



Pathway Analysis Report

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

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMjAyMjYwMzA0MDdfMTczMDA%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:

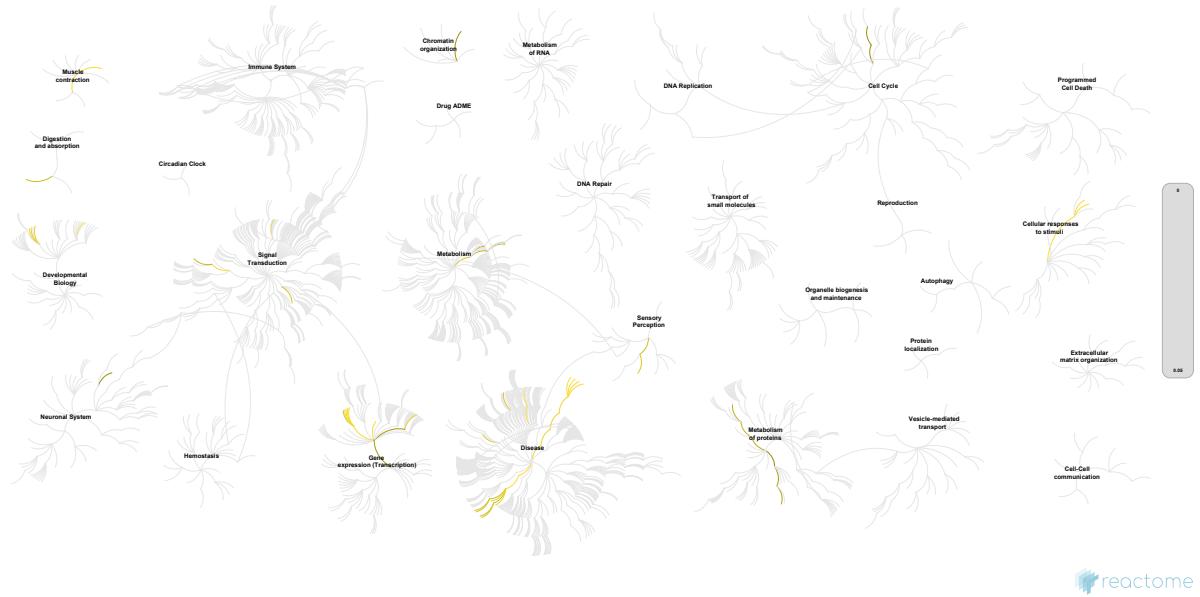
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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 Benjamani-Hochberg method. ↗
- 46 out of 78 identifiers in the sample were found in Reactome, where 336 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 MjAyMjAyMjYwMzA0MDdfMTczMDA%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
Oxidative Stress Induced Senescence	9 / 114	0.008	6.36e-08	2.16e-05	16 / 40	0.003
Oncogene Induced Senescence	6 / 42	0.003	3.73e-07	6.33e-05	13 / 19	0.001
MECP2 regulates transcription of neuronal ligands	4 / 13	8.63e-04	1.80e-06	2.03e-04	8 / 8	5.86e-04
Cellular Senescence	9 / 200	0.013	6.37e-06	5.42e-04	22 / 90	0.007
Transcriptional Regulation by MECP2	6 / 100	0.007	5.03e-05	0.003	73 / 77	0.006
Phase 0 - rapid depolarisation	4 / 34	0.002	7.59e-05	0.004	2 / 2	1.47e-04
Loss of MECP2 binding ability to 5hmC-DNA	2 / 2	1.33e-04	8.13e-05	0.004	1 / 1	7.33e-05
Regulation of MECP2 expression and activity	4 / 39	0.003	1.28e-04	0.005	12 / 14	0.001
Transcriptional Regulation by VENTX	4 / 48	0.003	2.82e-04	0.01	4 / 13	9.53e-04
Diseases of cellular response to stress	2 / 4	2.65e-04	3.23e-04	0.01	3 / 3	2.20e-04
Diseases of Cellular Senescence	2 / 4	2.65e-04	3.23e-04	0.01	3 / 3	2.20e-04
Class B/2 (Secretin family receptors)	5 / 99	0.007	4.77e-04	0.013	7 / 20	0.001
Loss of MECP2 binding ability to 5mC-DNA	2 / 5	3.32e-04	5.02e-04	0.013	2 / 2	1.47e-04
MECP2 regulates transcription of genes involved in GABA signaling	2 / 6	3.98e-04	7.20e-04	0.015	4 / 4	2.93e-04
Loss of Function of FBXW7 in Cancer and NOTCH1 Signaling	2 / 6	3.98e-04	7.20e-04	0.015	1 / 1	7.33e-05
FBXW7 Mutants and NOTCH1 in Cancer	2 / 6	3.98e-04	7.20e-04	0.015	1 / 1	7.33e-05
Loss of phosphorylation of MECP2 at T308	2 / 7	4.64e-04	9.75e-04	0.02	1 / 1	7.33e-05
Loss of MECP2 binding ability to the NCoR/SMRT complex	2 / 8	5.31e-04	0.001	0.023	1 / 1	7.33e-05
Interaction between L1 and Ankyrins	3 / 33	0.002	0.001	0.023	1 / 4	2.93e-04
MECP2 regulates transcription factors	2 / 10	6.64e-04	0.002	0.033	8 / 8	5.86e-04
Cardiac conduction	5 / 138	0.009	0.002	0.033	3 / 27	0.002
Disorders of Nervous System Development	2 / 16	0.001	0.005	0.064	5 / 5	3.66e-04
Pervasive developmental disorders	2 / 16	0.001	0.005	0.064	5 / 5	3.66e-04

