



# Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 78 on 30/11/2021. The web link to these results is:

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

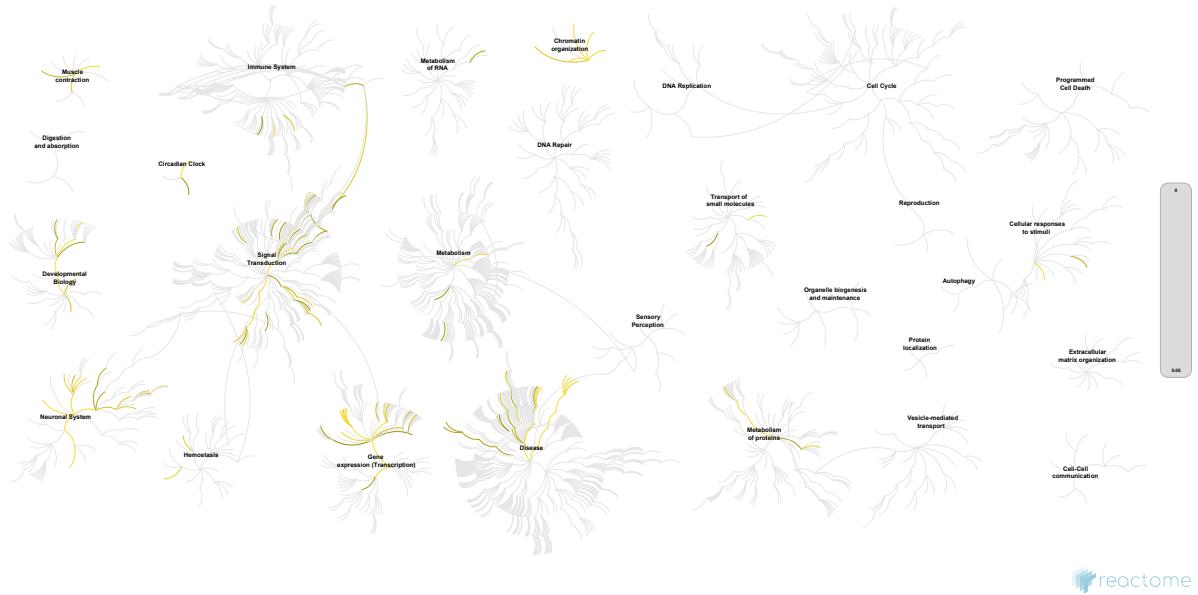
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 147 out of 205 identifiers in the sample were found in Reactome, where 1011 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 MjAyMTExMzAxMzQxMzVfNjAwMA%3D%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
Chromatin organization	27 / 256	0.018	2.81e-13	1.54e-10	32 / 85	0.006
Chromatin modifying enzymes	27 / 256	0.018	2.81e-13	1.54e-10	32 / 85	0.006
Neuronal System	36 / 489	0.034	9.52e-13	3.47e-10	88 / 216	0.016
Neurexins and neuroligins	14 / 60	0.004	8.21e-12	2.24e-09	17 / 19	0.001
Protein-protein interactions at synapses	14 / 93	0.007	2.26e-09	4.94e-07	21 / 33	0.002
Transmission across Chemical Synapses	22 / 343	0.024	3.37e-07	6.13e-05	65 / 163	0.012
Interaction between L1 and Ankyrins	7 / 33	0.002	2.74e-06	4.28e-04	4 / 4	2.95e-04
PKMTs methylate histone lysines	8 / 49	0.003	3.62e-06	4.92e-04	10 / 22	0.002
L1CAM interactions	12 / 130	0.009	5.16e-06	6.24e-04	18 / 54	0.004
Diseases of signal transduction by growth factor receptors and second messengers	24 / 498	0.035	1.30e-05	0.001	153 / 484	0.036
Nervous system development	26 / 621	0.044	5.98e-05	0.006	75 / 324	0.024
RUNX1 interacts with co-factors whose precise effect on RUNX1 targets is not known	6 / 39	0.003	8.39e-05	0.007	4 / 5	3.68e-04
Transcriptional regulation by RUNX1	15 / 261	0.018	8.85e-05	0.007	41 / 132	0.01
Transcriptional Regulation by MECP2	9 / 100	0.007	9.48e-05	0.007	73 / 77	0.006
Loss of MECP2 binding ability to 5mC-DNA	3 / 5	3.50e-04	1.10e-04	0.008	2 / 2	1.47e-04
Axon guidance	24 / 585	0.041	1.57e-04	0.011	69 / 298	0.022
Pervasive developmental disorders	4 / 16	0.001	2.17e-04	0.012	5 / 5	3.68e-04
Loss of function of MECP2 in Rett syndrome	4 / 16	0.001	2.17e-04	0.012	5 / 5	3.68e-04
Disorders of Nervous System Development	4 / 16	0.001	2.17e-04	0.012	5 / 5	3.68e-04
Disorders of Developmental Biology	4 / 16	0.001	2.17e-04	0.012	5 / 5	3.68e-04
HDMs demethylate histones	5 / 31	0.002	2.66e-04	0.014	8 / 17	0.001
LRR FLII-interacting protein 1 (LRRKIP1) activates type I IFN production	3 / 7	4.91e-04	2.94e-04	0.014	4 / 5	3.68e-04
MECP2 regulates neuronal receptors and channels	5 / 32	0.002	3.08e-04	0.014	26 / 26	0.002

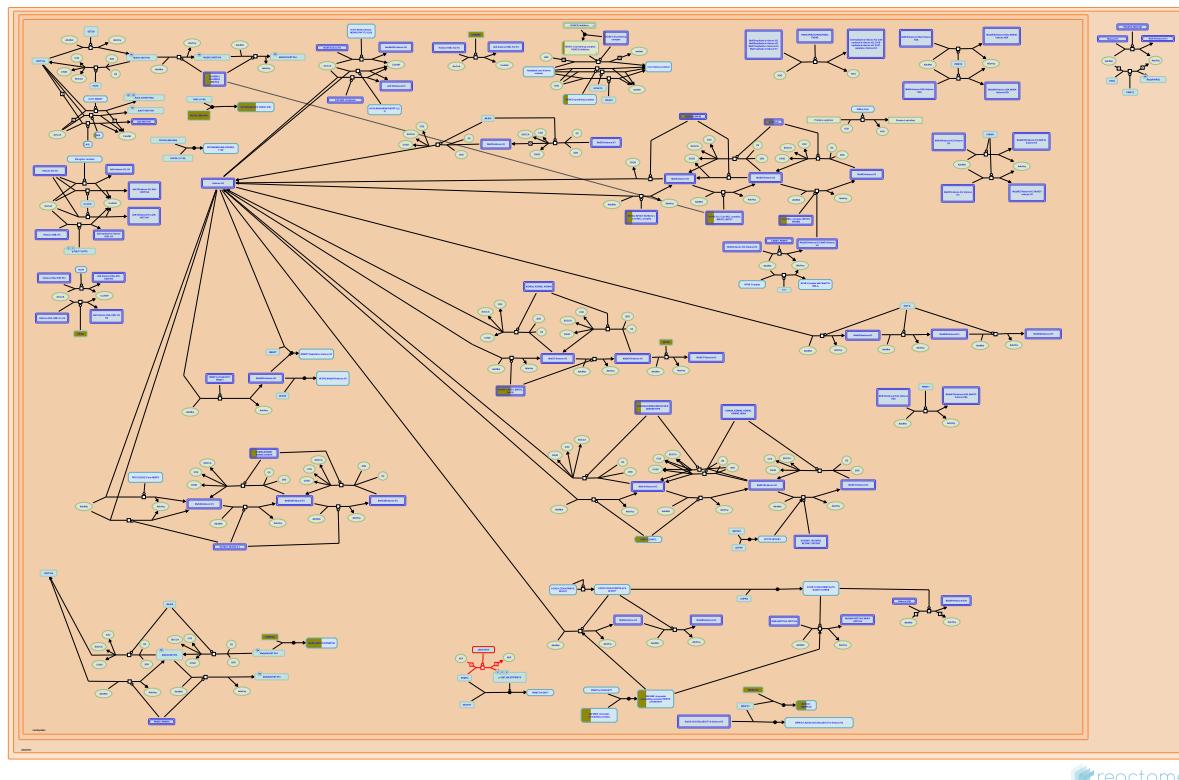
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Neurotransmitter receptors and postsynaptic signal transmission	13 / 232	0.016	3.30e-04	0.014	48 / 109	0.008
MAPK1/MAPK3 signaling	16 / 329	0.023	3.37e-04	0.014	45 / 82	0.006

\* 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. Chromatin organization (R-HSA-4839726)



 reactome

**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.

### References

- Gilchrist S, Bickmore WA & Gilbert N (2005). Chromatin organization in the mammalian nucleus. Int. Rev. Cytol., 242, 283-336. [🔗](#)
- Reinberg D & Li G (2011). Chromatin higher-order structures and gene regulation. Curr. Opin. Genet. Dev., 21, 175-86. [🔗](#)

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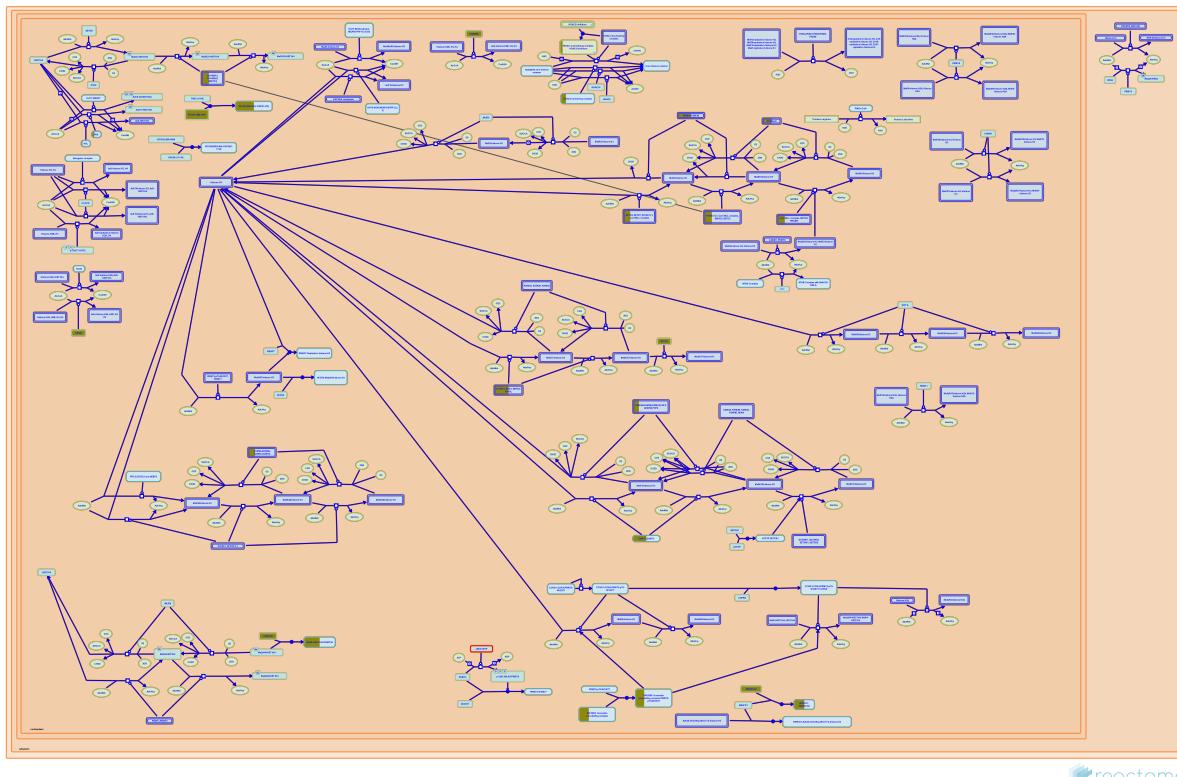
Date	Action	Author
2013-11-02	Edited	May B
2013-11-02	Authored	May B
2013-11-02	Created	May B

Date	Action	Author
2013-11-18	Reviewed	Karagiannis T
2021-09-10	Modified	Weiser JD

