar et al. 2012), and HTT (Huntingtin) (McFarland et al. 2013). The subnuclear localization of MECP2 may be affected by binding to the Lamin B receptor (LBR) (Guarda et al. 2009).

References

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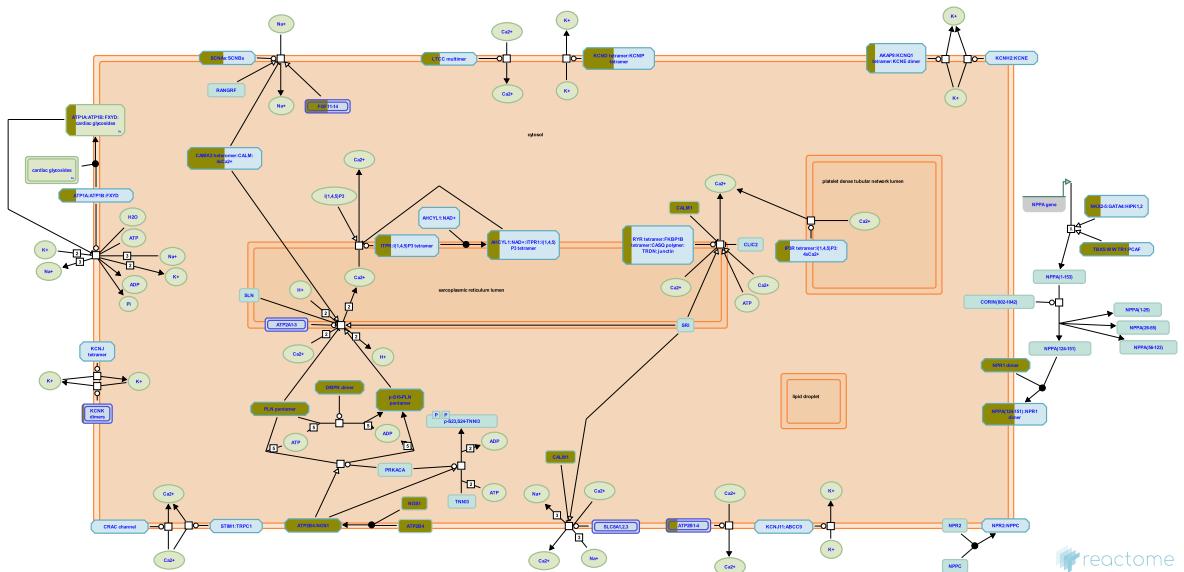
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2017-09-25	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

16 submitted entities found in this pathway, mapping to 17 Reactome entities

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2259	P0DP23	2290	P55316	23112	Q9UPQ9
25942	Q96ST3	26523	Q9UL18	27161	Q9UKV8
4204	P51608-1, P51608-2	6907	O60907	79718	Q9BZK7
814	Q16566	815	Q9UQM7	816	Q13554
9611	O75376				

12. Cardiac conduction (R-HSA-5576891)



The normal sequence of contraction of atria and ventricles of the heart require activation of groups of cardiac cells. The mechanism must elicit rapid changes in heart rate and respond to changes in autonomic tone. The cardiac action potential controls these functions. Action potentials are generated by the movement of ions through transmembrane ion channels in cardiac cells. Like skeletal myocytes (and axons), in the resting state, a given cardiac myocyte has a negative membrane potential. In both muscle types, after a delay (the absolute refractory period), K⁺ channels reopen and the resulting flow of K⁺ out of the cell causes repolarisation. The voltage-gated Ca²⁺ channels on the cardiac sarcolemma membrane are generally triggered by an influx of Na⁺ during phase 0 of the action potential. Cardiac muscle cells are so tightly bound that when one of these cells is excited the action potential spreads to all of them. The standard model used to understand the cardiac action potential is the action potential of the ventricular myocyte (Park & Fishman 2011, Grant 2009).

The action potential has 5 phases (numbered 0-4). Phase 4 describes the membrane potential when a cell is not being stimulated. The normal resting potential in the ventricular myocardium is between -85 to -95 mV. The K⁺ gradient across the cell membrane is the key determinant in the normal resting potential. Phase 0 is the rapid depolarisation phase in which electrical stimulation of a cell opens the closed, fast Na⁺ channels, causing a large influx of Na⁺ creating a Na⁺ current (I_{Na^+}). This causes depolarisation of the cell. The slope of phase 0 represents the maximum rate of potential change and differs in contractile and pacemaker cells. Phase 1 is the inactivation of the fast Na⁺ channels. The transient net outward current causing the small downward deflection (the "notch" of the action potential) is due to the movement of K⁺ and Cl⁻ ions. In pacemaker cells, this phase is due to rapid K⁺ efflux and closure of L-type Ca²⁺ channels. Phase 2 is the plateau phase which is sustained by a balance of Ca²⁺ influx and K⁺ efflux. This phase sustains muscle contraction. Phase 3 of the action potential is where a concerted action of two outward delayed currents brings about repolarisation back down to the resting potential (Bartos et al. 2015).

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Grant AO (2009). Cardiac ion channels. Circ Arrhythm Electrophysiol, 2, 185-94. [🔗](#)

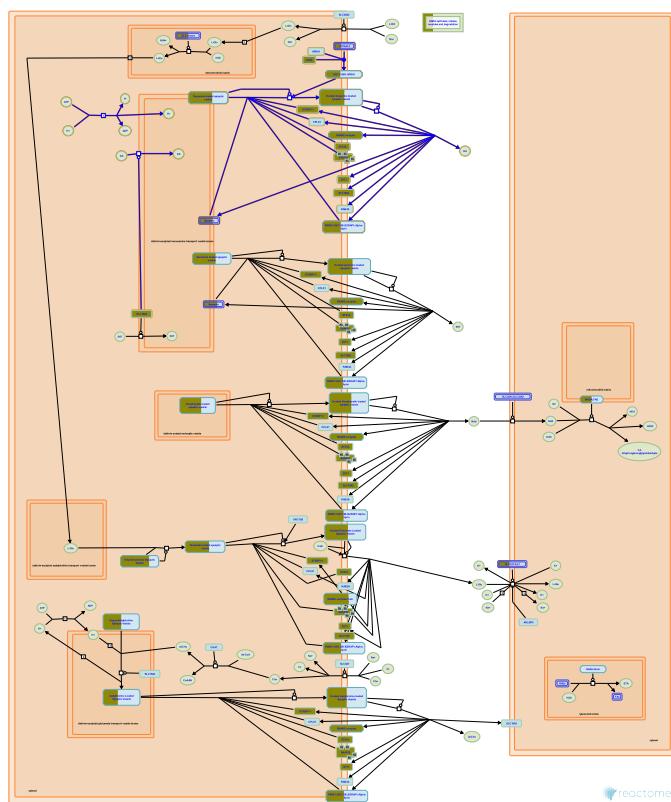
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2014-05-27	Edited	Jassal B
2014-05-27	Authored	Jassal B
2014-05-27	Created	Jassal B
2015-11-09	Reviewed	Colotti G
2021-09-10	Modified	Weiser JD

33 submitted entities found in this pathway, mapping to 35 Reactome entities

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2171	P14415	2258	P0DP23, Q92913	2259	P0DP23, Q92915
23229	Q9GZV5	3184	P29475	3708	Q14643
3751	Q9NZV8	3752	Q9UK17	476	P05023
478	P13637	493	P23634	5350	P26678
552	Q9NSA2	553	Q9NZV8	585	Q9Y5Y9
6323	P35498	6326	Q99250	6329	P35499
6334	Q9UQD0	6335	Q15858	747	P21817
775	Q13936	782	Q02641	783	Q08289
815	Q9UQM7	816	Q13554	8850	Q92831

13. Dopamine Neurotransmitter Release Cycle (R-HSA-212676)



Dopamine neurotransmitter cycle occurs in dopaminergic neurons. Dopamine is synthesized and loaded into the clathrin sculpted monoamine transport vesicles. The vesicles are docked, primed and fused with the plasmamembrane in the synapse to release dopamine into the synaptic cleft.

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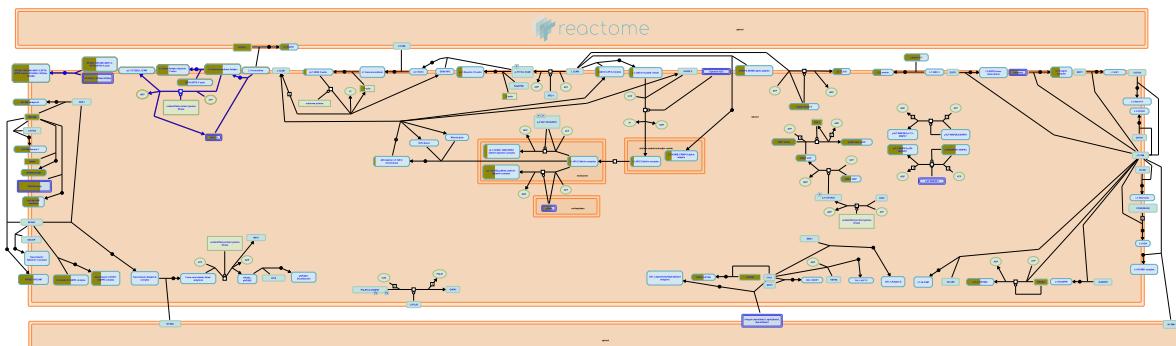
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2008-01-14	Authored	Mahajan SS
2008-02-13	Created	Mahajan SS
2008-04-24	Reviewed	Kavalali E
2008-11-18	Edited	Mahajan SS
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14 submitted entities found in this pathway, mapping to 14 Reactome entities

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6812	P61764-1	6844	P63027	6853	P17600
6854	Q92777	6857	P21579	8500	Q13136
8573	O14936	9256	O95153		

14. Interaction between L1 and Ankyrins (R-HSA-445095)



Ankyrins are a family of adaptor proteins that couple membrane proteins such as voltage gated Na^+ channels and the Na^+/K^+ anion exchanger to the spectrin actin cytoskeleton. Ankyrins are encoded by three genes (ankyrin-G, -B and -R) of which ankyrin-G and -B are the major forms expressed in the developing nervous system. Ankyrins bind to the cytoplasmic domain of L1 CAMs and couple them and ion channel proteins, to the spectrin cytoskeleton. This binding enhances the homophilic adhesive activity of L1 and reduces its mobility within the plasma membrane. L1 interaction with ankyrin mediates branching and synaptogenesis of cortical inhibitory neurons.