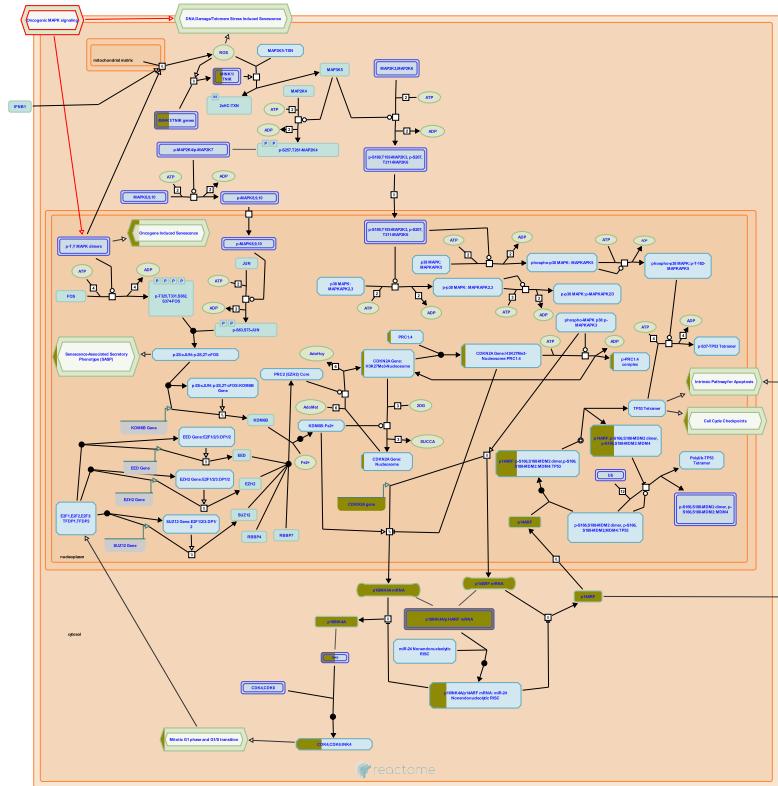
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Loss of function of MECP2 in Rett syndrome	2 / 16	0.001	0.005	0.064	5 / 5	3.66e-04
Disorders of Developmental Biology	2 / 16	0.001	0.005	0.064	5 / 5	3.66e-04

* 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. Oxidative Stress Induced Senescence (R-HSA-2559580)



Oxidative stress, caused by increased concentration of reactive oxygen species (ROS) in the cell, can happen as a consequence of mitochondrial dysfunction induced by the oncogenic RAS (Moiseeva et al. 2009) or independent of oncogenic signaling. Prolonged exposure to interferon-beta (IFNB, IFN-beta) also results in ROS increase (Moiseeva et al. 2006). ROS oxidize thioredoxin (TXN), which causes TXN to dissociate from the N-terminus of MAP3K5 (ASK1), enabling MAP3K5 to become catalytically active (Saitoh et al. 1998). ROS also stimulate expression of Ste20 family kinases MINK1 (MINK) and TNIK through an unknown mechanism, and MINK1 and TNIK positively regulate MAP3K5 activation (Nicke et al. 2005).