## 27 submitted entities found in this pathway, mapping to 27 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10765	Q9UGL1	10943	Q8N5Y2	1107	Q12873
1387	Q92793	1788	Q9Y6K1	2033	Q09472
23135	O15054	2670	Q8NB78	284058	Q7Z3B3
29072	Q9BYW2	4297	Q03164	51111	Q4FZB7
51317	Q96BD5	51780	Q7LBC6	55870	Q9NR48
55904	Q8IZD2	57492	Q8NFD5	58508	Q8NEZ4
60	P60709	64324	Q96L73	6595	P51531
6597	P51532	6601	Q8TAQ2	79718	Q9BZK7
79813	Q9H9B1	8242	P41229	8648	Q15788

## 2. Chromatin modifying enzymes (R-HSA-3247509)



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

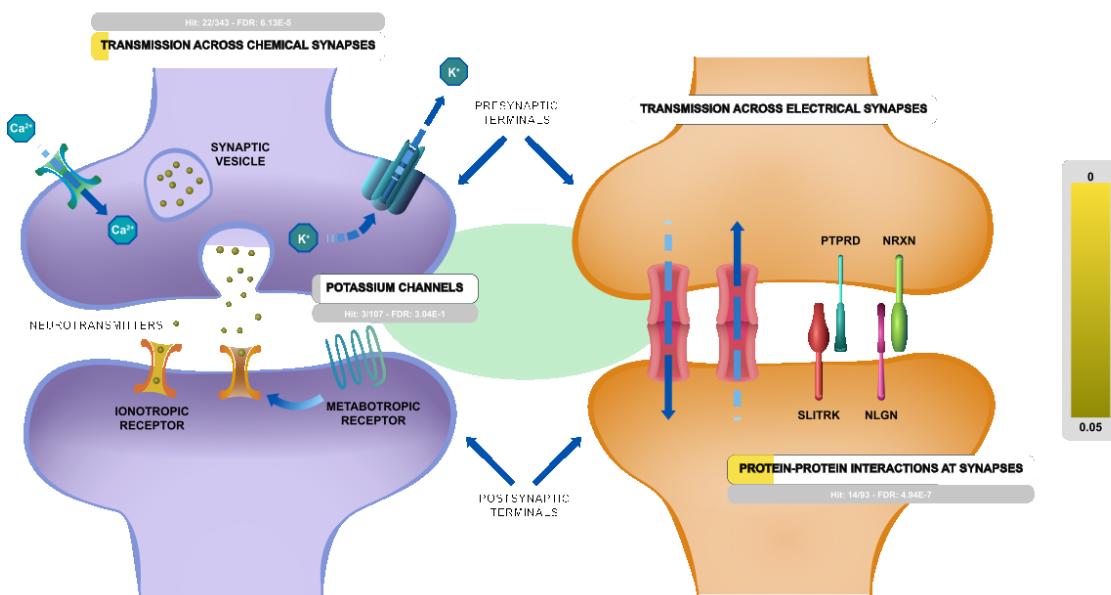
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Date	Action	Author
2013-03-12	Authored	Jupe S
2013-04-04	Created	Jupe S
2013-11-18	Edited	Jupe S
2013-11-18	Reviewed	Karagiannis T
2021-09-10	Modified	Weiser JD

### 27 submitted entities found in this pathway, mapping to 27 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10765	Q9UGL1	10943	Q8N5Y2	1107	Q12873
1387	Q92793	1788	Q9Y6K1	2033	Q09472
23135	O15054	2670	Q8NB78	284058	Q7Z3B3
29072	Q9BYW2	4297	Q03164	51111	Q4FZB7
51317	Q96BD5	51780	Q7LBC6	55870	Q9NR48
55904	Q8IZD2	57492	Q8NFD5	58508	Q8NEZ4
60	P60709	64324	Q96L73	6595	P51531
6597	P51532	6601	Q8TAQ2	79718	Q9BZK7
79813	Q9H9B1	8242	P41229	8648	Q15788

### 3. 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 Ca<sup>2+</sup> through voltage-gated channels, which gives rise to a transient increase in Ca<sup>2+</sup> concentration within the presynaptic terminal. The rise in Ca<sup>2+</sup> 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*.

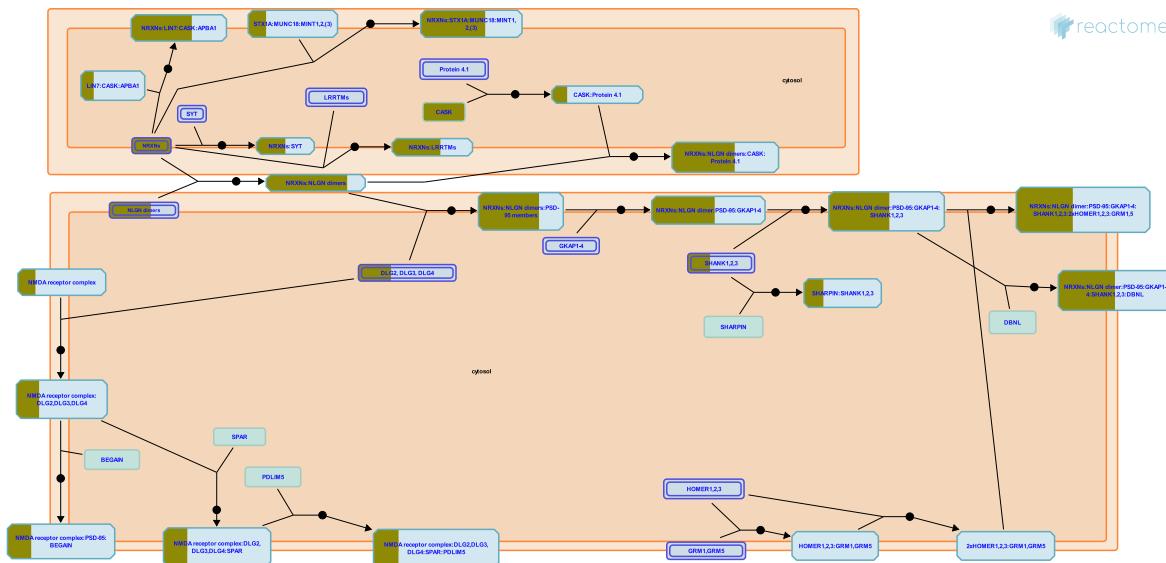
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Date	Action	Author
2004-04-22	Created	Joshi-Tope G
2005-11-10	Edited	Gillespie ME
2005-11-10	Authored	Gillespie ME
2021-09-10	Modified	Weiser JD

**31 submitted entities found in this pathway, mapping to 37 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1175	P53680-1	1742	P78352	22941	Q9UPX8
22999	Q86UR5	23229	O43307	2561	P47870
2562	P28472	26960	Q8NFP9	2770	P63096
2891	O94925, P42262	2904	Q13224	3265	P01112
373	P46098	3745	Q14721	3786	O43525, Q09428
473	Q05901	54413	Q9NZ94	546	Q14721
55799	Q8IZS8	57502	Q8N0W4	57555	Q8NFZ4
6529	P30531	6812	P61764, P61764-1	6853	P17600
773	O00555	777	Q15878	7915	P51649
8573	O14936	9369	Q9HDB5, Q9Y4C0	9378	P58400, Q9ULB1
9379	P58401, Q9P2S2				

## 4. 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 Nlgns. 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 LRRTMs: 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](#)

## Edit history

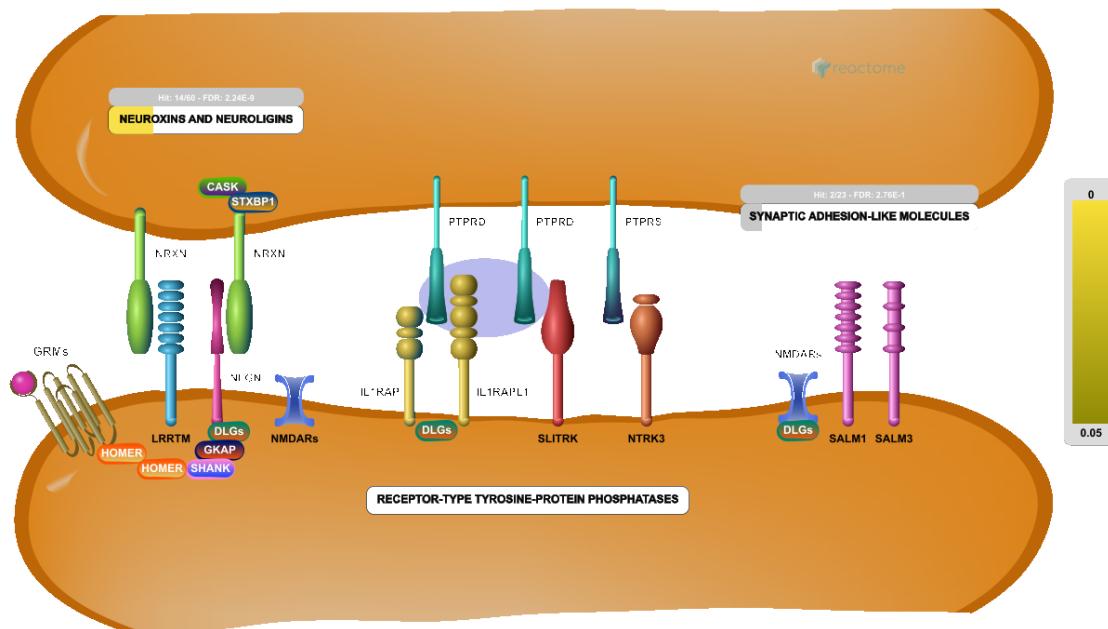
Date	Action	Author
2015-09-04	Edited	Garapati P V

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

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

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1742	P78352	22941	Q9UPX8	2904	Q13224
54413	Q9NZ94	57502	Q8N0W4	57555	Q8NFZ4
6812	P61764	8573	O14936	9369	Q9HDB5, Q9Y4C0
9378	P58400, Q9ULB1	9379	P58401, Q9P2S2		

## 5. 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. [\[link\]](#)
- Dresbach T & Dean C (2006). Neuroligins and neurexins: linking cell adhesion, synapse formation and cognitive function. *Trends Neurosci.*, 29, 21-9. [\[link\]](#)
- Südhof TC (2008). Neuroligins and neurexins link synaptic function to cognitive disease. *Nature*, 455, 903-11. [\[link\]](#)

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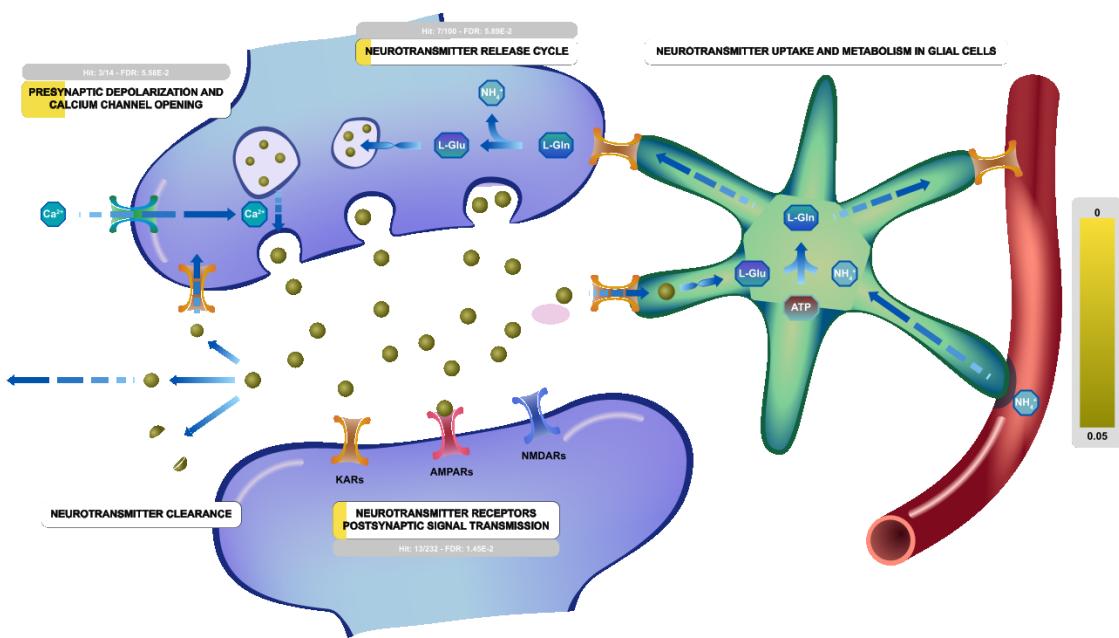
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2015-09-04	Edited	Garapati P V
2015-09-04	Authored	Garapati P V
2015-09-04	Created	Garapati P V
2015-11-09	Reviewed	Washbourne P

Date	Action	Author
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1742	P78352	22941	Q9UPX8	2904	Q13224
54413	Q9NZ94	57502	Q8N0W4	57555	Q8NFZ4
6812	P61764	8573	O14936	9369	Q9HDB5, Q9Y4C0
9378	P58400, Q9ULB1	9379	P58401, Q9P2S2		

## 6. 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  $\text{Ca}^{2+}$  concentration is approximately 10-3 M while the internal  $\text{Ca}^{2+}$  concentration is approximately 10-7 M. Opening of calcium channels causes a rapid influx of  $\text{Ca}^{2+}$  into the presynaptic terminal. The elevated presynaptic  $\text{Ca}^{2+}$  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*.