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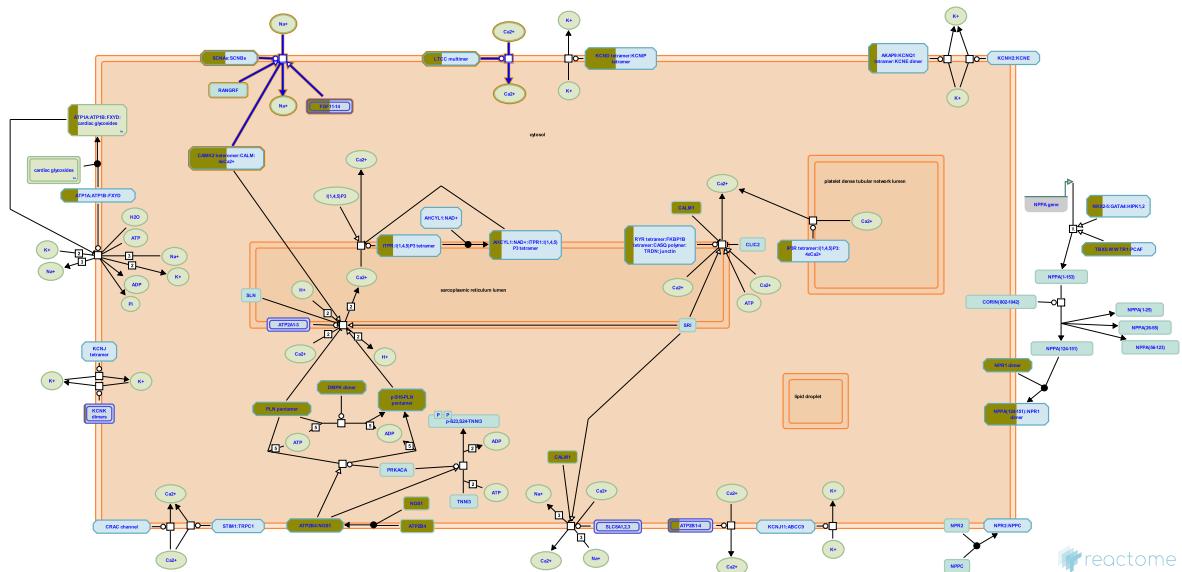
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2009-10-27	Created	Garapati P V
2010-02-16	Reviewed	Maness PF
2021-09-10	Modified	Weiser JD

14 submitted entities found in this pathway, mapping to 14 Reactome entities

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3785	O43526	3786	O43525	4897	Q92823
585	Q9Y5Y9	60	P60709	6323	P35498
6326	Q99250	6329	P35499	6334	Q9UQD0
6335	Q15858	6711	Q01082		

15. Phase 0 - rapid depolarisation (R-HSA-5576892)



Phase 0 is the rapid depolarisation phase in which electrical stimulation of a cell initiates events involving the influx and efflux of ions resulting in the production of a cell's action potential. The cell's excitation opens the closed, fast Na^+ channel proteins, causing a large influx of Na^+ creating a Na^+ current (I_{Na^+}). This causes depolarisation of the cell then voltage-dependent L-type calcium channels (LTCCs) transport Ca^{2+} into excitable cells. The slope of phase 0 represents the maximum rate of potential change and differs in contractile and pacemaker cells. The potential in this phase changes from around -90mV to around $+50\text{mV}$ (Park & Fishman 2011, Grant 2009).

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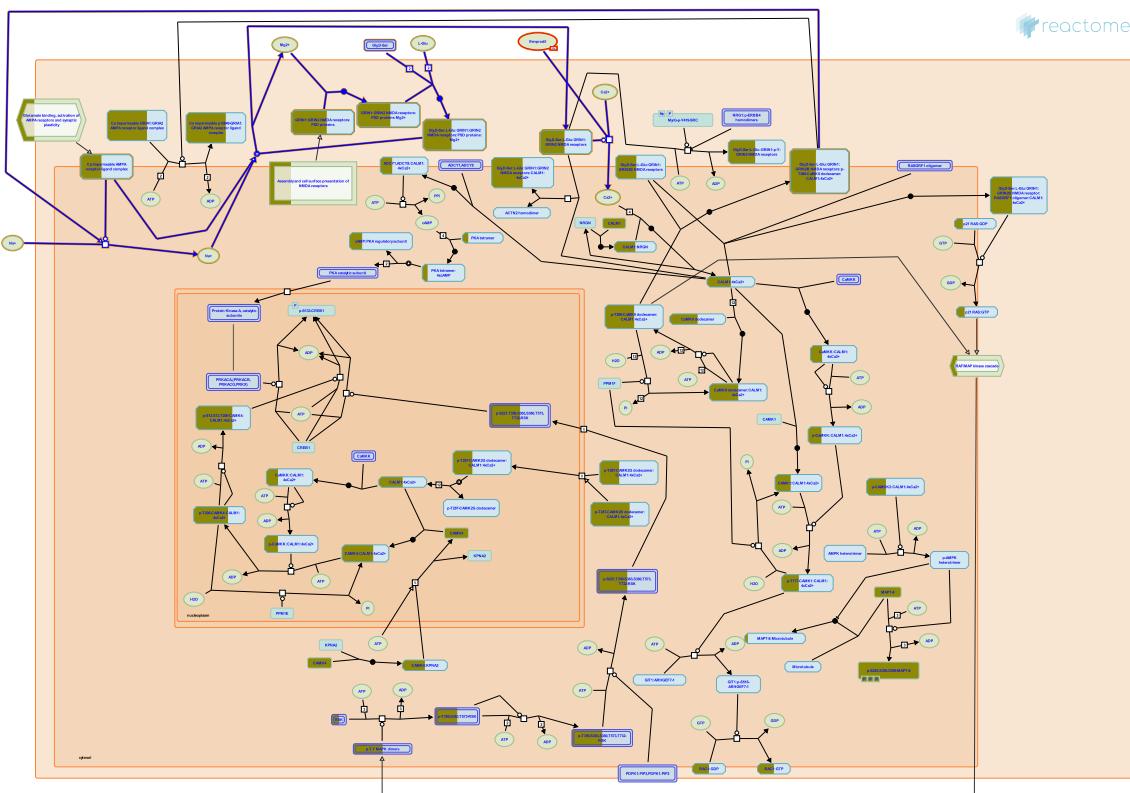
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2014-05-27	Authored	Jassal B
2014-05-27	Created	Jassal B
2015-11-09	Reviewed	Colotti G
2021-09-20	Modified	Weiser JD

13 submitted entities found in this pathway, mapping to 15 Reactome entities

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6334	Q9UQD0	6335	Q15858	775	Q13936
782	Q02641	783	Q08289	815	Q9UQM7
816	Q13554				

16. Unblocking of NMDA receptors, glutamate binding and activation (R-HSA-438066)



Cellular compartments: plasma membrane.

At resting membrane potential, the NMDA receptor ion channel is blocked by extracellular Mg²⁺ ions and is unable to mediate ion permeation upon binding of ligands (glutamate, glycine, D-serine, NMDA). The voltage block is removed upon depolarization of the post-synaptic cell membrane and Mg²⁺ is expelled from the NMDA receptor pore (channel), resulting in activated ligand-bound NMDA receptors. The depolarization of the membrane may happen in response to activation of Ca²⁺ impermeable AMPA receptors, which facilitates Na⁺ influx, contributing to the unblocking of NMDA receptors. For review, please refer to Traynelis et al. 2010, Paoletti et al. 2013, and Iacobucci and Popescu 2017.

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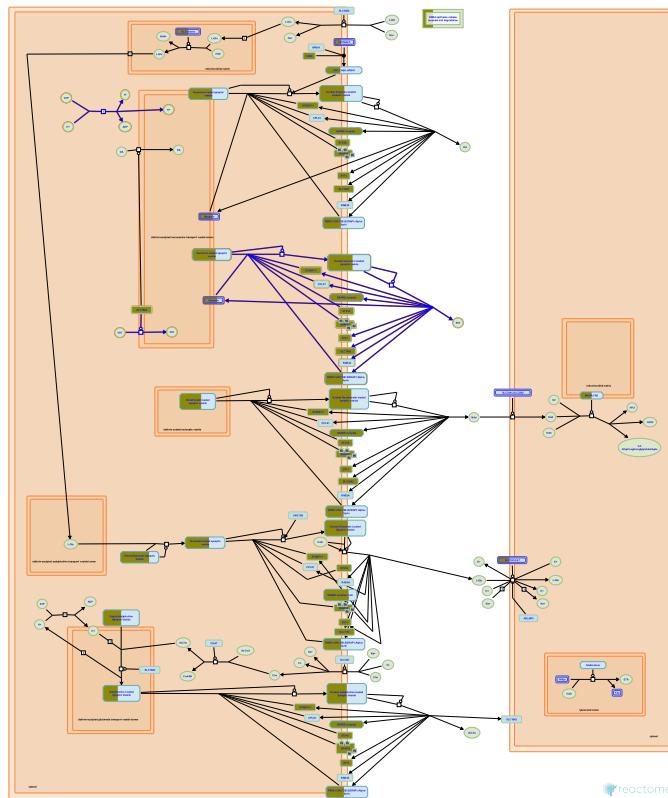
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2009-11-18	Reviewed	Tukey D
2009-11-19	Edited	Gillespie ME
2018-07-31	Edited	Orlic-Milacic M
2018-10-11	Revised	Orlic-Milacic M
2018-11-02	Reviewed	Hansen KB, Yi F
2018-11-07	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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2890	P42261	2891	P42262	2902	Q05586
2903	Q12879	2904	Q13224	815	Q9UQM7
816	Q13554				

17. Serotonin Neurotransmitter Release Cycle (R-HSA-181429)



Serotonin is synthesized in the serotonergic neurons in the central nervous system and the enterochromaffin cells of the gastrointestinal system. Serotonin is loaded into the clathrin sculpted monoamine transport vesicles. The vesicles are docked, primed and release after the change in the membrane potential that activates voltage gated calcium channels and the response by several proteins to the changes in intracellular Ca²⁺ increase leads to fusion of the vesicle and release of serotonin into the synapse.