MAP3K5 phosphorylates and activates MAP2K3 (MKK3) and MAP2K6 (MKK6) (Ichijo et al. 1997, Takekawa et al. 2005), which act as p38 MAPK kinases, as well as MAP2K4 (SEK1) (Ichijo et al. 1997, Matsuura et al. 2002), which, together with MAP2K7 (MKK7), acts as a JNK kinase.

MKK3 and MKK6 phosphorylate and activate p38 MAPK alpha (MAPK14) and beta (MAPK11) (Raingeaud et al. 1996), enabling p38 MAPKs to phosphorylate and activate MAPKAPK2 (MK2) and MAPKAPK3 (MK3) (Ben-Levy et al. 1995, Clifton et al. 1996, McLaughlin et al. 1996, Sithanandam et al. 1996, Meng et al. 2002, Lukas et al. 2004, White et al. 2007), as well as MAPKAPK5 (PRAK) (New et al. 1998 and 2003, Sun et al. 2007).

Phosphorylation of JNKs (MAPK8, MAPK9 and MAPK10) by MAP3K5-activated MAP2K4 (Deacon and Blank 1997, Fleming et al. 2000) allows JNKs to migrate to the nucleus (Mizukami et al. 1997) where they phosphorylate JUN. Phosphorylated JUN binds FOS phosphorylated by ERK1 or ERK2, downstream of activated RAS (Okazaki and Sagata 1995, Murphy et al. 2002), forming the activated protein 1 (AP-1) complex (FOS:JUN heterodimer) (Glover and Harrison 1995, Ainbinder et al. 1997).

Activation of p38 MAPKs and JNKs downstream of MAP3K5 (ASK1) ultimately converges on transcriptional regulation of CDKN2A locus. In dividing cells, nucleosomes bound to the CDKN2A locus are trimethylated on lysine residue 28 of histone H3 (HIST1H3A) by the Polycomb repressor complex 2 (PRC2), creating the H3K27Me3 (Me3K-28-HIST1H3A) mark (Bracken et al. 2007, Kotake et al. 2007). The expression of Polycomb constituents of PRC2 (Kuzmichev et al. 2002) - EZH2, EED and SUZ12 - and thereby formation of the PRC2, is positively regulated in growing cells by E2F1, E2F2 and E2F3 (Weinmann et al. 2001, Bracken et al. 2003). H3K27Me3 mark serves as a docking site for the Polycomb repressor complex 1 (PRC1) that contains BMI1 (PCGF4) and is therefore named PRC1.4, leading to the repression of transcription of p16INK4A and p14ARF from the CDKN2A locus, where PRC1.4 mediated repression of p14ARF transcription in humans may be context dependent (Voncken et al. 2005, Dietrich et al. 2007, Agherbi et al. 2009, Gao et al. 2012). MAPKAPK2 and MAPKAPK3, activated downstream of the MAP3K5-p38 MAPK cascade, phosphorylate BMI1 of the PRC1.4 complex, leading to dissociation of PRC1.4 complex from the CDKN2A locus and upregulation of p14ARF transcription (Voncken et al. 2005). AP-1 transcription factor, formed as a result of MAP3K5-JNK signaling, as well as RAS signaling, binds the promoter of KDM6B (JMJD3) gene and stimulates KDM6B expression. KDM6B is a histone demethylase that removes H3K27Me3 mark i.e. demethylates lysine K28 of HIST1H3A, thereby preventing PRC1.4 binding to the CDKN2A locus and allowing transcription of p16INK4A (Agger et al. 2009, Barradas et al. 2009, Lin et al. 2012).

p16INK4A inhibits phosphorylation-mediated inactivation of RB family members by CDK4 and CDK6, leading to cell cycle arrest (Serrano et al. 1993). p14ARF inhibits MDM2-mediated degradation of TP53 (p53) (Zhang et al. 1998), which also contributes to cell cycle arrest in cells undergoing oxidative stress. In addition, phosphorylation of TP53 by MAPKAPK5 (PRAK) activated downstream of MAP3K5-p38 MAPK signaling, activates TP53 and contributes to cellular senescence (Sun et al. 2007).