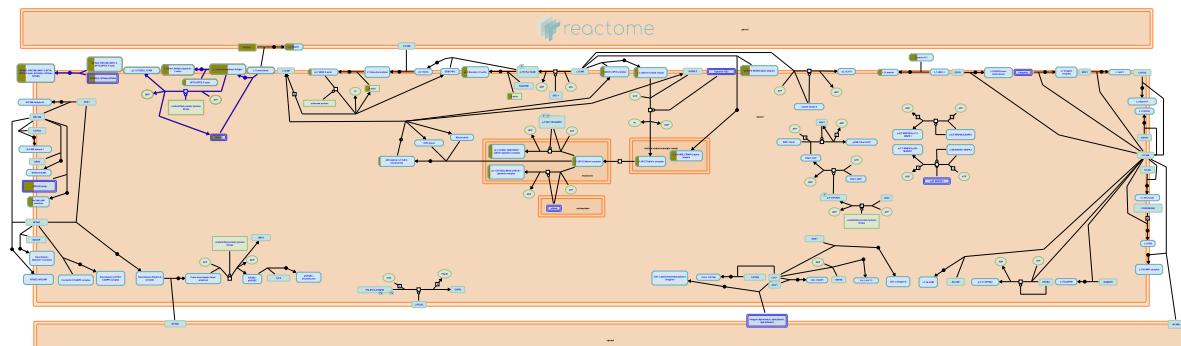
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2004-04-22	Created	Joshi-Tope G
2008-01-14	Edited	Mahajan SS
2008-01-14	Authored	Mahajan SS
2008-12-02	Reviewed	Restituito S, Kavalali E
2020-01-24	Reviewed	Wen H
2021-09-10	Modified	Weiser JD

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1175	P53680-1	1742	P78352	22999	Q86UR5
23229	O43307	2561	P47870	2562	P28472
26960	Q8NFP9	2770	P63096	2891	O94925, P42262
2904	Q13224	3265	P01112	373	P46098
473	Q05901	55799	Q8IZS8	6529	P30531
6812	P61764-1	6853	P17600	773	O00555
777	Q15878	7915	P51649	8573	O14936

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



Ankyrins are a family of adaptor proteins that couple membrane proteins such as voltage gated Na<sup>+</sup> channels and the Na<sup>+</sup>/K<sup>+</sup> 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.

### References

- Nagaraj K, Hortsch M & Godenschwege TA (2009). The interaction between L1-type proteins and ankyrins--a master switch for L1-type CAM function. *Cell Mol Biol Lett*, 14, 57-69. [🔗](#)
- Nagaraj K & Hortsch M (2006). Phosphorylation of L1-type cell-adhesion molecules--ankyrins away!. *Trends Biochem Sci*, 31, 544-6. [🔗](#)
- Maness PF & Guan H (2010). Perisomatic GABAergic Innervation in Prefrontal Cortex Is Regulated by Ankyrin Interaction with the L1 Cell Adhesion Molecule. *Cereb Cortex*. [🔗](#)
- Gunn-Moore FJ, Hill M, Herron LR & Davey F (2009). The intracellular interactions of the L1 family of cell adhesion molecules. *Biochem J*, 419, 519-31. [🔗](#)

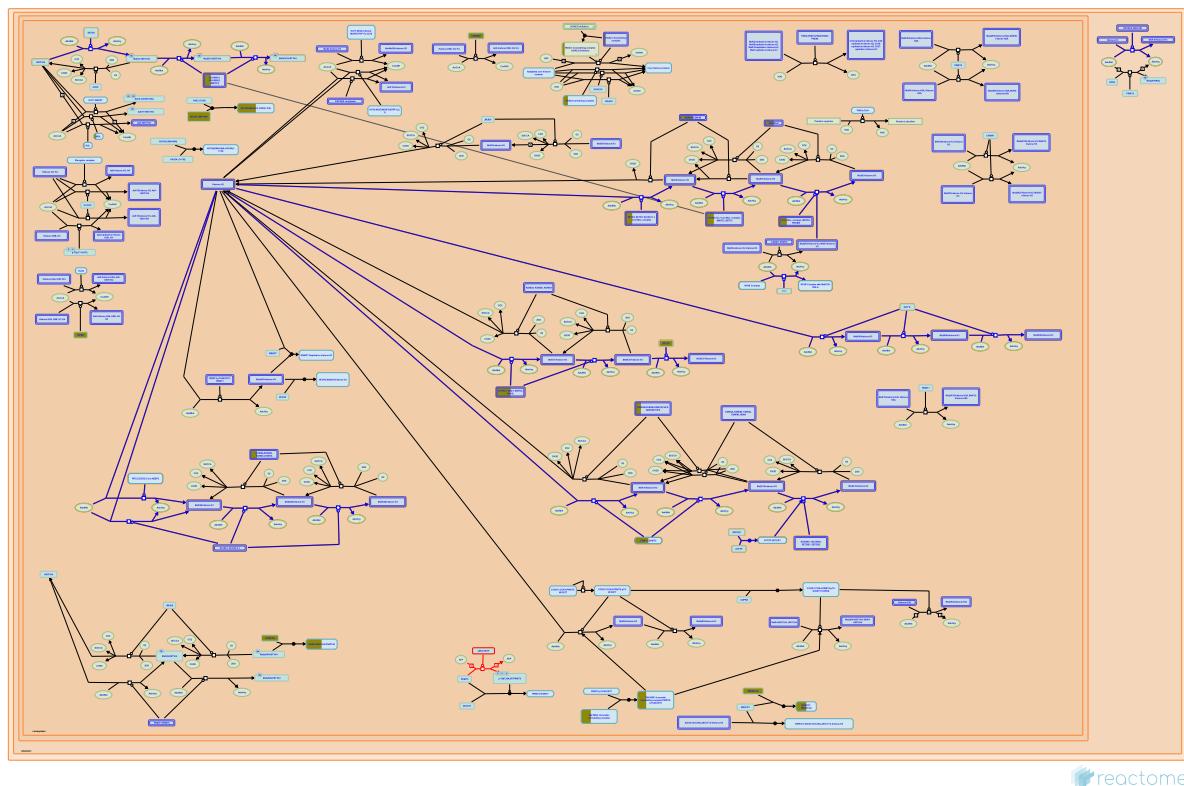
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2009-10-27	Created	Garapati P V
2010-02-16	Reviewed	Maness PF
2021-09-10	Modified	Weiser JD

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287	Q01484	288	Q12955	3786	O43525
60	P60709	6323	P35498	6326	Q99250
6334	Q9UQD0				

## 8. PKMTs methylate histone lysines (R-HSA-3214841)



Lysine methyltransferases (KMTs) and arginine methyltransferases (RMTs) have a common mechanism of catalysis. Both families transfer a methyl group from a common donor, S-adenosyl-L-methionine (SAM), to the nitrogen atom on the epsilon-amino group of lysine or arginine (Smith & Denu 2009) using a bimolecular nucleophilic substitution (SN2) methyl transfer mechanism (Smith & Denu 2009, Zhang & Bruice 2008). All human KMTs except DOT1L (KMT4) (Feng et al. 2002, van Leeuwen et al. 2002, Lacoste et al. 2002) have a ~130 amino acid catalytic domain referred to as the SET domain (Del Rizzo & Trievel 2011, Dillon et al. 2005, Herz et al. 2013).

Some KMTs selectively methylate a particular lysine residue on a specific histone type. The extent of this methylation (mono-, di- or tri-methylation) also can be stringent (Herz et al. 2013, Copeland et al. 2009). Many KMTs also have non-histone substrates (Herz et al 2013), which are not discussed in this module.

The coordinates of post-translational modifications represented and described here follow UniProt standard practice whereby coordinates refer to the translated protein before any processing. Histone literature typically refers to specific residues by numbers which are determined after the initiating methionine has been removed. Therefore the coordinates of post-translated residues in the Reactome database and described here are frequently +1 when compared to the histone literature.

SET domain-containing proteins are classified in one of 7 families (Dillon et al. 2005). First to be discovered were the SUV39 family named after founding member SUV39H1 (KMT1A), which selectively methylates lysine-10 of histone H3 (H3K9) (Rea et al. 2000). Family member EHMT2 (KMT1C, G9A) is the predominant H3K9 methyltransferase in mammals (Tachibana et al. 2002). SETDB1 (KMT1E, ESET) also predominantly methylates H3K9, most effectively when complexed with ATF7IP (MCAF, hAM) (Wang et al. 2003).

SETD2 (KMT3A, HYPB), a member of the SET2 family, specifically methylates histone H3 lysine-37 (H3K36) (Sun et al. 2005). WHSC1 (KMT3G, NSD2, MMSET) a member of the same family, targets H3K36 when provided with nucleosome substrates but also can methylate histone H4 lysine-45 when octameric native or recombinant nucleosome substrates are provided (Li et al. 2009); di-methylation of histone H3 at lysine-37 (H3K36me2) is thought to be the principal chromatin-regulatory activity of WHSC1 (Kuo et al. 2011). Relatives NSD1 (KMT3B) and WHSC1L1 (KMT3F, NSD3) also methylate nucleosomal H3K36. NSD1 is active on unmethylated or a mimetic monomethylated H3K36, but not di- or trimethylated H3K36 mimetics (Li et al. 2009). Human SETD7 (KMT7, SET7/9), not classified within the 7 SET-domain containing families, mono-methylates lysine-5 of histone H3 (H3K4) (Xiao et al. 2003).

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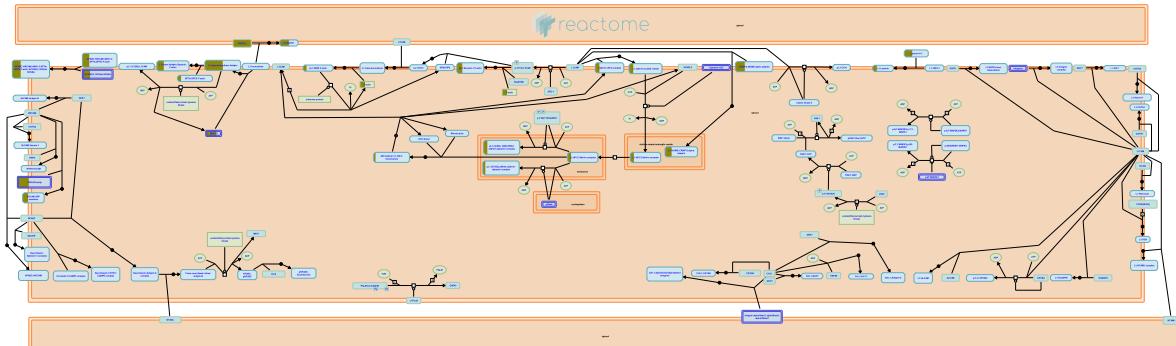
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Date	Action	Author
2013-03-12	Authored	Jupe S
2013-03-12	Created	Jupe S
2014-09-10	Edited	Jupe S
2014-11-17	Reviewed	Motamed M
2021-09-10	Modified	Weiser JD

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

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29072	Q9BYW2	4297	Q03164	51111	Q4FZB7
55870	Q9NR48	55904	Q8IZD2	58508	Q8NEZ4
64324	Q96L73	79813	Q9H9B1		