References

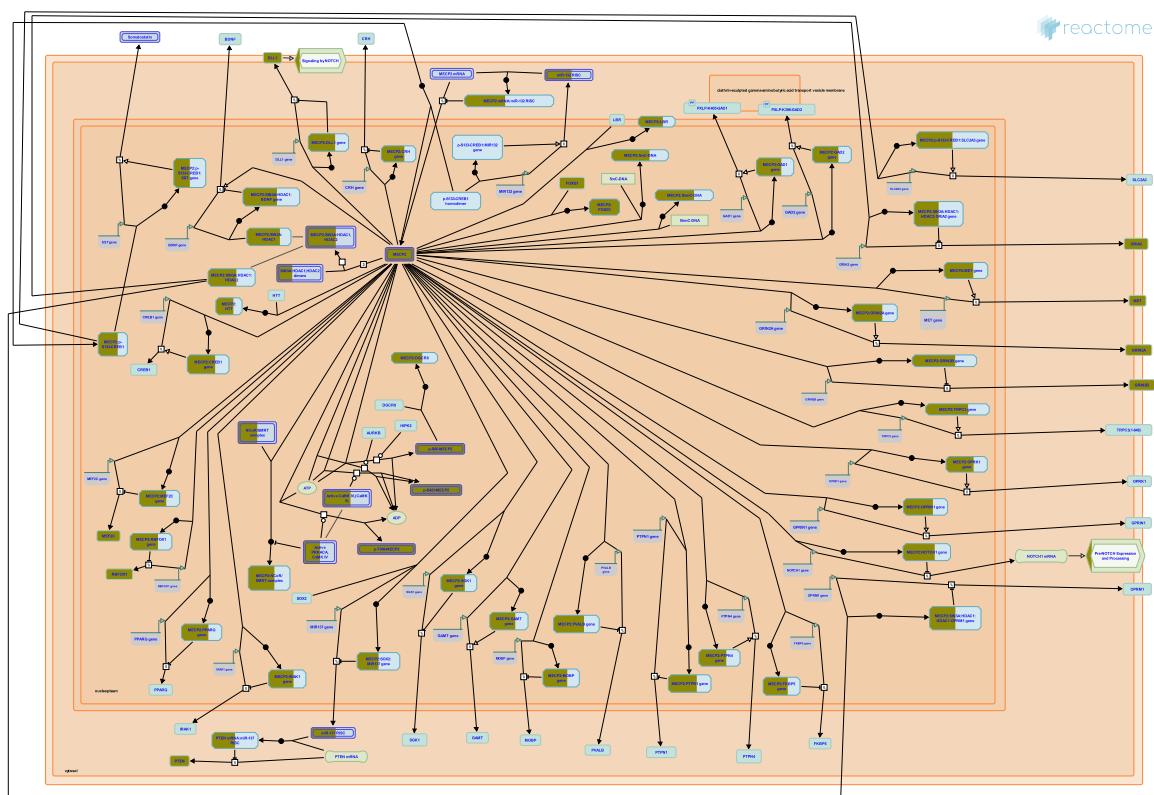
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2008-11-18	Edited	Mahajan SS
2021-09-10	Modified	Weiser JD

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6844	P63027	6853	P17600	6854	Q92777
6857	P21579	8500	Q13136	9256	O95153

18. Transcriptional Regulation by MECP2 (R-HSA-8986944)



MECP2 is an X chromosome gene whose loss-of-function mutations are an underlying cause of the majority of Rett syndrome cases. The MECP2 gene locus consists of four exons. Both exon 1 and exon 2 contain translation start sites. Alternative splicing of the second exon results in expression of two MECP2 transcript isoforms, MECP2_e1 (MECP2B or MECP2alpha) and MECP2_e2 (MECP2A or MECP2beta). The N-terminus of the MECP2_e1 isoform, in which exon 2 is spliced out, is encoded by exon 1. The N-terminus of the MECP2_e2 isoforms, which includes both exon 1 and exon 2, is encoded by exon 2, as the exon 2 translation start site is used. Exons 3 and 4 are present in both isoforms. The MECP2_e2 isoform was cloned first and is therefore more extensively studied. The MECP2_e1 isoform is more abundant in the brain (Mnatzakanian et al. 2004, Kriaucionis and Bird 2004, Kaddoum et al. 2013). Mecp2 isoforms show different expression patterns during mouse brain development and in adult brain regions (Dragich et al. 2007, Olson et al. 2014). While Rett syndrome mutations mainly occur in exons 3 and 4 of MECP2, thereby affecting both MECP2 isoforms (Mnatzakanian et al. 2004), some mutations occur in exon 1, affecting MECP2_e1 only. No mutations have been described in exon 2 (Gianakopoulos et al. 2012). Knockout of Mecp2_e1 isoform in mice, through a naturally occurring Rett syndrome point mutation which affects the first translation codon of MECP2_e1, recapitulates Rett-like phenotype. Knockout of Mecp2_e2 isoform in mice does not result in impairment of neurologic functions (Yasui et al. 2014). In Mecp2 null mice, transgenic expression of either Mecp2_e1 or Mecp2_e2 prevents development of Rett-like phenotype, with Mecp2_e1 rescuing more Rett-like symptoms than Mecp2_e2. This indicates that both splice variants can fulfill basic Mecp2 functions in the mouse brain (Kerr et al. 2012). Changes in gene expression upon over-expression of either MECP2_e1 or MECP2_e2 imply overlapping as well as distinct target genes (Orlic-Milacic et al. 2014).

Methyl-CpG-binding protein 2 encoded by the MECP2 gene binds to methylated CpG sequences in the DNA. The binding is not generic, however, but is affected by the underlying DNA sequence (Yoon et al. 2003). MECP2 binds to DNA containing 5 methylcytosine (5mC DNA), a DNA modification associated with transcriptional repression (Mellen et al. 2012), both in the context of CpG islands and outside of CpG islands (Chen et al. 2015). In addition, MECP2 binds to DNA containing 5 hydroxymethylcytosine (5hmC DNA), a DNA modification associated with transcriptional activation (Mellen et al. 2012). MECP2 binds to DNA as a monomer, occupying about 11 bp of the DNA. Binding of one MECP2 molecule facilitates binding of the second MECP2 molecule, and therefore clustering can occur at target sites. MECP2 binding to chromatin may be facilitated by nucleosome methylation (Ghosh et al. 2010).

MECP2 was initially proposed to act as a generic repressor of gene transcription. However, high throughput studies of MECP2-induced changes in gene expression in mouse hippocampus (Chahrour et al. 2008), and mouse and human cell lines (Orlic-Milacic et al. 2014) indicate that more genes are up-regulated than down-regulated when MECP2 is overexpressed. At least for some genes directly upregulated by MECP2, it was shown that a complex of MECP2 and CREB1 was involved in transcriptional stimulation (Chahrour et al. 2008, Chen et al. 2013).

MECP2 expression is the highest in postmitotic neurons compared to other cell types, with MECP2 being almost as abundant as core histones. Phosphorylation of MECP2 in response to neuronal activity regulates binding of MECP2 to DNA, suggesting that MECP2 may remodel chromatin in a neuronal activity-dependent manner. The resulting changes in gene expression would then modulate synaptic plasticity and behavior (reviewed by Ebert and Greenberg 2013). In human embryonic stem cell derived Rett syndrome neurons, loss of MECP2 is associated with a significant reduction in transcription of neuronally active genes, as well as the reduction in nascent protein synthesis. The reduction in nascent protein synthesis can at least in part be attributed to the decreased activity of the PI3K/AKT/mTOR signaling pathway. Neuronal morphology (reduced soma size) and the level of protein synthesis in Rett neurons can be ameliorated by treating the cells with growth factors which activate the PI3K/AKT/mTOR cascade or by inhibition of PTEN, the negative regulator of AKT activation. Mitochondrial gene expression is also downregulated in Rett neurons, which is associated with a reduced capacity of the mitochondrial electron transport chain (Ricciardi et al. 2011, Li et al. 2013). Treatment of Mecp2 null mice with IGF1 (insulin-like growth factor 1) reverses or ameliorates some Rett-like features such as locomotion, respiratory difficulties and irregular heart rate (Tropea et al. 2009).

MECP2 regulates expression of a number of ligands and receptors involved in neuronal development and function. Ligands regulated by MECP2 include BDNF (reviewed by Li and Pozzo-Miller 2014, and KhorshidAhmad et al. 2016), CRH (McGill et al. 2006, Samaco et al. 2012), SST (Somatostatin) (Chahrour et al. 2008), and DLL1 (Li et al. 2014). MECP2 also regulates transcription of genes involved in the synthesis of the neurotransmitter GABA – GAD1 (Chao et al. 2010) and GAD2 (Chao et al. 2010, He et al. 2014). MECP2 may be involved in direct stimulation of transcription from the GLUD1 gene promoter, encoding mitochondrial glutamate dehydrogenase 1, which may be involved in the turnover of the neurotransmitter glutamate (Lividé et al. 2015). Receptors regulated by MECP2 include glutamate receptor GRIA2 (Qiu et al. 2012), NMDA receptor subunits GRIN2A (Durand et al. 2012) and GRIN2B (Lee et al. 2008), opioid receptors OPRK1 (Chahrour et al. 2008) and OPRM1 (Hwang et al. 2009, Hwang et al. 2010, Samaco et al. 2012), GPRIN1 (Chahrour et al. 2008), MET (Plummer et al. 2013), NOTCH1 (Li et al. 2014). Channels/transporters regulated by MECP2 include TRPC3 (Li et al. 2012) and SLC2A3 (Chen et al. 2013). MECP2 regulates transcription of FKBP5, involved in trafficking of glucocorticoid receptors (Nuber et al. 2005, Urdinguio et al. 2008). MECP2 is implicated in regulation of expression of SEMA3F (semaphorin 3F) in mouse olfactory neurons (Degano et al. 2009). In zebrafish, Mecp2 is implicated in sensory axon guidance by direct stimulation of transcription of Sema5b and Robo2 (Leong et al. 2015). MECP2 may indirectly regulate signaling by neuronal receptor tyrosine kinases by regulating transcription of protein tyrosine phosphatases, PTPN1 (Krishnan et al. 2015) and PTPN4 (Williamson et al. 2015).