References

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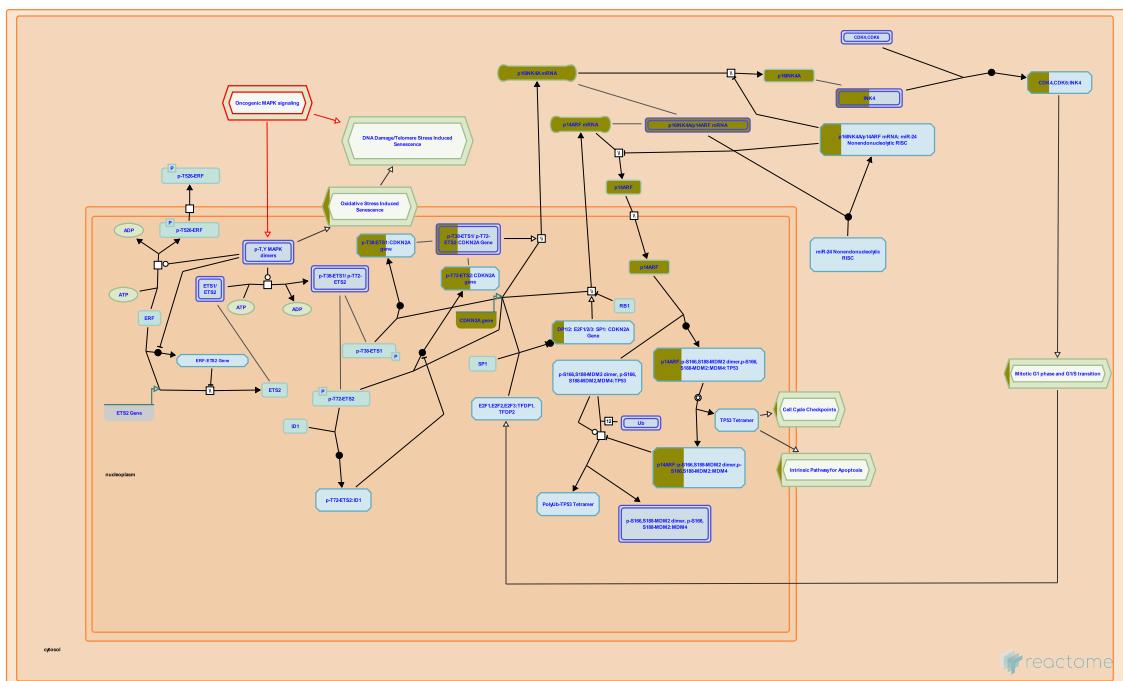
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2013-07-15	Edited	Mathews L, D'Eustachio P
2013-07-15	Authored	Orlic-Milacic M
2013-09-03	Reviewed	Samarajiwa S
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CBX6	O95503	CDKN2A	P42771, P42772, Q8N726	MINK1	Q8N4C8
Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755	MINK1	ENSG00000141503		

2. Oncogene Induced Senescence (R-HSA-2559585)



Oncogene-induced senescence (OIS) is triggered by high level of RAS/RAF/MAPK signaling that can be caused, for example, by oncogenic mutations in RAS or RAF proteins, or by oncogenic mutations in growth factor receptors, such as EGFR, that act upstream of RAS/RAF/MAPK cascade. Oncogene-induced senescence can also be triggered by high transcriptional activity of E2F1, E2F2 or E2F3 which can be caused, for example, by the loss-of-function of RB1 tumor suppressor.