## 9. 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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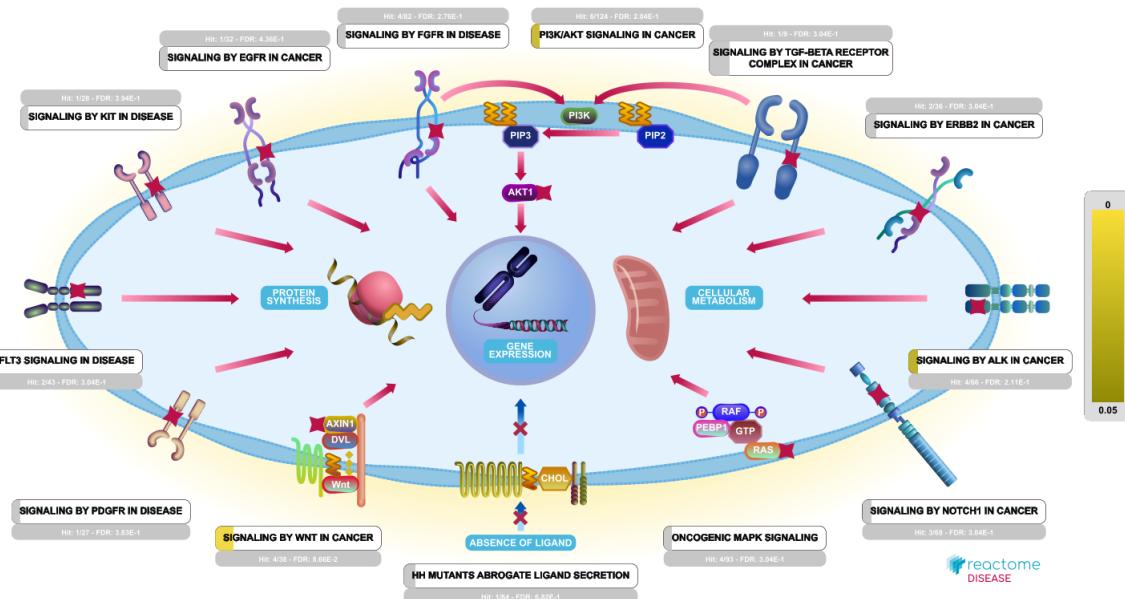
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Date	Action	Author
2008-07-16	Created	Garapati P V
2008-07-30	Edited	Garapati P V
2008-07-30	Authored	Garapati P V
2010-02-16	Reviewed	Maness PF
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1175	P53680	1742	P78352	1808	P11362-1, Q16555
23001	P25391	287	Q01484	288	Q12955
3786	O43525	60	P60709	6323	P35498
6326	Q99250	6334	Q9UQD0		

## 10. 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.

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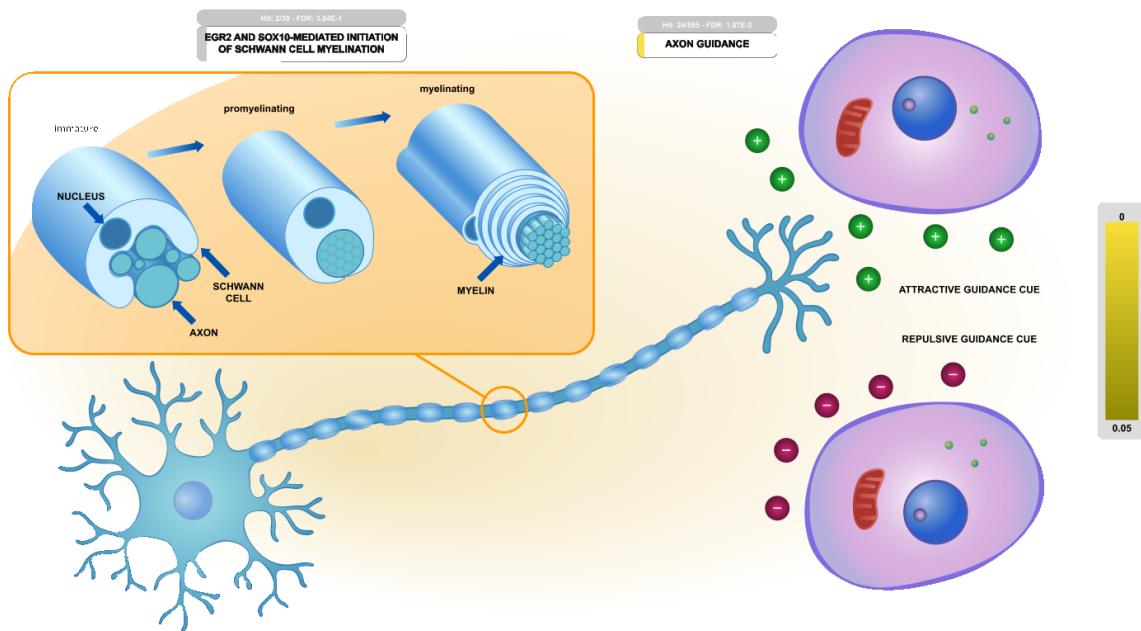
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Date	Action	Author
2015-01-16	Created	D'Eustachio P
2021-03-29	Modified	Rothfels K

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1387	Q92793	1499	P35222	1788	P36897
1808	P11362, P11362-1, P11362-19	1995	P48729	2033	Q09472
2561	P04626	3192	P06748	3265	P01112
4204	P51608-1, P51608-2	4763	P21359	53335	Q9H165
5528	Q14738	5718	O00232	5728	P60484
5781	Q06124	60	P60709	673	P15056
6934	Q9NQB0	7249	P49815	79718	Q9BZK7

## 11. 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).

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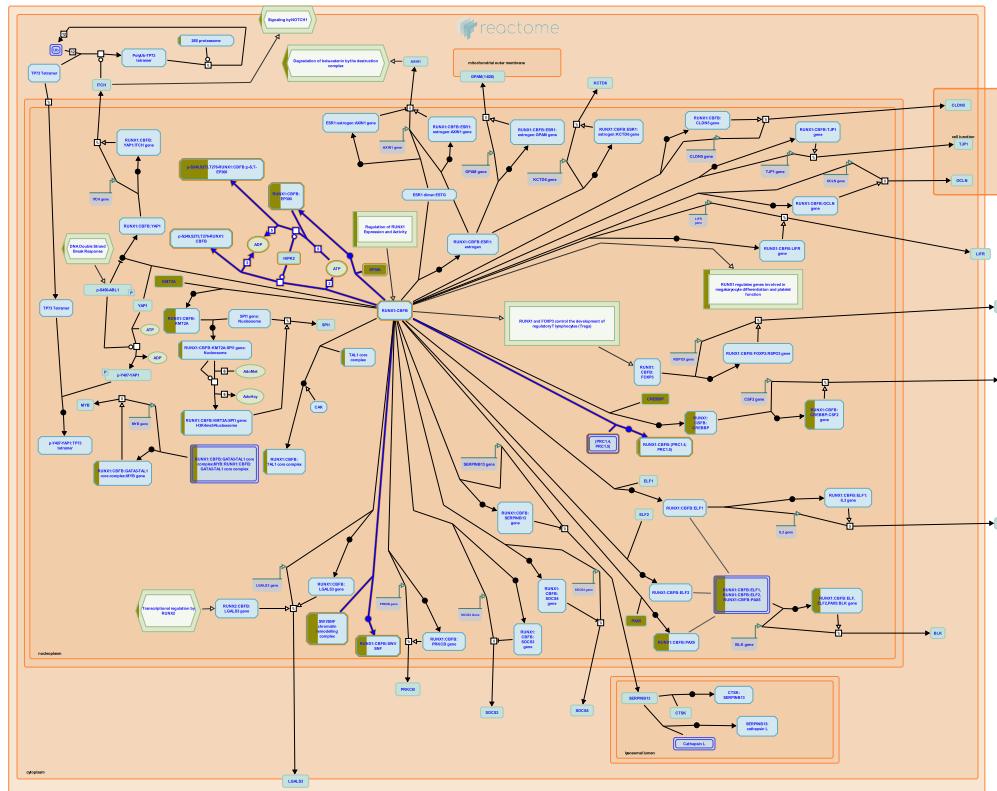
Date	Action	Author
2020-01-23	Reviewed	Orlic-Milacic M
2020-01-31	Edited	Rothfels K
2020-01-31	Authored	Rothfels K
2020-01-31	Created	Rothfels K
2021-09-10	Modified	Weiser JD

24 submitted entities found in this pathway, mapping to 26 Reactome entities

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1175	P53680	1499	Q16539	1742	P78352
1808	P11362-1, Q16555	1826	O60469, Q9UF33	23001	P25391
23229	Q9GZV5	287	Q01484	288	Q12955
2904	Q13224	3265	P01112	3786	O43525

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
5649	P78509	5718	O00232	5781	Q06124
60	P60709	6323	P35498	6326	Q99250
6334	Q9UQD0	65109	Q9BZI7	6597	P51532
7204	O75962	775	Q13936	8861	Q86U70

## 12. RUNX1 interacts with co-factors whose precise effect on RUNX1 targets is not known (R-HSA-8939243)



The transcriptional activity of the RUNX1:CBFB complex is regulated by interaction with co-factors and posttranslational modifications of RUNX1. Protein serine/threonine kinase HIPK2 can phosphorylate RUNX1 and affect transcriptional activity of the RUNX1:CBFB complex during hematopoiesis. Some CBFB mutations found in leukemia interfere with HIPK2-mediated phosphorylation of RUNX1. HIPK2 can simultaneously phosphorylate RUNX1 and EP300 (p300) bound to the RUNX1:CBFB1 complex (Aikawa et al. 2006, Wee et al. 2008).

The RUNX1:CBFB complex can associate with the polycomb repressor complex 1 (PRC1). PRC1 complexes are found at many RUNX1 target promoters and can act either as co-activators or co-repressors in the transactivation of RUNX1 targets (Yu et al. 2011).

RUNX1 recruits the SWI/SNF chromatin remodeling complex to many RUNX1 target promoters by directly interacting with several SWI/SNF subunits (Bakshi et al. 2010).

Other co-factors of the RUNX1:CBFB complex are annotated in the context of transcriptional regulation of specific genes.

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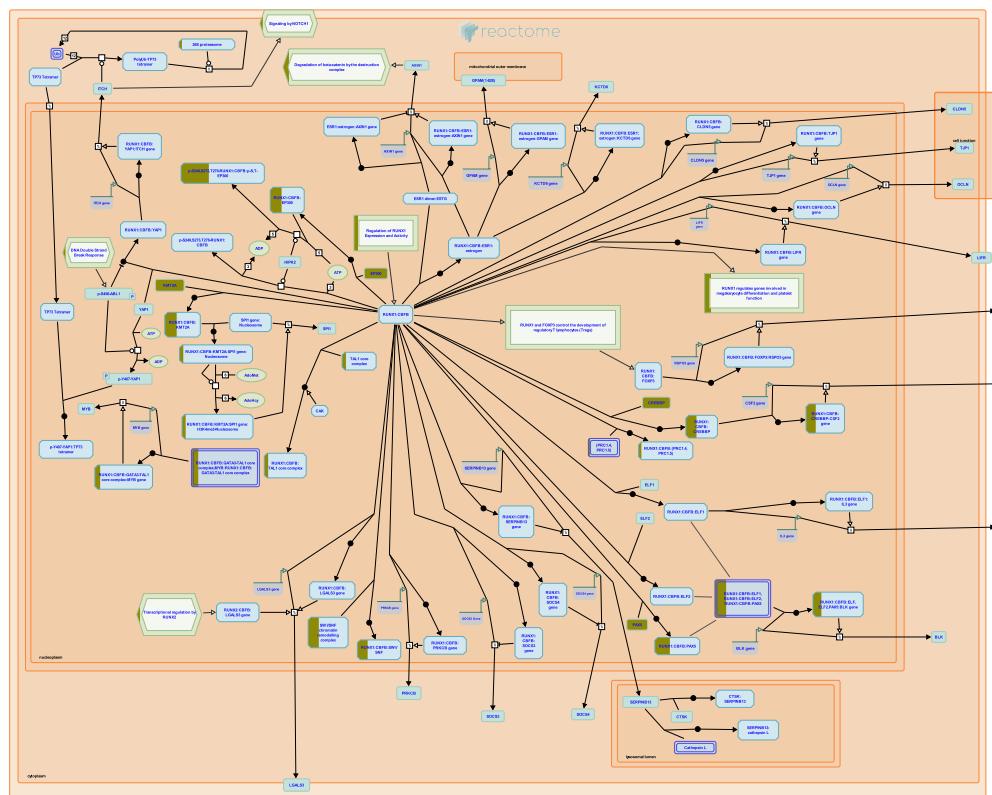
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Date	Action	Author
2016-09-14	Authored	Orlic-Milacic M
2016-09-17	Created	Orlic-Milacic M
2016-12-20	Reviewed	Ito Y, Chuang LS
2017-05-09	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

**6 submitted entities found in this pathway, mapping to 6 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
2033	Q09472	26053	Q8WXX7	57492	Q8NFD5
6595	P51531	6597	P51532	6601	Q8TAQ2

### 13. Transcriptional regulation by RUNX1 ([R-HSA-8878171](#))



The RUNX1 (AML1) transcription factor is a master regulator of hematopoiesis (Ichikawa et al. 2004) that is frequently translocated in acute myeloid leukemia (AML), resulting in formation of fusion proteins with altered transactivation profiles (Lam and Zhang 2012, Ichikawa et al. 2013). In addition to RUNX1, its heterodimerization partner CBFB is also frequently mutated in AML (Shigesada et al. 2004, Mangan and Speck 2011).