MECP2 regulates transcription of several transcription factors involved in functioning of the nervous system, such as CREB1, MEF2C, RBFOX1 (Chahrour et al. 2008) and PPARG (Mann et al. 2010, Joss-Moore et al. 2011).

MECP2 associates with transcription and chromatin remodeling factors, such as CREB1 (Chahrour et al. 2008, Chen et al. 2013), the HDAC1/2-containing SIN3A co-repressor complex (Nan et al. 1998), and the NCoR/SMRT complex (Lyst et al. 2013, Ebert et al. 2013). There are contradictory reports on the interaction of MECP2 with the SWI/SNF chromatin-remodeling complex (Harikrishnan et al. 2005, Hu et al. 2006). Interaction of MECP2 with the DNA methyltransferase DNMT1 has been reported, with a concomitant increase in enzymatic activity of DNMT1 (Kimura and Shiota 2003).

In addition to DNA binding-dependent regulation of gene expression by MECP2, MECP2 may influence gene expression by interaction with components of the DROSHA microprocessor complex and the consequent change in the levels of mature microRNAs (Cheng et al. 2014, Tsujimura et al. 2015).

Increased MECP2 promoter methylation is observed in both male and female autism patients (Nagarajan et al. 2008). Regulatory elements that undergo methylation are found in the promoter and the first intron of MECP2 and their methylation was shown to regulate Mecp2 expression in mice (Liyanage et al. 2013). Mouse Mecp2 promoter methylation was shown to be affected by stress (Franklin et al. 2010).

The Rett-like phenotype of Mecp2 null mice is reversible (Guy et al. 2007), but appropriate levels of Mecp2 expression need to be achieved (Alvarez-Saavedra et al. 2007). When Mecp2 expression is restored in astrocytes of Mecp2 null mice, amelioration of Rett symptoms occurs, involving non-cell-autonomous positive effect on mutant neurons and increasing level of the excitatory glutamate transporter VGLUT1 (Lioy et al. 2011). Microglia derived from Mecp2 null mice releases higher than normal levels of glutamate, which has toxic effect on neurons. Increased glutamate secretion may be due to increased levels of glutaminase (Gls), involved in glutamate synthesis, and increased levels of connexin-32 (Gjb1), involved in glutamate release, in Mecp2 null microglia (Maezawa and Jin 2010). Targeted deletion of Mecp2 from Sim1-expressing neurons of the mouse hypothalamus recapitulates some Rett syndrome-like features and highlights the role of Mecp2 in feeding behavior and response to stress (Fyffe et al. 2008).

Mecp2 overexpression, similar to MECP2 duplication syndrome, causes neurologic phenotype similar to Rett (Collins et al. 2004, Luikenhuis et al. 2004, Van Esch et al. 2005, Alvarez-Saavedra 2007, Van Esch et al. 2012). The phenotype of the mouse model of the MECP2 duplication syndrome in adult mice is reversible when Mecp2 expression levels are corrected (Sztainberg et al. 2015).

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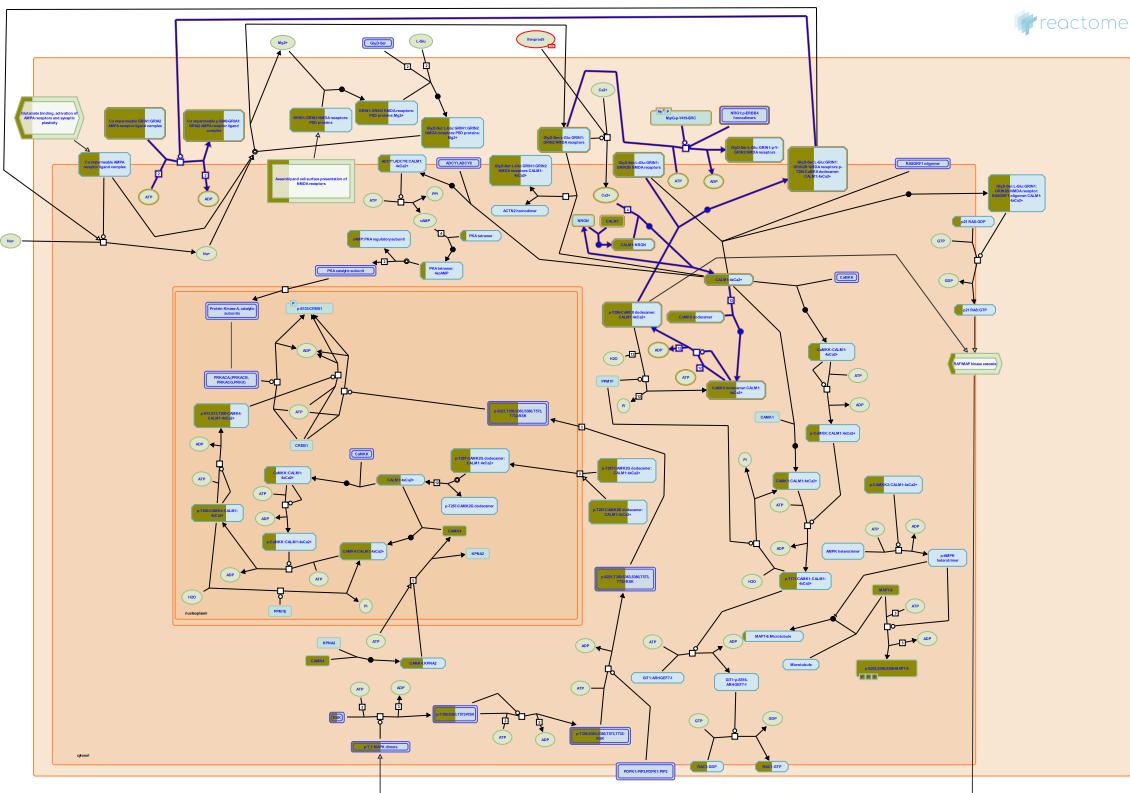
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2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
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2904	Q13224	4204	P51608-1, P51608-2	4208	Q06413
4233	P08581	54715	Q9NWB1	5728	P60484
6907	O60907	79718	Q9BZK7	814	Q16566
815	Q9UQM7	816	Q13554	9611	O75376

19. Long-term potentiation (R-HSA-9620244)



In long-term potentiation (LTP), involved in learning and memory, a brief period of synaptic activity induces a lasting increase in the strength of the synapse. LTP is initiated by NMDA receptor-mediated activation of calcium/calmodulin-dependent protein kinase II (CaMKII), followed by binding of CaMKII to the NMDA receptor and CaMKII-mediated phosphorylation of AMPA receptor sub-units (reviewed by Lisman et al. 2012 and Lüscher and Malenka 2012).

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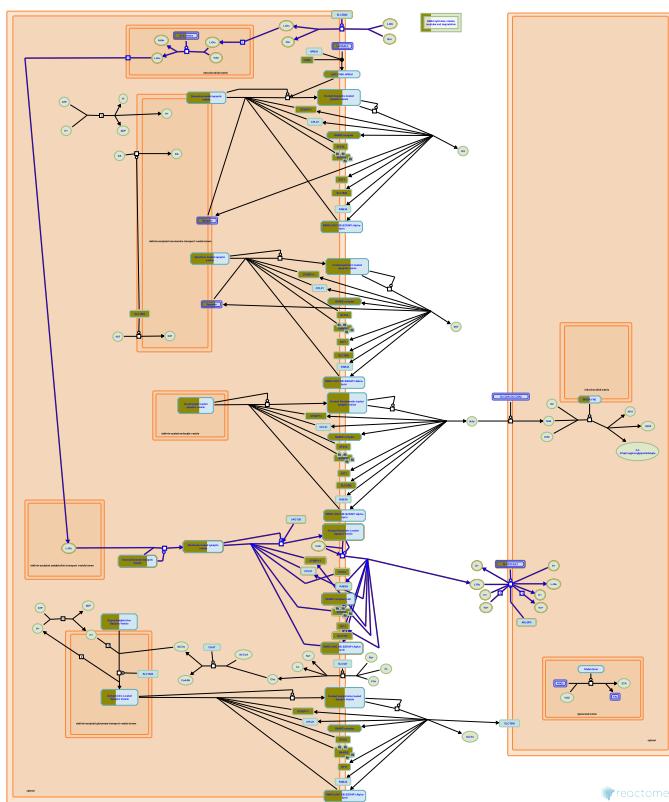
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816	Q13554				

20. Glutamate Neurotransmitter Release Cycle (R-HSA-210500)



Communication at the synapse involves the release of glutamate from the presynaptic neuron and its binding to glutamate receptors on the postsynaptic cell to generate a series of events that lead to propagation of the synaptic transmission. This process begins with the formation of synaptic vesicles in the presynaptic neuron, proceeds to the loading of glutamate into the vesicles, and concludes with the release of glutamate into the synaptic cleft.