Oncogenic signals trigger transcription of CDKN2A locus tumor suppressor genes: p16INK4A and p14ARF. p16INK4A and p14ARF share exons 2 and 3, but are expressed from different promoters and use different reading frames (Quelle et al. 1995). Therefore, while their mRNAs are homologous and are both translationally inhibited by miR-24 microRNA (Lal et al. 2008, To et al. 2012), they share no similarity at the amino acid sequence level and perform distinct functions in the cell. p16INK4A acts as the inhibitor of cyclin-dependent kinases CDK4 and CDK6 which phosphorylate and inhibit RB1 protein thereby promoting G1 to S transition and cell cycle progression (Serrano et al. 1993). Increased p16INK4A level leads to hypophosphorylation of RB1, allowing RB1 to inhibit transcription of E2F1, E2F2 and E2F3-target genes that are needed for cell cycle progression, which results in cell cycle arrest in G1 phase. p14-ARF binds and destabilizes MDM2 ubiquitin ligase (Zhang et al. 1998), responsible for ubiquitination and degradation of TP53 (p53) tumor suppressor protein (Wu et al. 1993, Fuchs et al. 1998, Fang et al. 2000). Therefore, increased p14-ARF level leads to increased level of TP53 and increased expression of TP53 target genes, such as p21, which triggers p53-mediated cell cycle arrest and, depending on other factors, may also lead to p53-mediated apoptosis. CDKN2B locus, which encodes an inhibitor of CDK4 and CDK6, p15INK4B, is located in the vicinity of CDKN2A locus, at the chromosome band 9p21. p15INK4B, together with p16INK4A, contributes to senescence of human T-lymphocytes (Erickson et al. 1998) and mouse fibroblasts (Malumbres et al. 2000). SMAD3, activated by TGF-beta-1 signaling, controls senescence in the mouse multistage carcinogenesis model through regulation of MYC and p15INK4B gene expression (Vijayachandra et al. 2003). TGF-beta-induced p15INK4B expression is also important for the senescence of hepatocellular carcinoma cell lines (Senturk et al. 2010).

MAP kinases MAPK1 (ERK2) and MAPK3 (ERK1), which are activated by RAS signaling, phosphorylate ETS1 and ETS2 transcription factors in the nucleus (Yang et al. 1996, Seidel et al. 2002, Foulds et al. 2004, Nelson et al. 2010). Phosphorylated ETS1 and ETS2 are able to bind RAS response elements (RREs) in the CDKN2A locus and stimulate p16INK4A transcription (Ohtani et al. 2004). At the same time, activated ERKs (MAPK1 i.e. ERK2 and MAPK3 i.e. ERK1) phosphorylate ERF, the repressor of ETS2 transcription, which leads to translocation of ERF to the cytosol and increased transcription of ETS2 (Sgouras et al. 1995, Le Gallic et al. 2004). ETS2 can be sequestered and inhibited by binding to ID1, resulting in inhibition of p16INK4A transcription (Ohtani et al. 2004).

Transcription of p14ARF is stimulated by binding of E2F transcription factors (E2F1, E2F2 or E2F3) in complex with SP1 to p14ARF promoter (Parisi et al. 2002).

Oncogenic RAS signaling affects mitochondrial metabolism through an unknown mechanism, leading to increased generation of reactive oxygen species (ROS), which triggers oxidative stress induced senescence pathway. In addition, increased rate of cell division that is one of the consequences of oncogenic signaling, leads to telomere shortening which acts as another senescence trigger.

While OIS has been studied to considerable detail in cultured cells, establishment of in vivo role of OIS has been difficult due to lack of specific biomarkers and its interconnectedness with other senescence pathways (Baek and Ryeom 2017, reviewed in Sharpless and Sherr 2015).