The core domain of CBFB binds to the Runt domain of RUNX1, resulting in formation of the RUNX1:CBFB heterodimer. CBFB does not interact with DNA directly. The Runt domain of RUNX1 mediated both DNA binding and heterodimerization with CBFB (Tahirov et al. 2001), while RUNX1 regions that flank the Runt domain are involved in transactivation (reviewed in Zhang et al. 2003) and negative regulation (autoinhibition). CBFB facilitates RUNX1 binding to DNA by stabilizing Runt domain regions that interact with the major and minor grooves of the DNA (Tahirov et al. 2001, Backstrom et al. 2002, Bartfeld et al. 2002). The transactivation domain of RUNX1 is located C-terminally to the Runt domain and is followed by the negative regulatory domain. Autoinhibition of RUNX1 is relieved by interaction with CBFB (Kanno et al. 1998).

Transcriptional targets of the RUNX1:CBFB complex involve genes that regulate self-renewal of hematopoietic stem cells (HSCs) (Zhao et al. 2014), as well as commitment and differentiation of many hematopoietic progenitors, including myeloid (Friedman 2009) and megakaryocytic progenitors (Goldfarb 2009), regulatory T lymphocytes (Wong et al. 2011) and B lymphocytes (Boller and Grosschedl 2014).

RUNX1 binds to promoters of many genes involved in ribosomal biogenesis (Ribi) and is thought to stimulate their transcription. RUNX1 loss-of-function decreases ribosome biogenesis and translation in hematopoietic stem and progenitor cells (HSPCs). RUNX1 loss-of-function is therefore associated with a slow growth, but at the same time it results in reduced apoptosis and increases resistance of cells to genotoxic and endoplasmic reticulum stress, conferring an overall selective advantage to RUNX1 deficient HSPCs (Cai et al. 2015).

RUNX1 is implicated as a tumor suppressor in breast cancer. RUNX1 forms a complex with the activated estrogen receptor alpha (ESR1) and regulates expression of estrogen-responsive genes (Chimge and Frenkel 2013).

RUNX1 is overexpressed in epithelial ovarian carcinoma where it may contribute to cell proliferation, migration and invasion (Keita et al. 2013).

RUNX1 may cooperate with TP53 in transcriptional activation of TP53 target genes upon DNA damage (Wu et al. 2013).

RUNX1 is needed for the maintenance of skeletal musculature (Wang et al. 2005).

During mouse embryonic development, Runx1 is expressed in most nociceptive sensory neurons, which are involved in the perception of pain. In adult mice, Runx1 is expressed only in nociceptive sensory neurons that express the Ret receptor and is involved in regulation of expression of genes encoding ion channels (sodium-gated, ATP-gated and hydrogen ion-gated) and receptors (thermal receptors, opioid receptor MOR and the Mrgpr class of G protein coupled receptors). Mice lacking Runx1 show defective perception of thermal and neuropathic pain (Chen CL et al. 2006). Runx1 is thought to activate the neuronal differentiation of nociceptive dorsal root ganglion cells during embryonal development possibly through repression of Hes1 expression (Kobayashi et al. 2012). In chick and mouse embryos, Runx1 expression is restricted to the dorso-medial domain of the dorsal root ganglion, to TrkA-positive cutaneous sensory neurons. Runx3 expression in chick and mouse embryos is restricted to ventro-lateral domain of the dorsal root ganglion, to TrkC-positive proprioceptive neurons (Chen AI et al. 2006, Kramer et al. 2006). RUNX1 mediated regulation of neuronally expressed genes will be annotated when mechanistic details become available.

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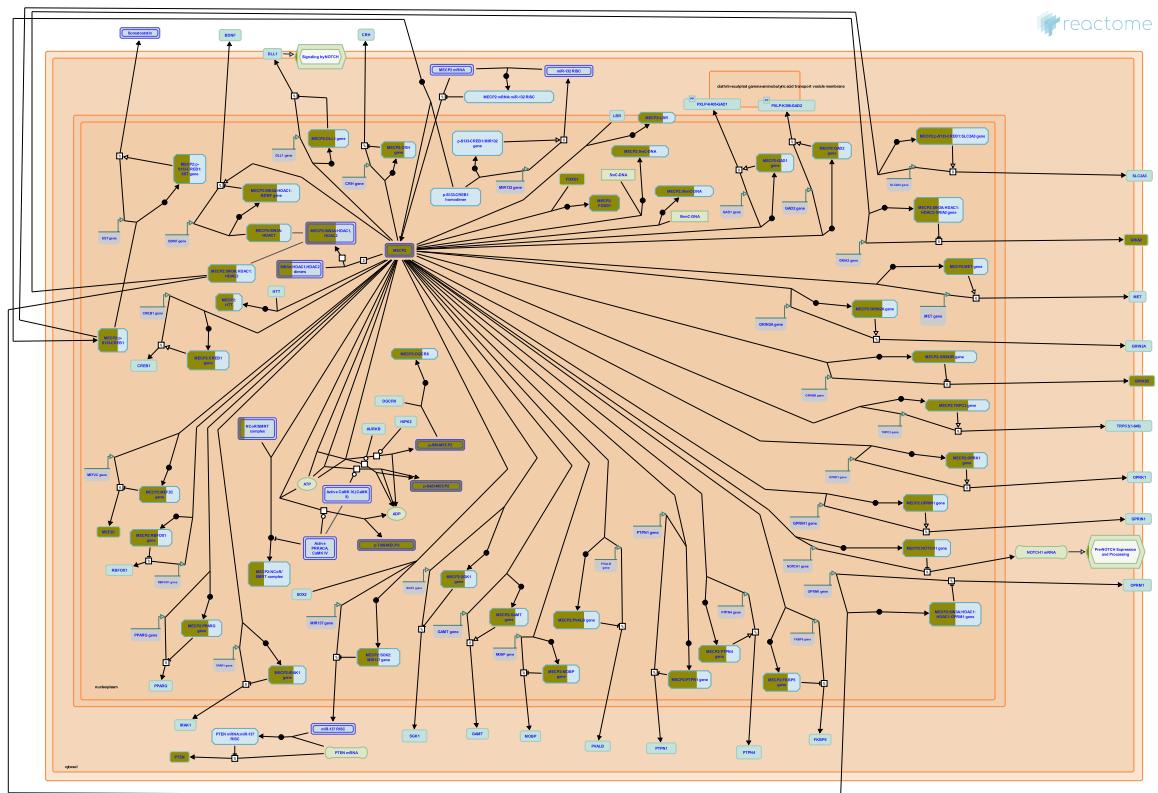
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2016-09-14	Authored	Orlic-Milacic M
2016-12-20	Reviewed	Ito Y, Chuang LS
2017-05-09	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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

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55904	Q8IZD2	5718	O00232	57492	Q8NFD5
5781	Q06124	58508	Q8NEZ4	6595	P51531
6597	P51532	6601	Q8TAQ2	8861	Q86U70

## 14. 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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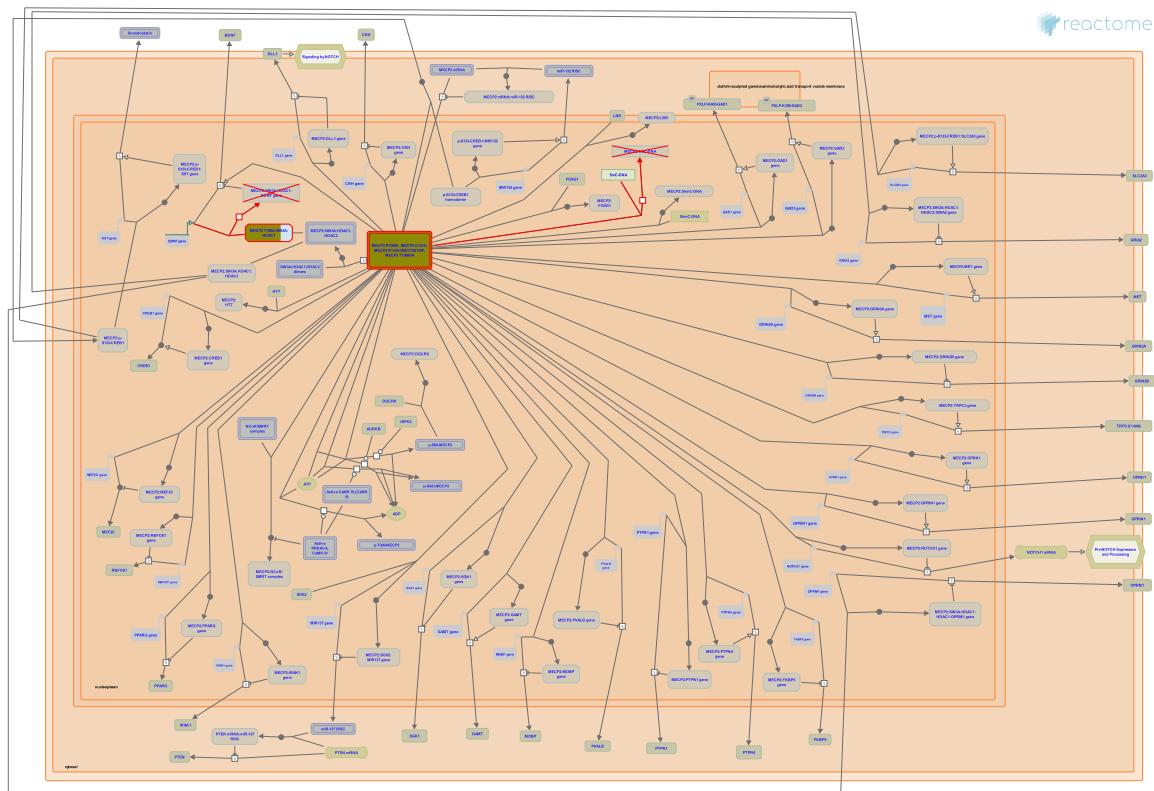
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2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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

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Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
2904	Q13224	4204	P51608-1, P51608-2	4208	Q06413
5728	P60484	79718	Q9BZK7		

## 15. Loss of MECP2 binding ability to 5mC-DNA (R-HSA-9022538)



**Cellular compartments:** nucleoplasm.

**Diseases:** Rett syndrome.

Missense mutations in the methyl-CpG binding domain (MBD) of methyl-CpG-binding protein 2 (MECP2), spanning amino acids 90 to 162, negatively affect the binding ability of MECP2 to methylated DNA (Ghosh et al. 2008, Ho et al. 2008, Goffin et al. 2012, Mellen et al. 2012).