The glutamate life cycle in the neuron begins with the loading of the nascent synaptic vesicles with cytosolic glutamate with the help the transporter protein, VGLUT1, located in the synaptic vesicular membrane. Glutamate loaded vesicles are formed in the cytoplasm and then transported to a site close to the plasma membrane where the vesicle is docked with the help of several proteins. One of the key players in the docking process is Munc 18, which interacts with syntaxin (in the plasma membrane), MINT (Munc18 interacting molecule), and DOC2. These interactions along with the secondary interactions are needed for docking the synaptic vesicle to the plasma membrane.

The docked synaptic vesicle is not ready for release until it undergoes molecular changes to prime it for fusion with the plasma membrane. Munc13 is one of the main players in the priming process. Munc 13 interacts with RIM (Rab3A interacting molecule) located in the synaptic vesicle. Munc 13 also interacts with DOC2. The precise molecular mechanisms of the interactions that result in docking versus priming are not clear and the docking and priming process have been combined in this annotation of this pathway. Once primed the synaptic vesicle is ready for release.

Synaptic transmission involves an action potential that is generated in the presynaptic cell which induces the opening of voltage gated Ca²⁺ channels (VGCC) located in the plasma membrane of the presynaptic neuron. Typically N, P/Q and R type of VGCCs are involved in the neurotransmitter release. Ca²⁺ influx through these channels results in the rise of intracellular Ca²⁺ concentration. In the microdomain of glutamatergic synapses, the Ca²⁺ concentration could rise between 10-25 micro molar. Synaptotagmin, a Ca²⁺-binding protein located in the synaptic vesicular membrane, responds to the rise in the Ca²⁺ levels in the microdomain and induces a synaptic vesicle membrane curvature that favors vesicle fusion. Fusion of the synaptic vesicle with the plasma membrane is characterized by the formation of a trimeric trans-SNARE complex that involves VAMP2 from the synaptic vesicle membrane, and syntaxin and SNAP-25 from plasma membrane. Vesicle fusion incorporates the synaptic vesicle membrane into the plasma membrane, releasing the vesicle contents (glutamate) into the synaptic cleft. Postfusion the synaptic vesicle membrane proteins (VAMP2, Rab3A, VGLUT1, and synaptotagmin) are also found in the plasma membrane.

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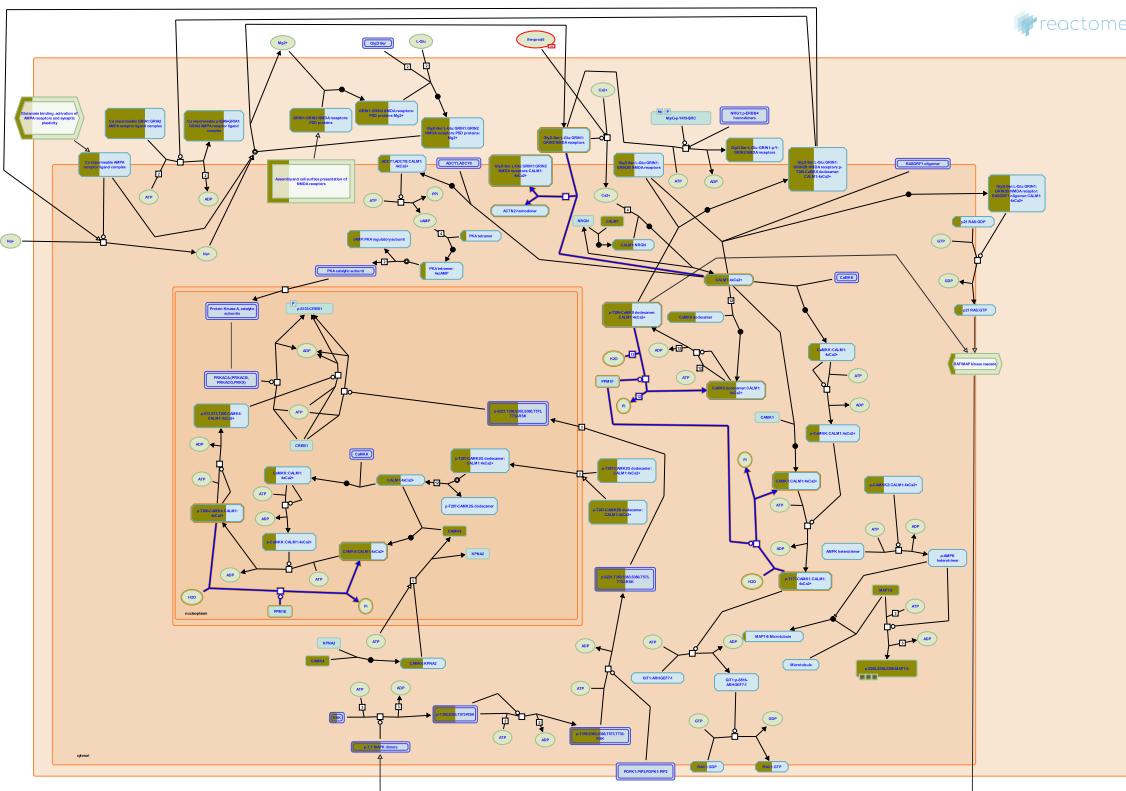
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3949	P63027	6505	P43005	6506	P43004
6616	P60880	6804	Q16623	6812	P61764-1
6844	P63027	6857	P21579	8500	Q13136
9256	O95153				

21. Negative regulation of NMDA receptor-mediated neuronal transmission (R-HSA-9617324)



The duration of NMDA receptor-mediated neuronal transmission can be limited by binding of the activated calmodulin to the activated NMDA receptor. In addition to shortening the NMDA channel pore open state, calmodulin interferes with ACTN2-mediated anchoring of NMDA receptors to the postsynaptic density (Ehlers et al. 1996, Wyszynski et al. 1997). Protein phosphatases PPM1E and PPM1F dephosphorylate activated calcium/calmodulin-dependent kinases (CaMKs), thus halting CaMK-mediated signaling (Ishida, Okuno et al. 1998, Ishida et al. 1998, Kitani et al. 2003).

References

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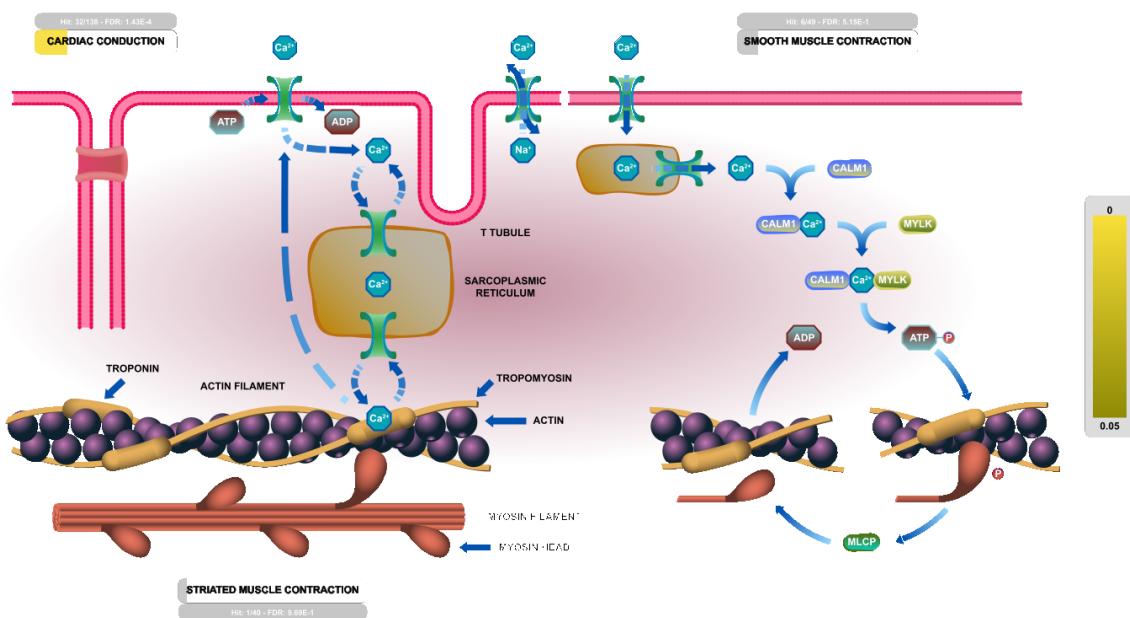
Edit history

Date	Action	Author
2018-08-23	Created	Orlic-Milacic M
2018-10-11	Authored	Orlic-Milacic M
2018-11-02	Reviewed	Hansen KB, Yi F
2018-11-07	Edited	Orlic-Milacic M
2021-09-20	Modified	Weiser JD

12 submitted entities found in this pathway, mapping to 12 Reactome entities

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1739	Q12959	1740	Q15700	1742	P78352
2258	P0DP23	2259	P0DP23	2739	Q14957
2902	Q05586	2903	Q12879	2904	Q13224
814	Q16566	815	Q9UQM7	816	Q13554

22. Muscle contraction (R-HSA-397014)



Cellular compartments: plasma membrane, cytosol.

In this module, the processes by which calcium binding triggers actin - myosin interactions and force generation in smooth and striated muscle tissues are annotated.