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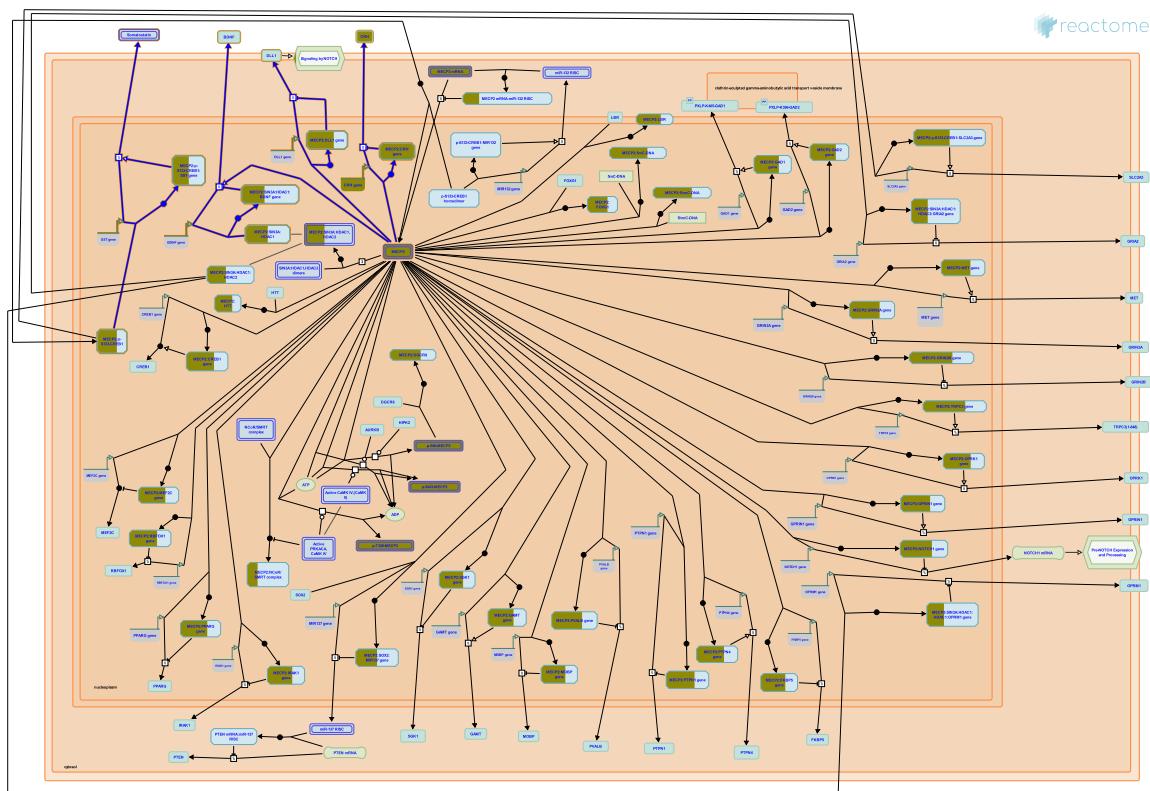
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2013-07-15	Edited	Matthews L, D'Eustachio P
2013-07-15	Authored	Orlic-Milacic M
2013-09-03	Reviewed	Samarajiwa S
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
CDKN2A	P42771, P42772, Q8N726

Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755

3. MECP2 regulates transcription of neuronal ligands ([R-HSA-9022702](#))



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).

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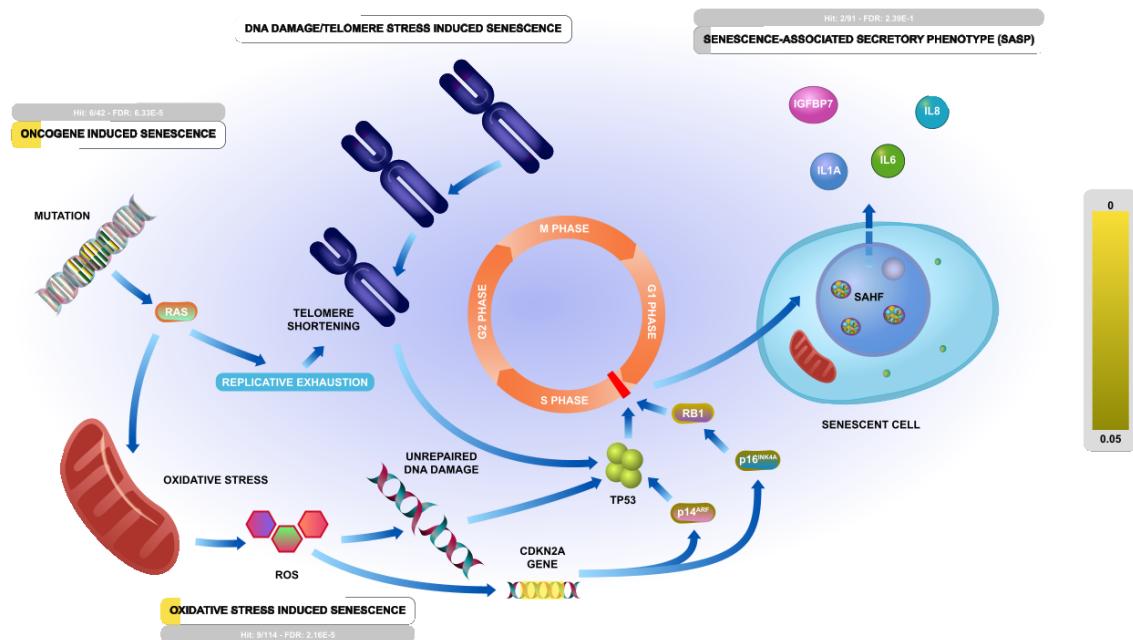
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2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

2 submitted entities found in this pathway, mapping to 4 Reactome entities

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CRH	P06850	MECP2	P51608-1, P51608-2
Input	Ensembl Id		
CRH	ENSG00000147571		

4. Cellular Senescence (R-HSA-2559583)



Cellular senescence involves irreversible growth arrest accompanied by phenotypic changes such as enlarged morphology, reorganization of chromatin through formation of senescence-associated heterochromatic foci (SAHF), and changes in gene expression that result in secretion of a number of proteins that alter local tissue environment, known as senescence-associated secretory phenotype (SASP).