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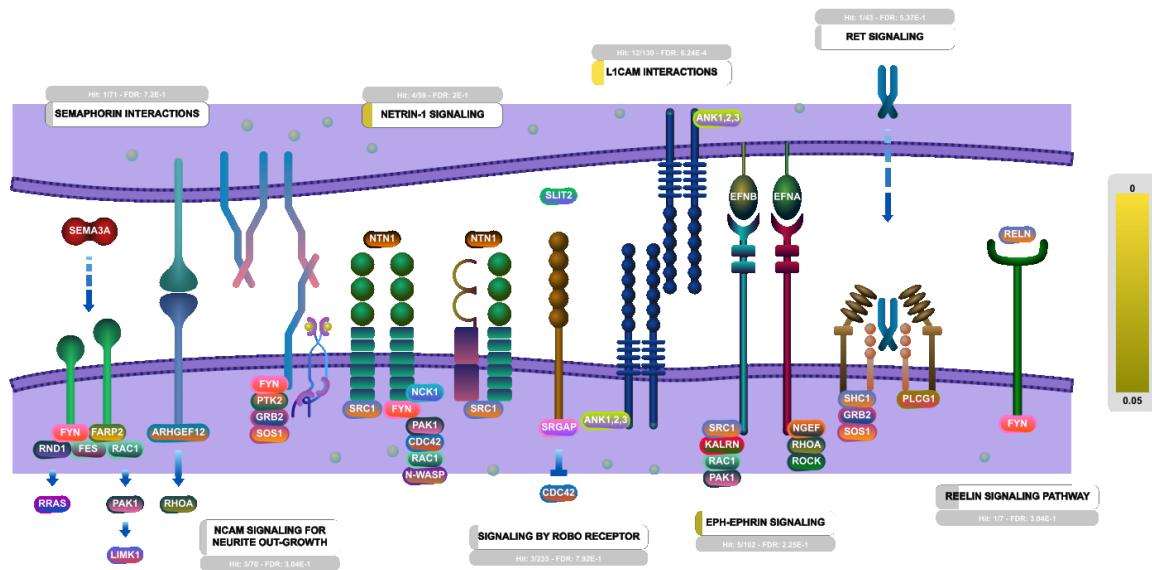
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Date	Action	Author
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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25942	Q96ST3	4204	P51608-1, P51608-2

## 16. 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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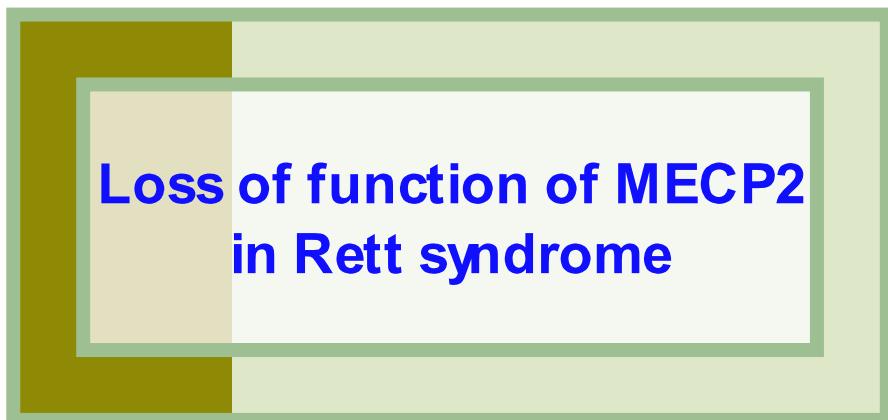
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2009-05-29	Edited	Garapati P V
2009-05-29	Authored	Garapati P V
2009-05-31	Created	Garapati P V
2021-09-10	Modified	Weiser JD

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287	Q01484	288	Q12955	2904	Q13224
3265	P01112	3786	O43525	5649	P78509
5718	O00232	5781	Q06124	60	P60709
6323	P35498	6326	Q99250	6334	Q9UQD0
65109	Q9BZI7	7204	O75962	775	Q13936
8861	Q86U70				

## 17. Pervasive developmental disorders ([R-HSA-9005895](#))



**Diseases:** pervasive developmental disorder.

Pervasive developmental disorders (PDDs) largely overlap with the autism spectrum disorders (ASDs). PDDs manifest in childhood and mainly affect social interaction, including communication and behavior. PDDs can be caused by mutations in genes involved in brain development and function, environmental insults, or the combination of environmental factors and genetic susceptibility. For review of this topic, please refer to Pickett and London 2005, Currenti 2010, Elsabbagh et al. 2012, Ferreri 2014.

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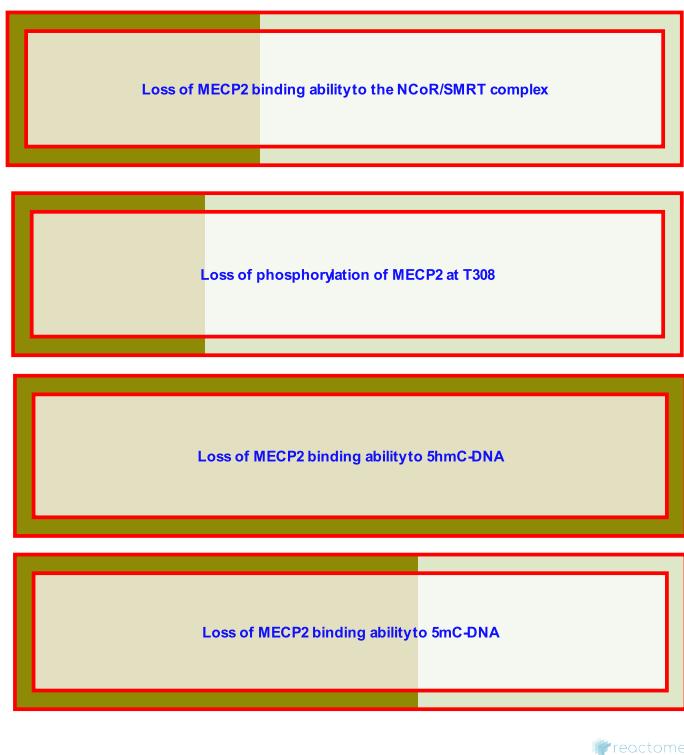
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2017-10-03	Authored	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

Date	Action	Author
2018-08-09	Modified	Orlic-Milacic M

**3 submitted entities found in this pathway, mapping to 4 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
25942	Q96ST3	4204	P51608-1, P51608-2	79718	Q9BZK7

## 18. Loss of function of MECP2 in Rett syndrome ([R-HSA-9005891](#))



**Diseases:** Rett syndrome.

Loss of function mutations in methyl-CpG-binding protein 2 (MECP2), an epigenetic regulator of transcription, are the major cause of Rett syndrome, a neurodevelopmental disorder that affects 1 in 10,000-15,000 female births. The symptoms of Rett syndrome appear after 6-18 months of apparently normal postnatal development and include regression of acquired language and motor skills, stereotypic hand movements, intellectual disability, epileptic seizures and respiratory disturbances. Besides Rett syndrome, aberrant MECP2 expression is implicated as an underlying cause of other neuropsychiatric disorders (reviewed by Banerjee et al. 2012, Ebert and Greenberg 2013, Lyst and Bird 2015). Only functionally characterized MECP2 mutations are annotated. For a comprehensive list of MECP2 mutations reported in Rett syndrome, please refer to the RettBASE (<http://mecp2.chw.edu.au>), a database dedicated to curation of disease variants of MECP2, CDKL5 and FOXG1 in Rett syndrome (Krishnaraj et al. 2017).

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2017-10-03	Authored	Orlic-Milacic M
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2018-08-08	Edited	Orlic-Milacic M
2018-09-05	Modified	Shorser S

**3 submitted entities found in this pathway, mapping to 4 Reactome entities**

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## 19. 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).

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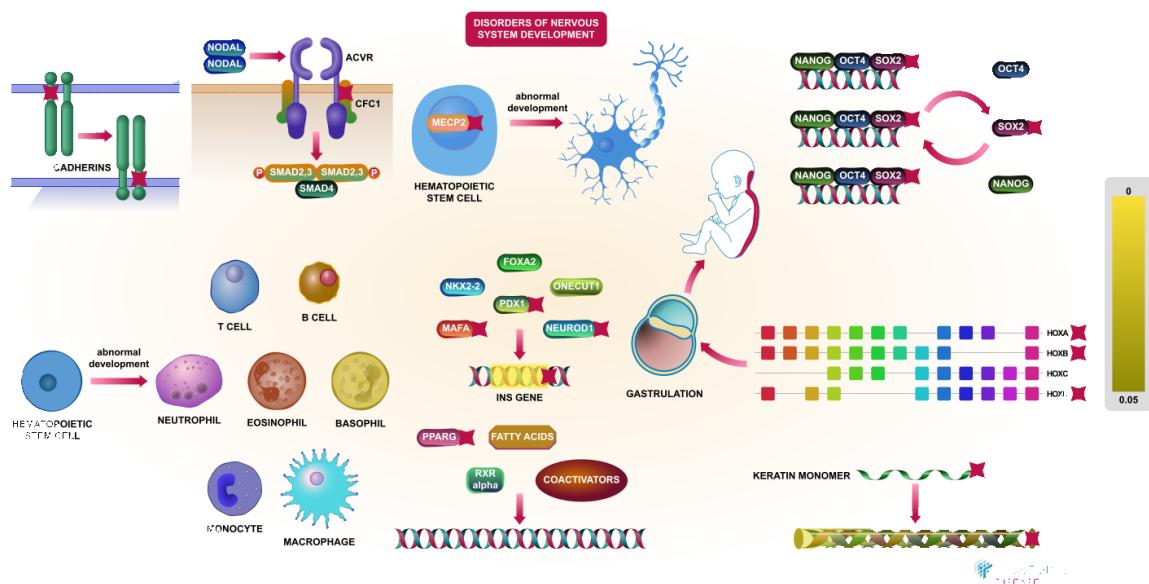
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2020-08-14	Reviewed	D'Eustachio P
2020-08-17	Edited	Orlic-Milacic M
2020-09-10	Modified	Orlic-Milacic M

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## 20. 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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Phadke R (2019). Myopathology of Congenital Myopathies: Bridging the Old and the New. Semin Pediatr Neurol, 29, 55-70. [🔗](#)

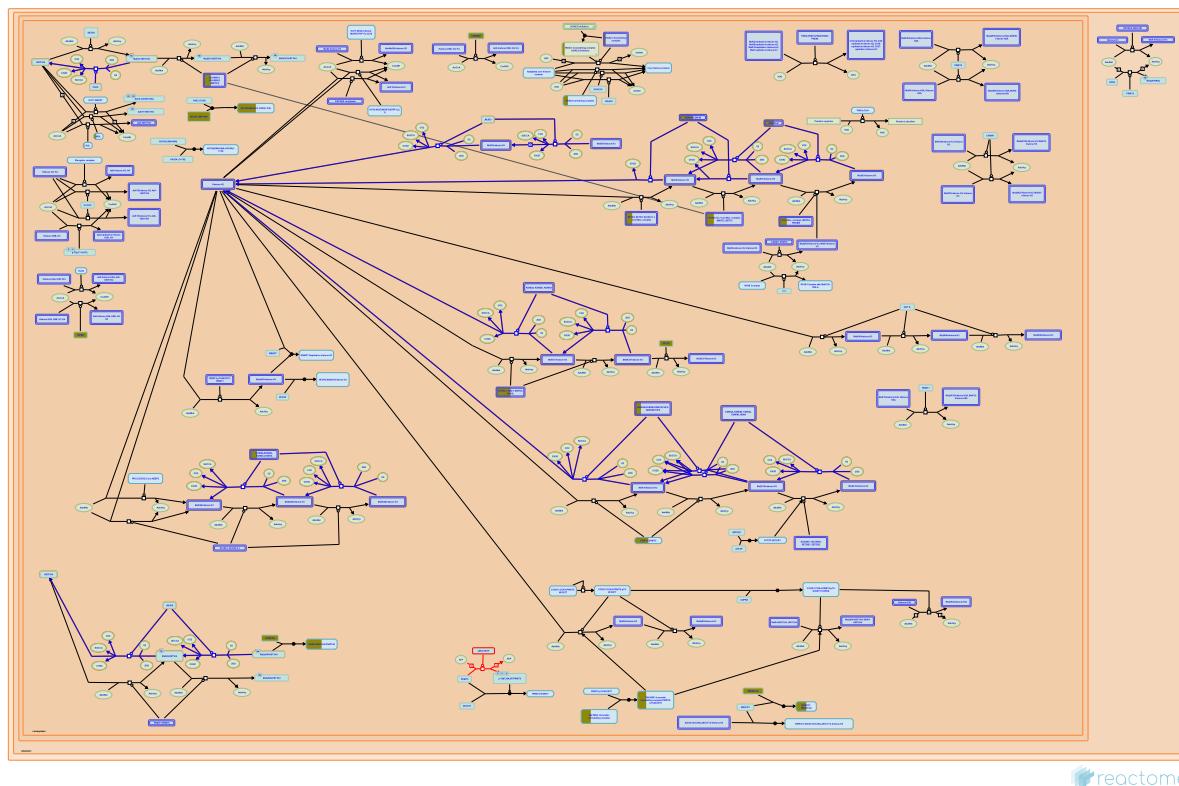
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2020-08-18	Reviewed	D'Eustachio P
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2020-08-25	Modified	Matthews L

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## 21. HDMs demethylate histones (R-HSA-3214842)



reactome

Histone lysine demethylases (KDMs) are able to reverse N-methylations of histones and probably other proteins. To date KDMs have been demonstrated to catalyse demethylation of N-epsilon methylated lysine residues. Biochemically there are two distinct groups of N-epsilon methylated lysine demethylases with different catalytic mechanisms, both of which result in methyl group oxidation to produce formaldehyde. KDM1A, formerly known as Lysine Specific Demethylase 1 (LSD1), belongs to the flavin adenine dinucleotide (FAD)-dependent amino oxidase family. The KDM1A reaction mechanism requires a protonatable lysine epsilon-amine group, not available in trimethylated lysines, which consequently are not KDM1 substrates. Other KDMs belong to the Jumonji C (JmjC) -domain containing family. These are members of the Cupin superfamily of mononuclear Fe (II)-dependent oxygenases, which are characterised by the presence of a double-stranded beta-helix core fold. They require 2-oxoglutarate (2OG) and molecular oxygen as co-substrates, producing, in addition to formaldehyde, succinate and carbon dioxide. This hydroxylation-based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC-containing demethylases are able to demethylate tri-, di- and monomethylated lysines.