References

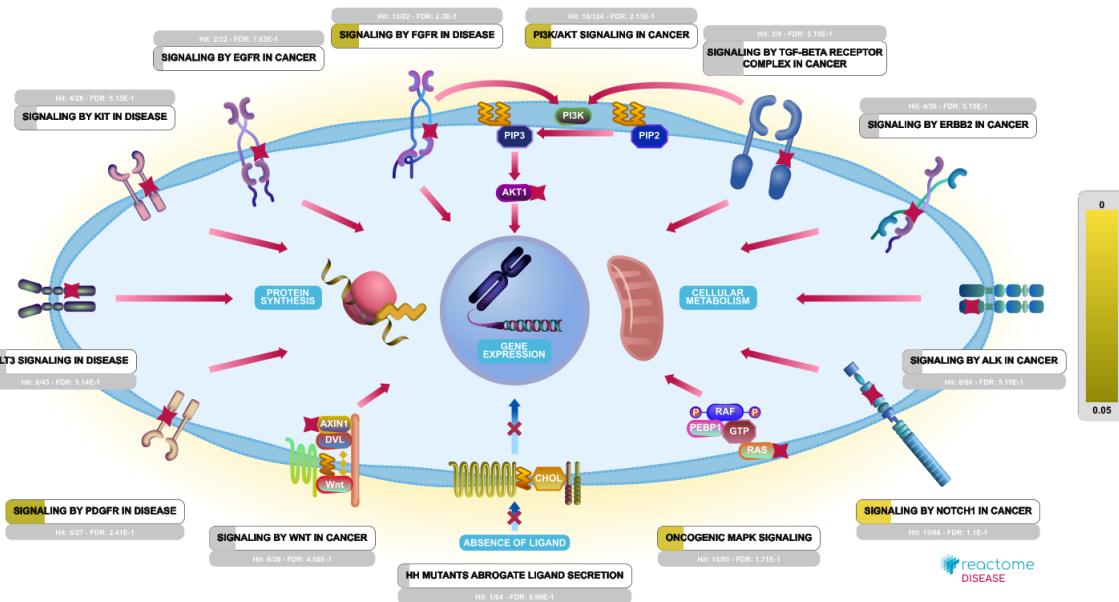
Edit history

Date	Action	Author
2009-02-10	Authored	Gillespie ME
2009-03-11	Edited	Gillespie ME
2009-03-11	Created	May B
2021-09-10	Modified	Weiser JD

39 submitted entities found in this pathway, mapping to 41 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10089	Q9Y2U2	10142	Q99996	1747	P16066
1756	P11532	1760	Q09013	2033	Q86Z02
2167	P05023	2171	P14415	2258	P0DP23, Q92913
2259	P0DP23, Q92915	23229	Q9GZV5	2977	P33402
301	P04083	3184	P29475	3708	Q14643
3751	Q9NZV8	3752	Q9UK17	4638	Q15746
476	P05023	478	P13637	493	P23634
5058	Q13153	5062	Q13177	5350	P26678
552	Q9NSA2	553	Q9NZV8	585	Q9Y5Y9
6323	P35498	6326	Q99250	6329	P35499
6334	Q9UQD0	6335	Q15858	747	P21817
775	Q13936	782	Q02641	783	Q08289
815	Q9UQM7	816	Q13554	8850	Q92831

23. Diseases of signal transduction by growth factor receptors and second messengers (R-HSA-5663202)



Signaling processes are central to human physiology (e.g., Pires-da Silva & Sommer 2003), and their disruption by either germ-line and somatic mutation can lead to serious disease. Here, the molecular consequences of mutations affecting visual signal transduction and signaling by diverse growth factors are annotated.

References

Pires-daSilva A & Sommer RJ (2003). The evolution of signalling pathways in animal development. *Nat. Rev. Genet.*, 4, 39-49. [View](#)

Edit history

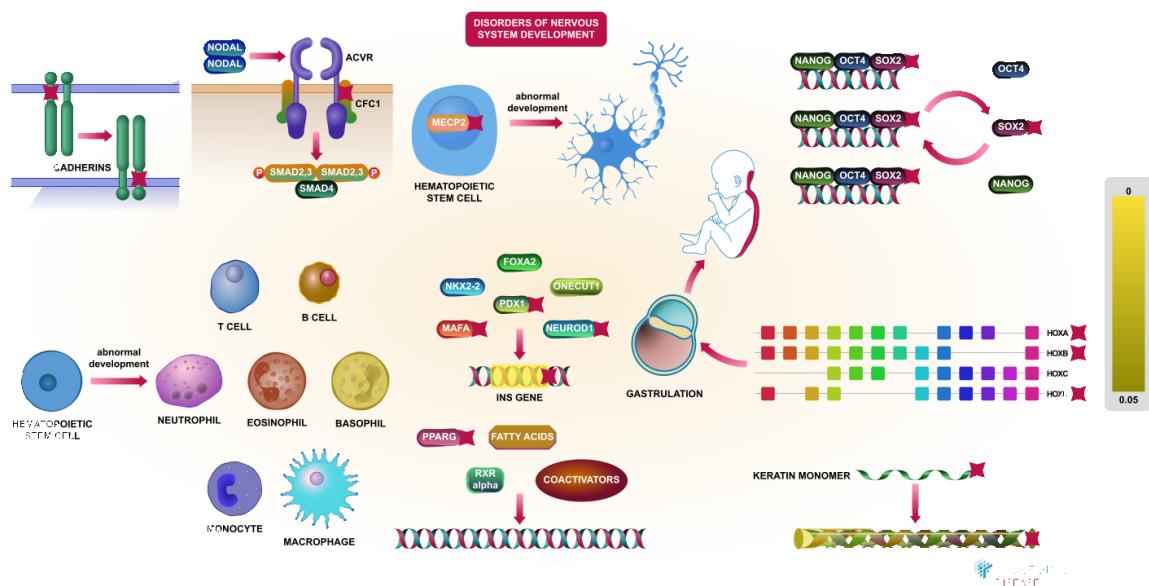
Date	Action	Author
2015-01-16	Created	D'Eustachio P
2021-03-29	Modified	Rothfels K

67 submitted entities found in this pathway, mapping to 77 Reactome entities

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10142	Q99996	1024	P49336	1387	Q92793
1499	P35222	1523	P39880	1788	P36897
1803	P16234	1804	P09619	1808	P11362, P11362-1, P11362-19
1809	P21802, P21802-1, P21802-17, P21802-18, P21802-3, P21802-5	1813	P35968	1995	P48729
2033	Q09472	2048	O60674	2100	Q92731
2109	P42345	2200	Q07817	2243	P02671
2258	P0DP23	2259	P0DP23	2260	P11362, P11362-1, P11362-19
22866	Q8WXI2	23189	Q14678	23236	P42345
2475	P42345	2561	P04626	2620	Q9UKV0

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
27044	Q7KZF4	28514	O00548	2861	P46531
3192	P06748	3265	P01112	3690	P05106
4089	Q13485	4204	P51608-1, P51608-2	4233	P08581
4627	P35579	4763	P21359	51107	Q96BI3
5245	P35232	5290	P42336	5296	O00459
53335	Q9H165	5515	P67775	5519	P30154
5528	Q14738	55869	Q9BY41	55914	Q96RT1
5595	P27361	5718	O00232	5728	P60484
57448	Q9NR09	5781	Q06124	5879	P63000
60	P60709	6711	Q01082	673	P15056
6907	O60907	6934	Q9NQB0	7249	P49815
7750	Q9UBW7	79718	Q9BZK7	815	Q9UQM7
816	Q13554	8850	Q92831	9611	O75376
9759	P56524				

24. Disorders of Developmental Biology (R-HSA-9675151)



Developmental disorders affect formation of body organs and organ systems. The causes of defects in human development are diverse and incompletely understood, and include environmental insults such as nutrient deficiency, exposure to toxins and infections (Gilbert 2000, National Research Council (US) Committee on Developmental Toxicology 2000, Taylor and Rogers 2005, Zilbauer et al. 2016, Izvolskaia et al. 2018), as well as genetic causes such as aneuploidy and other chromosomal abnormalities, and germline mutations in genes that regulate normal development. It is estimated that about 40% of human developmental disabilities can be attributed to genetic aberrations (Sun et al. 2015), of which at least 25% are due to mutations affecting single genes (Chong et al. 2015), and this latter group of Mendelian developmental disorders is the focus of curation in Reactome.

Disorders of nervous system development affect the function of the central nervous system (CNS) and impair motor skills, cognition, communication and/or behavior (reviewed by Ismail and Shapiro 2019). So far, we have annotated the role of loss-of-function mutations in methyl-CpG-binding protein 2 (MECP2), an epigenetic regulator of transcription, in Rett syndrome, a pervasive developmental disorder (Pickett and London 2005, Ferreri 2014).

Disorders of myogenesis are rare hereditary muscle diseases that in the case of congenital myopathies are defined by architectural abnormalities in the muscle fibres (Pelin and Wallgren-Pettersson 2019, Phadke 2019, Radke et al. 2019, Claeys 2020) and in the case of muscular dystrophies by increased muscle breakdown that progresses with age (Pasrija and Tadi 2020). Mutations in cadherin family genes are present in some types of muscular dystrophy (Puppo et al. 2015).

Disorders of pancreas development result in pancreatic agenesis, where a critical mass of pancreatic tissue is congenitally absent. For example, the PDX1 gene is a master regulator of beta cell differentiation and homozygous deletions or inactivating mutations in PDX1 gene cause whole pancreas agenesis. PDX1 gene haploinsufficiency impairs glucose tolerance and leads to development of diabetes mellitus (Hui and Perfetti 2002, Babu et al. 2007, Chen et al. 2008).

Left-right asymmetry disorders are caused by mutations in genes that regulate the characteristic asymmetry of internal organs in vertebrates. Normally, cardiac apex, stomach and spleen are positioned towards the left side, while the liver and gallbladder are on the right. Loss-of-function mutations in the CFC1 gene, whose protein product functions as a co-factor in Nodal signaling, result in heterotaxic phenotype in affected patients, manifested by randomized organ positioning (Bamford et al. 2000).

Congenital lipodystrophies are characterized by a lack of adipose tissue, which predisposes affected patient to development of insulin resistance and related metabolic disorders. The severity of metabolic complications is correlates with the extent of adipose tissue loss. Loss-of-function mutations in the PPARG gene, encoding a key transcriptional regulator of adipocyte development and function, are a well-established cause of familial partial lipodystrophy type 3 (FPLD3) (Broekema et al. 2019).

Congenital stem cell disorders are caused by mutations in genes that regulate the balance between stem cells maintenance and commitment to differentiated lineages. Loss-of-function mutations in the SOX2 gene, which encodes a transcription factor involved in the maintenance of totipotency during embryonic preimplantation period, pluripotency of embryonic stem cells, and multipotency of neural stem cells, are the cause of anophthalmia (the absence of an eye) and microphthalmia (the presence of a small eye within the orbit) (Verma and Fitzpatrick 2007, Sarlak and Vincent 2016).