Senescence is considered to be a cancer protective mechanism and is also involved in aging. Senescent cells accumulate in aged tissues (reviewed by Campisi 1997 and Lopez-Otin 2013), which may be due to an increased senescence rate and/or decrease in the rate of clearance of senescent cells. In a mouse model of accelerated aging, clearance of senescent cells delays the onset of age-related phenotypes (Baker et al. 2011).

Cellular senescence can be triggered by the aberrant activation of oncogenes or loss-of-function of tumor suppressor genes, and this type of senescence is known as the oncogene-induced senescence, with RAS signaling-induced senescence being the best studied. Oxidative stress, which may or may not be caused by oncogenic RAS signaling, can also trigger senescence. Finally, the cellular senescence program can be initiated by DNA damage, which may be caused by reactive oxygen species (ROS) during oxidative stress, and by telomere shortening caused by replicative exhaustion which may be due to oncogenic signaling. The senescent phenotype was first reported by Hayflick and Moorhead in 1961, when they proposed replicative senescence as a mechanism responsible for the cessation of mitotic activity and morphological changes that occur in human somatic diploid cell strains as a consequence of serial passaging, preventing the continuous culture of untransformed cells—the Hayflick limit (Hayflick and Moorhead 1961).

Secreted proteins that constitute the senescence-associated secretory phenotype (SASP), also known as the senescence messaging secretome (SMS), include inflammatory and immune-modulatory cytokines, growth factors, shed cell surface molecules and survival factors. The SASP profile is not significantly affected by the type of senescence trigger or the cell type (Coppe et al. 2008), but the persistent DNA damage may be a deciding SASP initiator (Rodier et al. 2009). SASP components function in an autocrine manner, reinforcing the senescent phenotype (Kuilman et al. 2008, Acosta et al. 2008), and in the paracrine manner, where they may promote epithelial-to-mesenchymal transition (EMT) and malignancy in the nearby premalignant or malignant cells (Coppe et al. 2008).

Senescent cells may remain viable for years, such as senescent melanocytes of moles and nevi, or they can be removed by phagocytic cells. The standard marker for immunohistochemical detection of senescent cells is senescence-associated beta-galactosidase (SA-beta-Gal), a lysosomal enzyme that is not required for senescence.

For reviews of this topic, please refer to Collado et al. 2007, Adams 2009, Kuilman et al. 2010. For a review of differential gene expression between senescent and immortalized cells, please refer to Fridman and Tainsky 2008.