The coordinates of post-translational modifications represented and described here follow 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 residues in the Reactome database and described here are frequently +1 when compared with the literature.

In general, methylation at histone H3 lysine-5 (H3K4) and lysine-37 (H3K36), including di- and trimethylation at these sites, has been linked to actively transcribed genes (reviewed in Martin & Zhang 2005). In contrast, lysine-10 (H3K9) promoter methylation is considered a repressive mark for euchromatic genes and is also one of the landmark modifications associated with heterochromatin (Peters et al. 2002).

The first reported JmjC-containing demethylases were KDM2A/B (JHDM1A/B, FBXL11/10). These catalyse demethylation of histone H3 lysine-37 when mono- or di-methylated (H3K36Me1/2) (Tsukada et al. 2006). They were found to contain a JmjC catalytic domain, previously implicated in chromatin-dependent functions (Clissold & Ponting 2001). Subsequently, many other JmjC enzymes have been identified and discovered to have lysine demethylase activities with distinct methylation site and state specificities.

KDM3A/B (JHDM2A/B) are specific for mono or di-methylated lysine-10 on histone H3 (H3K9Me1/2) (Yamane et al. 2006, Kim et al. 2012). KDM4A-C (JMJD2A-C/JHDM3A-C) catalyse demethylation of di- or tri-methylated histone H3 at lysine-10 (H3K9Me2/3) (Cloos et al. 2006, Fodor et al. 2006), with a strong preference for Me3 (Whetstine et al. 2007). KDM4D (JMJD2D) also catalyses demethylation of H3K9Me2/3 (Whetstine et al. 2007). KDM4A-C (JHDM3A-C) can also catalyse demethylation of lysine-37 of histone H3 (H3K36Me2/3) (Klose et al. 2006). KDM5A-D (JARID1A-D) catalyses demethylation of di- or tri-methylated lysine-5 of histone H3 (H3K4Me2/3) (Christensen et al. 2007, Klose et al. 2007, Lee et al. 2007, Secombe et al. 2007, Seward et al. 2007, Iwase et al. 2007). KDM6A and KDM6B (UTX/JMJD3) catalyse demethylation of di- or tri-methylated lysine-28 of histone H3 (H3K27Me2/3) (Agger et al. 2007, Cho et al. 2007, De Santra et al. 2007, Lan et al. 2007, Lee et al. 2007).

KDM7A (KIAA1718/JHDM1D) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) and mono- and di-methylated lysine-28 of histone H3 (H3K27Me1/2) (Horton et al. 2010, Huang et al. 2010). PHF8 (JHDM1E) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) and mono-methylated lysine-21 of histone H4 (H4K20Me1) (Loenarz et al. 2010, Horton et al. 2010, Feng et al. 2010, Kleine-Kohlbrecher et al. 2010, Fortschegger et al. 2010, Qi et al. 2010, Liu et al. 2010). PHF2 (JHDM1E) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) (Wen et al. 2010, Baba et al. 2011). JMJD6 was initially characterized as an arginine demethylase that catalyses demethylation of mono or di methylated arginine 3 of histone H3 (H3R2Me1/2) and arginine 4 of histone H4 (H4R3Me1/2) (Chang et al. 2007) although it was subsequently also characterized as a lysine hydroxylase (Webby et al. 2009).

N.B. The coordinates of post-translational modifications represented and described here follow 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 residues in the Reactome database and described here are frequently +1 when compared with the literature.

## References

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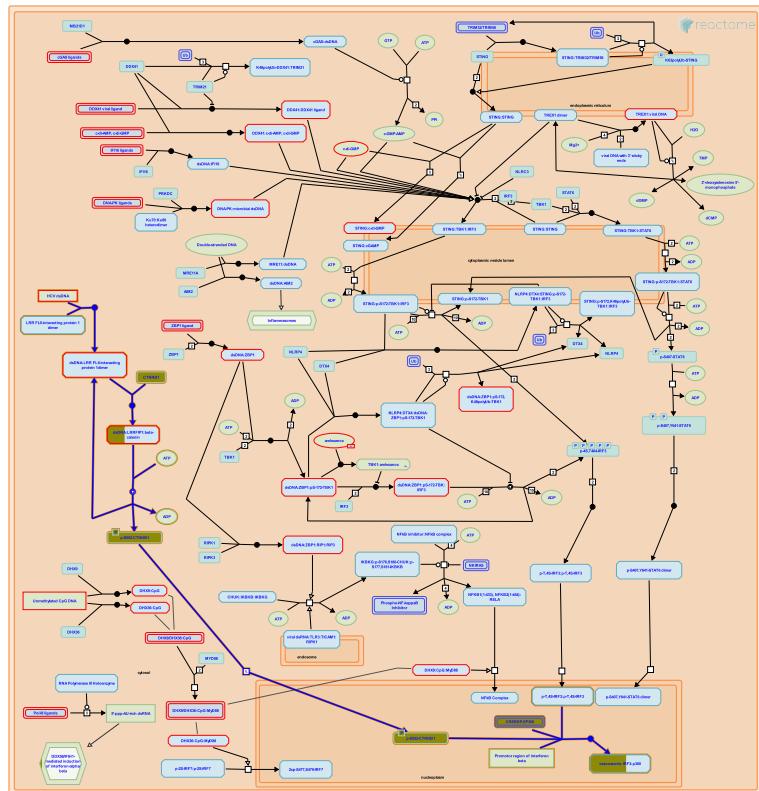
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2013-03-12	Created	Jupe S
2014-02-05	Edited	Jupe S
2014-05-08	Reviewed	Schofield CJ, Hopkinson J, Walport LJ

Date	Action	Author
2021-09-10	Modified	Weiser JD

## 5 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10765	Q9UGL1	23135	O15054	2670	Q8NB78
51780	Q7LBC6	8242	P41229		

## 22. LRR FLII-interacting protein 1 (LRRFIP1) activates type I IFN production (R-HSA-3134973)



Leucine-rich repeat flightless-interacting protein 1 (LRRFIP1) can bind exogenous double-stranded RNA and double-stranded DNA (Wilson SA et al. 1998; Yang P et al. 2010). LRRFIP1 was shown to mediate *Listeria monocytogenes*- and vesicular stomatitis virus (VSV)-induced IFN-beta production in mouse primary macrophages by regulating beta-catenin activity. Beta-catenin possibly functions as a transcriptional cofactor of IRF3 to initiate Ifnb1 transcription (Yang P et al. 2010).

### References

- Wilson SA, Kingsman AJ, Brown EC & Kingsman SM (1998). TRIP: a novel double stranded RNA binding protein which interacts with the leucine rich repeat of flightless I. Nucleic Acids Res., 26, 3460-7. [\[CrossRef\]](#)
- Wen M, Rui Y, Liu X, Yang P, Cao X, Zheng Y & An H (2010). The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a beta-catenin-dependent pathway. Nat. Immunol., 11, 487-94. [\[CrossRef\]](#)

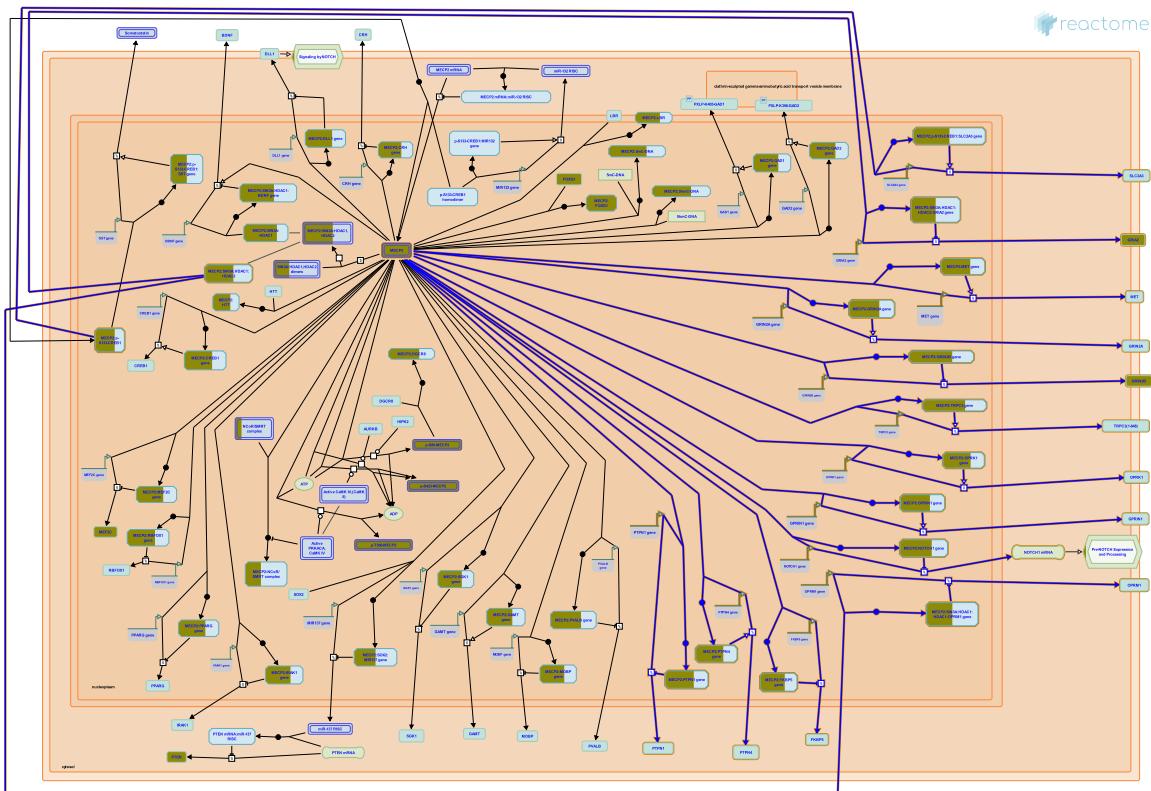
### Edit history

Date	Action	Author
2013-02-06	Authored	Shamovsky V
2013-02-11	Reviewed	D'Eustachio P
2013-02-13	Created	Shamovsky V
2013-05-17	Edited	Shamovsky V
2013-05-22	Reviewed	Wu J, Jin L
2021-09-10	Modified	Weiser JD

**3 submitted entities found in this pathway, mapping to 3 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1387	Q92793	1499	P35222	2033	Q09472

## 23. MECP2 regulates neuronal receptors and channels (R-HSA-9022699)



Receptors directly transcriptionally 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), and NOTCH1 (Li et al. 2014). Channels/transporters regulated by MECP2 include TRPC3 (Li et al. 2012) and SLC2A3 (Chen et al. 2013). MECP2 also regulates transcription of FKBP5, involved in trafficking of glucocorticoid receptors (Nuber et al. 2005, Urdinguio et al. 2008) and 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 PT-PN4 (Williamson et al. 2015).