HOX-related structural birth defects are caused by loss-of-function mutations in HOX family genes. HOX transcription factors play a fundamental role in body patterning during embryonic development, and HOX mutation are an underlying cause of many congenital limb malformations (Goodman 2002).

Congenital keratinization disorders are caused by dominant negative mutation in keratin genes and depending on where the affected keratin gene is expressed, they affect epithelial tissues such as skin, cornea, hair and/or nails (McLean and Moore 2011).

Disorders of immune system development are caused by mutations in genes that regulate differentiation of blood cell lineages involved in immune defense, leading to immune system defects. For example, mutations in the gene encoding CSF3R, a receptor for the granulocyte-colony stimulating factor, result in congenital neutropenia, characterized by a maturation arrest of granulopoiesis at the level of promyelocytes. Patients with severe congenital neutropenia are prone to recurrent, often life-threatening infections from an early age and may be predisposed to myelodysplastic syndromes or acute myeloid leukemia (Germeshausen et al. 2008; Skokowa et al. 2017).

References

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Edit history

Date	Action	Author
2020-01-31	Created	Orlic-Milacic M
2020-02-21	Authored	Orlic-Milacic M
2020-02-24	Edited	Orlic-Milacic M
2020-02-24	Reviewed	D'Eustachio P
2020-08-18	Reviewed	D'Eustachio P
2020-08-24	Edited	Orlic-Milacic M
2020-08-25	Modified	Matthews L

8 submitted entities found in this pathway, mapping to 9 Reactome entities

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2258	P0DP23	2259	P0DP23	25942	Q96ST3
4204	P51608-1, P51608-2	6907	O60907	79718	Q9BZK7
814	Q16566	9611	O75376		

25. Disorders of Nervous System Development ([R-HSA-9697154](#))

Pervasive developmental disorders



Diseases: nervous system disease.

Neurodevelopmental disorders are chronic disorders that affect the function of the central nervous system (CNS) and impair motor skills, cognition, communication and/or behavior. While these disorders frequently stem from mutations in genes that directly control CNS development, they can also be a consequence of environmental insults such as hypoxic/ischemic injury, trauma, exposure to toxins, infections and nutritional deficiencies, or be indirectly caused by mutations in metabolic genes (reviewed by Ismail and Shapiro 2019). Disorders of nervous system development have been traditionally classified based on phenotypic traits (clinical presentation). Molecular genetics studies have revealed, however, that indistinguishable clinical presentations may result from pathogenic variants in different genes whose protein products function in connected biological pathways. On the other hand, distinct clinical presentations may be caused by pathogenic mutations in a single gene that functions in multiple biological pathways (Desikan and Bakrovich 2018). In the future, phenotype-based classification of neurodevelopmental disorders may be replaced by a more informative pathway-based nomenclature (Desikan and Bakrovich 2018). Biological pathways frequently impaired in neurodevelopmental disorders are signal transduction pathways such as the mTOR pathway in tuberous sclerosis complex (TSC) (Wong 2019) and the RAS/RAF/MAPK pathway in RASopathies (Kang and Lee 2019), neurotransmission pathways as in some autism spectrum disorders (ASD) (Burnashev and Szepetowski 2015, Hu et al. 2016), and pathways that regulate gene expression as in Mendelian disorders of epigenetic machinery (MDEM) (Fahrner and Bjornsson 2019).

So far, we have annotated the role of loss-of-function mutations in methyl-CpG-binding protein 2 (MECP2), an epigenetic regulator of transcription, in Rett syndrome, a pervasive developmental disorder that belongs to the MDEM category (Pickett and London 2005, Ferreri 2014).

References

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Fahrner JA & Bjornsson HT (2019). Mendelian disorders of the epigenetic machinery: postnatal malleability and therapeutic prospects. *Hum. Mol. Genet.*, 28, R254-R264. [🔗](#)

Wong M (2019). The role of glia in epilepsy, intellectual disability, and other neurodevelopmental disorders in tuberous sclerosis complex. *J Neurodev Disord*, 11, 30. [🔗](#)

Edit history

Date	Action	Author
2020-08-06	Authored	Orlic-Milacic M
2020-08-06	Created	Orlic-Milacic M
2020-08-14	Reviewed	D'Eustachio P
2020-08-17	Edited	Orlic-Milacic M
2020-09-10	Modified	Orlic-Milacic M

8 submitted entities found in this pathway, mapping to 9 Reactome entities

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4204	P51608-1, P51608-2	6907	O60907	79718	Q9BZK7
814	Q16566	9611	O75376		

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.

762 of the submitted entities were found, mapping to 975 Reactome entities

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1007	Q9P2U7	10071	Q9UKN1	10075	Q7Z6Z7
1008	Q9Y6N8	10082	Q9Y625	10089	Q9Y2U2
1009	Q8NDX2	1012	Q05940	10142	Q99996
10207	Q8NI35	10236	O43390	1024	P49336
10243	Q9NQX3	10288	Q8N423	10295	O14874
10347	Q8IZY2	10349	Q8WWZ4	10479	Q92581
10482	Q9UBU9	10499	Q15596	10518	O75838
10575	P50991	10585	Q9Y6A1	10640	O00471
10664	P49711	10743	Q7Z5J4	10765	Q9UGL1
10787	Q9Y2A7	109	O60266	10943	Q8N5Y2
10999	Q6P1M0	1105	O14646	11059	Q9H0M0
11069	Q8WZA2	1107	Q12873	111	O95622
11103	Q13601	11128	O14802	11133	Q9Y664
11141	Q9NZN1	11151	P31146	11198	Q9Y5B9
1120	Q7RTT9	1131	P20309	11336	O60645
1139	P36544	1142	Q05901	114785	Q96DN6
114791	Q96RT8	114805	Q8IUC8	116442	Q96DA2
116986	Q99490	1175	P53680-1	1183	P51793
122553	Q86SZ2	123169	Q8WVC0	123606	Q7RTP0
1268	P21554	128239	Q86VI3	132	P55263
135	P29274	1376	P23786	137970	Q6UXZ4
1387	Q92793	140	P0DMS8	142686	A6NK59
144165	Q96MT3	1454	P49674	1457	P68400
1460	P67870	147694	Q8NEK5	147968	Q6ZSI9
1496	P45983	1499	Q16539	150094	P57059
1501	P53778	1523	O75582	152330	Q8IWV2
1524	O75676	154	P07550	154664	Q86UQ4
158	P30566	1584	P15538	159	P30520
1593	P15086	161357	Q7Z553	161725	Q8TE49
1630	P43146	1636	P12821	1644	P20711
1654	O00571	170572	Q8WXA8	1717	Q5VWK5
1739	Q12959	1740	Q15700	1742	P78352
1746	Q9GZZ7	1747	P16066	1750	P25092
1756	P11532	1760	Q09013	1762	Q9Y239
1778	Q14204	1788	Q9Y6K1	1793	Q14185
18	P80404	1803	P16234	1804	P09619
1806	P07333	1808	P11362-1, Q16555	1809	Q14195
1812	P17948	1813	P35968	1814	P35916
1826	O60469, Q9UF33	1857	Q92997	1859	Q15262
186	P50052	1917	Q05639	192669	Q9H9G7

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197131	Q8IWV7	1977	Q00535	1981	Q04637
1993	Q12926	1995	P48729	199777	Q68DY1
200424	O43151	2020	O75460	202559	Q5VWX1
2033	Q09472	2048	O60674	2055	P53671
2078	Q99759	2100	Q92731	2103	O95718
2109	P42345	2131	Q5VST9	2167	P05023
2171	P14415	2195	P54687	220	P24530, P47895
2200	Q07817	221037	Q15652	221656	Q8NB78
222537	Q8IZT8	222962	Q7RTT9	2239	Q15569
2243	P02671	2258	P0DP23	2259	P0DP23
2260	P11362-1	22829	Q8NFZ3	22845	Q9UPQ8
22846	Q7L8A9	22854	Q9Y2I2	22866	Q8WXI2
22871	Q8N2Q7	2290	P55316	22907	P78357
22941	Q9UPX8	22954	Q13049	22981	Q9Y2I6
22986	P42568	22999	Q86UR5	23001	P25391
23013	Q96T58	23019	A5YKK6	23030	O94953
23067	Q9UPS6	23081	Q9H3R0	23097	Q9BWU1
23112	Q9UPQ9	23133	Q9UPP1	23135	O15054
2315	P60033	23189	Q14678	23191	Q7L576
23211	P07237	23229	O43307	23236	Q9NQ66
23259	O94830	23293	Q86US8	23303	Q9NQT8
23309	O75182	23314	Q9UPW6	2332	P13569
23332	Q7Z460	2334	P00736	23345	Q8NF91
23362	O60673	23380	O75044	23389	Q71F56
23451	O75533	23476	O60885	23503	Q9NSE4
23522	Q8WYB5	23545	Q9Y487	23649	Q14181
23705	Q9BY67	2395	Q16595	2444	P08648
2475	P42345	2483	O75881	253559	Q8N3J6
253980	Q8WZ19	2547	P12956	2556	P34903
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2567	Q99928	257194	Q7Z3B1	25769	Q96T83
25836	Q6KC79	25865	Q9BZL6	2590	P07148
25913	Q9NUX5	25942	Q96ST3	26019	Q9HAU5
26047	P55087	26050	O94991	26053	Q8WXX7
26057	Q5D862	26058	O15033	26115	Q9NR81
26122	O43307	26173	Q16558	26188	Q8WXH4
2620	Q9UKV0	2628	P50440	26280	Q9NP60
26290	Q9NY28	26470	Q13797	26512	Q9UL03
26523	Q9UL18	26610	Q96EB1	2670	Q8NB78
26960	Q8NFP9	270	Q9NS75	27044	Q7KZF4
27071	Q9UN19	27086	Q9H334-8	27131	P00973
27161	Q9UKV8	27185	Q96BT3	27255	Q9UQ52
27328	Q15825	27347	Q9NS84	27352	Q8WVB6
2739	Q14957	2742	P23416, Q13255	275	P21453
2770	P63096	2778	P63092, Q5JWF2	2820	O43566
28234	Q9NPD5	284058	Q7Z3B3	284217	P25391
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2861	P46531	287	Q01484	2876	Q16526

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2902	Q05586	2903	Q12879	2904	Q13224
29072	Q9BYW2	2915	P41594	2917	P06213
2944	P09488	2969	Q6IA17	2977	P33402
29781	Q6IBW4	29929	Q9Y672	29994	P28566
29998	P46098	30010	Q96D96	301	P04083
3054	P51610	3069	Q00341	3097	P28300
3105	P04439	3106	P29372	3115	P04440
3123	P01911	3135	Q8WTT0	3150	Q5EBL8
3184	P29475	3185	P52597	3188	P55795
3190	P61978	3192	P06748	3198	P25929
321	Q99767	322	O43614	3265	P01112
3290	Q9UM07	3351	P28222	3359	P46098
3382	Q08209	339122	Q86YS6	340267	Q2UY09
340385	Q6ZMY9	342132	Q6NX45	3479	P05019
348980	O60741	349075	Q8N859	353288	Q7Z3Y9
3608	Q12905	3628	P49441	367	P47901
3690	P05106	3708	Q14643	3720	P48764
373	P46098	3745	Q14721	3746	P48547
3751	Q9NZV8	3752	Q9UK17	375775	Q6ZV29
3766	P78508	3772	Q99712	3778	Q12791
3785	O43526, P61764	3786	O43525, Q09428	3790	Q9BQ31
3800	O60282	3827	P01042	3912	P07942
392636	Q6ZNB7	394	Q13017	3949	P63027
3952	P41159	4035	Q07954	4036	P98164
4089	Q13485	4128	P21397	4129	P27338
4137	P10636-8	4152	Q9UIS9	4173	P33991
4175	Q14566	4204	P51608-1, P51608-2	4208	Q06413
4233	P08581	4241	P08582	4297	Q03164
43	P22303	4306	P08235-1, P08235-2, P08235-3, P08235-4	4308	Q7Z4N2
4359	P25189	438	P78508	440193	Q9P219
4481	P21757	4482	Q9UJ68	4488	P35548
4524	P42898	4585	Q99102	4627	P35579
4628	P35580	4638	Q15746	4644	Q9Y4I1
4650	Q13459	4698	Q16718	473	Q05901
4756	Q92859	476	Q07001	4763	P21359
4774	Q12857	478	P13637	4781	O00712
4784	Q14938	4821	O95096	4849	O75175
4862	Q99743	4864	O15118	4897	Q92823
4914	P04629, P04629-1	4915	Q16620	4916	Q16288
4929	P43354	493	P23634	4952	Q01968
4983	O60890	5020	P01178	5021	P30559
5026	Q93086	5049	P68402	5053	P00439
5054	P05121	5058	Q13153	5062	Q13177
5067	Q9P232	5071	O60260	5079	Q02548
5080	P26367	5087	P40424	50937	Q4KMG0
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Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
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51317	Q96BD5	51322	Q9BTA9	5133	Q15116
5137	Q14123	51412	O94805	51592	Q9UPN9
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51720	Q96RL1	51725	Q9UH90	51741	Q9NZC7
51760	O76082	51780	Q7LBC6	5187	O15534
5191	O00628	5245	P35232	5252	O43189
5290	P42336	5294	P48736	5296	O00459
5329	Q03405	53335	Q9H165	5350	P26678
53615	O95983	5364	O43157	53942	O94779
54221	Q8WZA1	54413	Q9NZ94	5444	P27169
54536	Q96QF0	546	Q14721	547	Q92953
54715	Q9NWB1	54790	Q6N021	54806	Q8N157
54898	Q9NXB9	55015	Q70EL2	55023	Q8WWQ0
55055	Q9H900	5515	P67775	5519	P30154
552	Q9NSA2	55209	Q6P4F2	55217	Q9NVH6
55227	Q9BTT6	55250	Q6IA86	5528	Q14738
553	Q9NZV8	5530	Q08209	55356	Q8IZD6
5536	P53041	55553	P35712	55558	P51805
55568	Q86SR1	55624	Q8WZA1	55689	Q9ULM3
55690	Q6VY07	55746	Q8WUM0	5575	P31321
55777	Q9P267	5578	P17252	5579	P05771
55799	Q8IZS8	55869	Q9BY41	5587	Q15139
55870	Q9NR48	55904	Q8IZD2	5591	P78527
55914	Q96RT1	5595	P27361	56135	P15882
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56144	P07093	56145	Q9BZX2	56147	Q9BZV2
56160	Q96MG7	5625	O43272	563	P56696
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57580	Q8TCU6	57634	Q96L91	57680	Q9HCK8
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5862	P61019	5879	P63000	5885	O60216
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6014	Q99578	6092	Q9HCK4	6095	P35398
6096	Q92753	6134	P27635	6196	Q15349
6197	P51812	6304	Q01826	6305	O95248
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6334	Q9UQD0	6335	Q15858	6342	P22307
6383	P34741	64130	Q9HAP6	6418	Q01105
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6529	P30531	6531	Q01959	6532	P31645
6535	P48029	6595	P51531	6597	P51532
6601	Q8TAQ2	6616	P60880	6624	Q16658
6647	P00441	667	Q03001, Q9NYV9	6683	Q9UBP0
6694	Q13103	6711	Q01082	673	P15056
6734	P08240	6749	Q08945	675	P59534
6804	Q16623	6812	P61764, P61764-1	683	Q10588
6844	P63027	6853	P17600	6854	Q92777
6855	P08247	6857	P21579	6872	P21675
6878	P49848	6907	O60907	6934	Q9NQB0
6999	P48775	7007	O75443	7010	Q02763
7014	Q15554	7025	P10589	7057	P07996
7067	P10827	7102	P41732	7173	P07202
7204	O75962	721	P0C0L5	7225	Q9Y210
7248	Q92574	7249	P49815	7276	P02766
7328	P62256	7337	Q05086	7403	O15550
7421	P11473	7468	O96028	747	P21817
7471	P04628	7508	Q01831	7514	O14980
7528	P25490	7531	P62258	7532	P61981
7566	P17022	765	Q8WWZ4	7704	Q05516
773	O00555	774	Q00975	775	Q13936
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778	O95342	781	O15438	782	Q02641
783	Q08289	7837	Q92626	7850	P27930
7874	Q93009	79143	Q96N66	7915	P51649
79623	Q96FL9	79648	Q8NEM0	79718	Q9BZK7
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80204	Q86XK2	81	P32249	8128	Q92186
814	Q16566	8140	Q01650	815	Q9UQM7
816	Q13554	81614	Q8N8Q9	81704	Q8NF50
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8242	P41229	8243	Q14683	8295	Q9Y4A5
83692	Q8TCZ2	83696	P0C0S5	83852	Q96T68
8404	Q14515	84152	Q9UD71	84231	Q6Q0C0
84282	Q8IUD6	84433	Q9BXL7	8452	Q13618
84527	Q9BR84	84623	Q8IZU9	84628	Q96CW9
8481	O75665	84812	Q9BRC7	84871	Q5VU57
84889	Q8WY07	8493	O15297	84952	P33527
8500	Q13136	85015	Q70EL2	85358	Q75V66
85445	O15033	85458	A1A4S6	8573	O14936
8604	O75746	8621	Q14004	8648	Q15788
8666	O75821	881	Q6PXP3	8812	O75909
8828	O60462	8831	Q96PV0	8850	Q92831
8861	Q86U70	8864	O15055	8867	O43426
8905	P56377	8911	Q9P0X4	8912	O95180
8913	O43497	8924	O95714	8930	O95243
8936	Q92558	8945	Q9Y297	8970	P06899

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9228	Q9P1A6	9229	O14490	9256	O95153
92737	Q8NFT8	9295	Q05519	9320	Q14669
93426	Q8N0S2	93594	O43752	93664	Q96PV0
9369	Q9HDB5, Q9Y4C0	9378	P58400, Q9ULB1	9379	P58401, Q9P2S2
9416	Q9BUQ8	9456	Q86YM7	9481	O95847
95	O00155	952	Q14940	9568	O75899
95681	Q9BYV8	9572	P20393	9578	Q9Y5S2
9611	O75376	9631	O75694	9639	O15013
9662	Q66GS9	9681	O75140	9690	Q15386
9732	Q8N1I0	9739	O15047	9743	A7KAX9
9759	P56524	9820	Q14999	9869	Q15047
987	Q8N697	9877	O75152	9891	O60285
9915	Q9HBZ2	9928	Q15058	9958	Q9Y4E8
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Input	ChEBI Id	Input	ChEBI Id	Input	ChEBI Id
2290	2290	26523	26523	29119	29119
4208	4208	4638	4638	57634	57634
57705	57705	6532	6532		

7. Identifiers not found

These 257 identifiers were not found neither mapped to any entity in Reactome.

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158800	166336	168400	170302	196385	205428	220296	221035
221092	2272	22924	22982	23025	23026	23036	23040
23096	23152	23167	23181	23233	23241	23245	23312
23316	23328	23371	23394	23469	23613	254048	254065
254170	254827	259266	26040	26056	26137	26245	26262
27245	27443	283078	283450	283489	284451	29123	339479
340533	343413	344148	344558	392862	4010	401145	406928
4076	4130	4139	4212	4288	4335	4622	4643
4858	5013	5047	50651	50945	5101	51319	51366
51533	51629	5307	53944	54329	54439	5455	54551
54584	54714	54768	54862	54870	54897	55079	55116
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56899	56946	57178	57231	57466	57471	57479	57496
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84687	8532	8537	8562	8618	8632	8853	8940
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