## References

- Lee S, Kim W, Yoon BJ, Ham BJ, Bear MF & Chen W (2008). Activity-dependent NR2B expression is mediated by MeCP2-dependent epigenetic regulation. *Biochem. Biophys. Res. Commun.*, 377, 930-4. [🔗](#)
- Lim ZH, Leong WY, Goh EL, Pietri T & Korzh V (2015). Methyl-CpG Binding Protein 2 (MeCP2) Regulates Sensory Function Through Sema5b and Robo2. *Front Cell Neurosci*, 9, 481. [🔗](#)
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Zhong X, Jin P, Chau KF, Maslia J, Kong G, Chi J, ... Zhao X (2014). Cell cycle-linked MeCP2 phosphorylation modulates adult neurogenesis involving the Notch signalling pathway. Nat Commun, 5, 5601. [🔗](#)

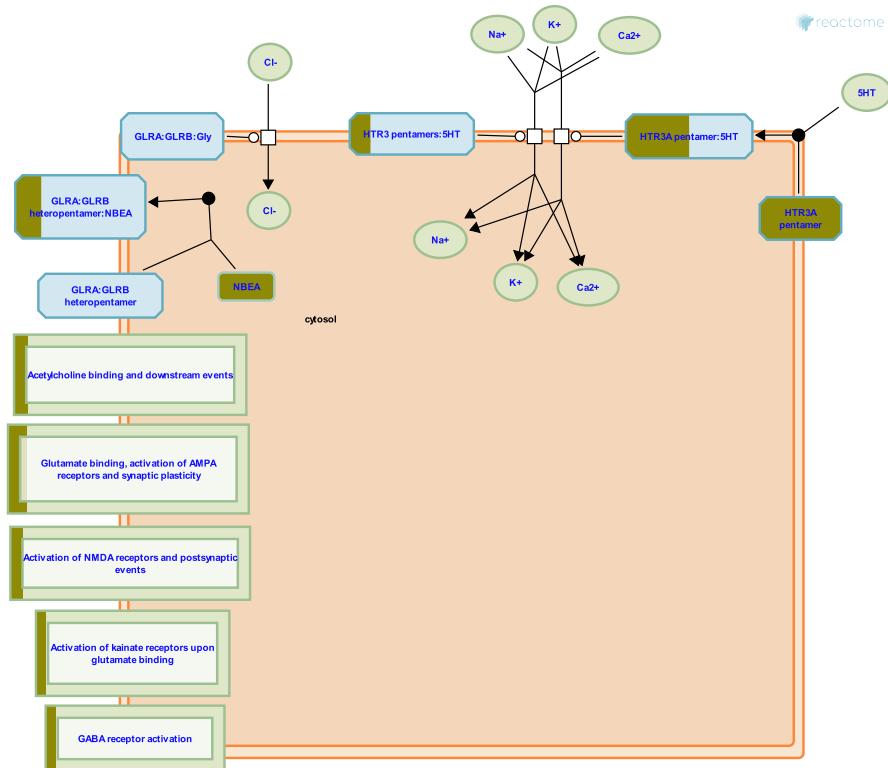
## Edit history

Date	Action	Author
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	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

**4 submitted entities found in this pathway, mapping to 5 Reactome entities**

Input	UniProt Id	Input	UniProt Id
25942	Q96ST3	2891	P42262
2904	Q13224	4204	P51608-1, P51608-2

## 24. 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

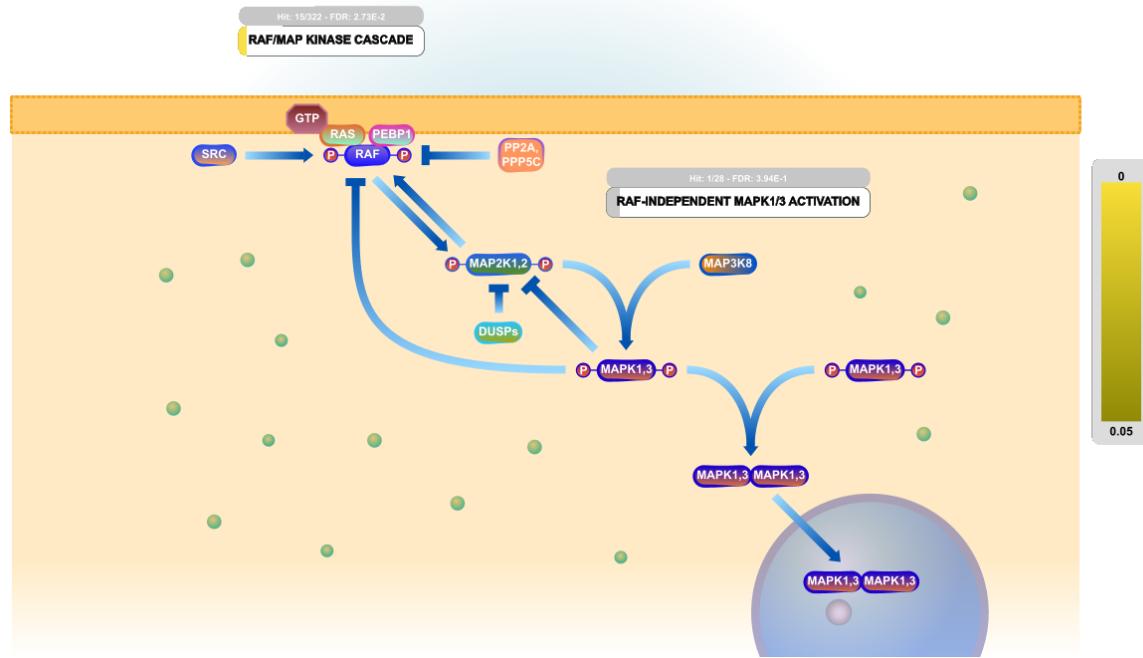
### Edit history

Date	Action	Author
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

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1175	P53680-1	1742	P78352	23229	O43307
2561	P47870	2562	P28472	26960	Q8NFP9
2770	P63096	2891	P42262	2904	Q13224
3265	P01112	373	P46098	473	Q05901
8573	O14936				

## 25. MAPK1/MAPK3 signaling (R-HSA-5684996)



The extracellular signal regulated kinases (ERKs) 1 and 2, also known as MAPK3 and MAPK1, are phosphorylated by the MAP2Ks 1 and 2 in response to a wide range of extracellular stimuli to promote differentiation, proliferation, cell motility, cell survival, metabolism and transcription, among others (reviewed in Roskoski, 2012b; McKay and Morrison, 2007; Raman et al, 2007). In the classical pathway, MAPK1/3 activation is triggered by the GEF-mediated activation of RAS at the plasma membrane, leading to the activation of the RAF MAP3Ks (reviewed in McKay and Morrison, 2007; Matallanas et al, 2011; Wellbrock et al, 2004). However, many physiological and pathological stimuli have been found to activate MAPK1/3 independently of RAF and RAS, acting instead through MAP3Ks such as MOS, TPL2 and AMPK (Dawson et al, 2008; Wang et al, 2009; Kuriakose et al, 2014; Awane et al, 1999). Activated MAPK1/3 phosphorylate numerous targets in both the nucleus and cytoplasm (reviewed in Yoon and Seger, 2006; Roskoski 2012b).

### References

- Wellbrock C, Karasarides M & Marais R (2004). The RAF proteins take centre stage. *Nat Rev Mol Cell Biol*, 5, 875-85. [\[link\]](#)
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- Morris MA, Tramoutanis G, Laverick L, Dawson CW & Young LS (2008). Epstein-Barr virus-encoded LMP1 regulates epithelial cell motility and invasion via the ERK-MAPK pathway. *J. Virol.*, 82, 3654-64. [\[link\]](#)
- Kuriakose T, Rada B & Watford WT (2014). Tumor progression locus 2-dependent oxidative burst drives phosphorylation of extracellular signal-regulated kinase during TLR3 and 9 signaling. *J. Biol. Chem.*, 289, 36089-100. [\[link\]](#)

Chen W, Raman M & Cobb MH (2007). Differential regulation and properties of MAPKs. *Oncogene*, 26, 3100-12. [View](#)

## Edit history

Date	Action	Author
2015-03-11	Authored	Rothfels K
2015-03-24	Created	Rothfels K
2015-04-29	Reviewed	Roskoski R Jr
2021-09-10	Modified	Weiser JD

## 15 submitted entities found in this pathway, mapping to 16 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1742	P78352	1808	P11362-1, P11362-19	2561	P04626
2904	Q13224	3265	P01112	4763	P21359
5528	Q14738	5536	P53041	5718	O00232
5781	Q06124	60	P60709	673	P15056
7010	Q02763	8452	Q13618	8831	Q96PV0

## 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.

**147 of the submitted entities were found, mapping to 197 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10295	O14874	10479	Q92581	10664	P49711
10743	Q7Z5J4	10765	Q9UGL1	10787	Q9Y2A7
10943	Q8N5Y2	1107	Q12873	11151	P31146
1175	P53680-1	1387	Q92793	1499	P35222
158	P30566	1654	O00571	1717	Q9UBM7
1742	P78352	1760	Q09013	1778	Q14204
1788	Q9Y6K1	1808	P11362-1, Q16555	1826	O60469, Q9UF33
1859	Q15262	197131	Q8IWV7	1995	P48729
2033	Q09472	2290	P55316	22941	Q9UPX8
22999	Q86UR5	23001	P25391	23135	O15054
23229	O43307	2332	Q92560	2334	P00736
23389	Q71F56	2561	P47870	2562	P28472
25836	Q6KC79	25942	Q96ST3	26053	Q8WXX7
26058	O15033	26115	Q9NR81	2670	Q8NB78
26960	Q8NFP9	27086	Q9H334-8	2770	P63096
284058	Q7Z3B3	287	Q01484	288	Q12955
2891	O94925, P42262	2904	Q13224	29072	Q9BYW2
29994	P28566	3069	Q00341	3097	P28300
3188	P55795	3192	P06748	3265	P01112
373	P46098	3745	Q14721	3786	O43525, Q09428
4204	P51608-1, P51608-2	4208	Q06413	4297	Q03164
4306	P08235-1, P08235-2, P08235-3, P08235-4	473	Q05901	4763	P21359
4849	O75175	4864	O15118	4929	P43354
5053	P00439	5079	Q02548	5096	P05166
51111	Q4FZB7	51317	Q96BD5	51322	Q9BTA9
51780	Q7LBC6	5252	O43189	53335	Q9H165
54413	Q9NZ94	546	Q14721	55023	Q8WWQ0
55209	Q6P4F2	5528	Q14738	5536	P53041
55624	Q8WZA1	55690	Q6VY07	55777	Q9P267
55799	Q8IZS8	55870	Q9NR48	55904	Q8IZD2
5649	P78509	5718	O00232	5728	P60484
57492	Q8NFD5	57502	Q8N0W4	57551	Q7L7X3
57555	Q8NFZ4	57680	Q9HCK8	5781	Q06124
58508	Q8NEZ4	60	P60709	6096	Q92753
6304	Q01826	6323	P35498	6326	Q99250
6334	Q9UQD0	64324	Q96L73	6497	P12755
65109	Q9BZI7	6529	P30531	6595	P51531
6597	P51532	6601	Q8TAQ2	6683	Q9UBP0
673	P15056	6734	P08240	6812	P61764, P61764-1
6853	P17600	6934	Q9NQB0	7010	Q02763
7204	O75962	7248	Q92574	7249	P49815

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
7337	Q05086	773	O00555	775	Q13936
777	Q15878	79143	Q96N66	7915	P51649
79718	Q9BZK7	79813	Q9H9B1	8239	Q93008
8242	P41229	84231	Q6Q0C0	8452	Q13618
85358	Q75V66	8573	O14936	8648	Q15788
8666	O75821	8831	Q96PV0	8861	Q86U70
9320	Q14669	9369	Q9HDB5, Q9Y4C0	9378	P58400, Q9ULB1
9379	P58401, Q9P2S2	9631	O75694	9969	Q9UHV7
Input	ChEBI Id	Input	ChEBI Id		
2290	2290	4208	4208		

## 7. Identifiers not found

These 58 identifiers were not found neither mapped to any entity in Reactome.

10522	10716	10847	11011	1106	112939	139411	157680
170302	22924	23036	23040	23096	23152	23181	23394
23469	23613	26040	26137	27245	283078	283450	283489
29123	4076	4130	4212	54551	54897	55636	56853
57479	57526	5754	57616	57649	57689	58499	5991
64207	64599	6651	6660	6792	6942	7716	7812
80155	80816	8216	83473	84687	9024	93627	93986
9777	9778						