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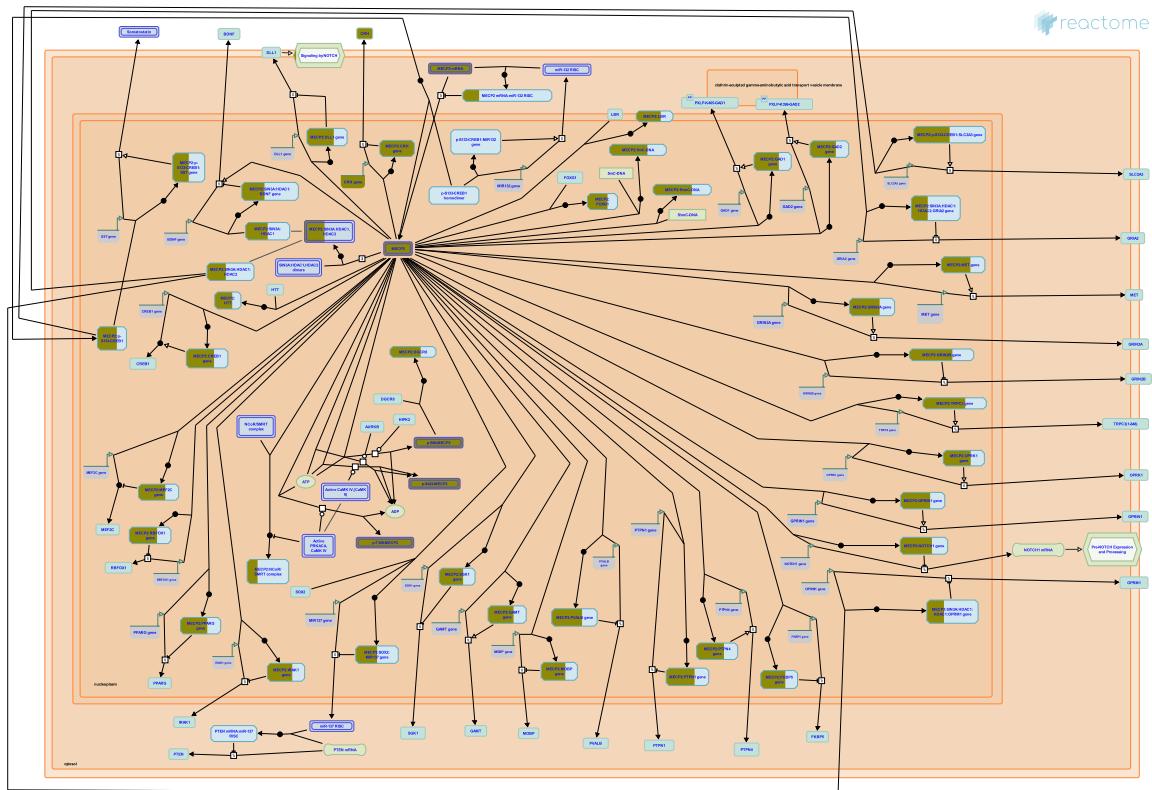
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2013-09-03	Reviewed	Samarajiwa S
2013-09-30	Revised	Orlic-Milacic M
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CBX6	O95503	CDKN2A	P42771, P42772, Q8N726	MINK1	Q8N4C8

Input	Ensembl Id	Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755	MINK1	ENSG00000141503

5. 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 (Livide 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 (Liyo 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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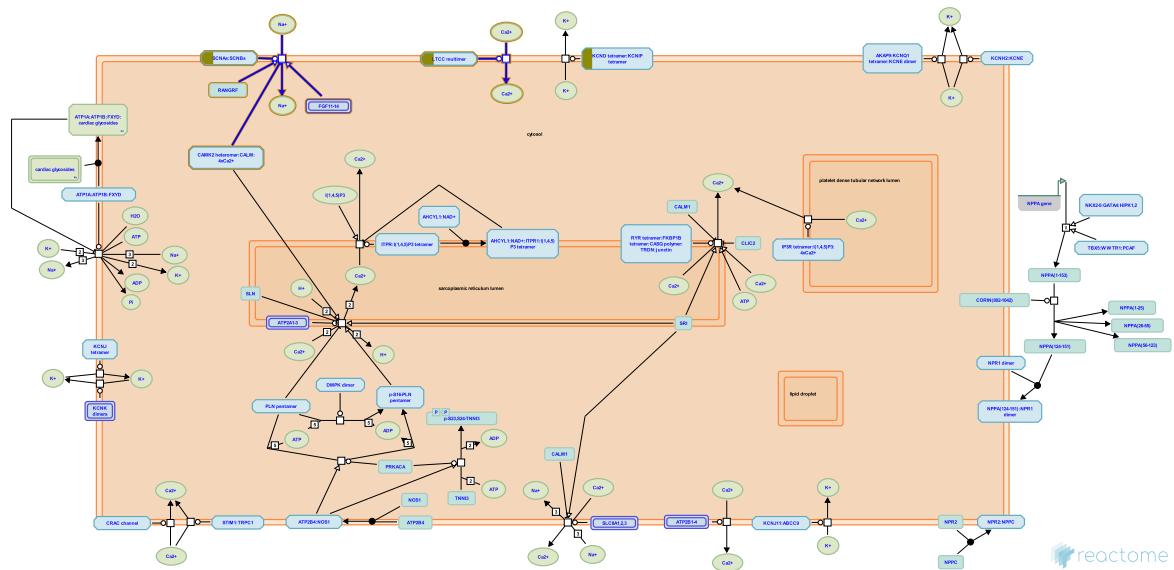
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
CRH	P06850	MECP2	P51608-1, P51608-2

Input	Ensembl Id	Input	Ensembl Id
CRH	ENSG00000147571	MECP2	ENST00000303391, ENST00000453960

6. 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 Ca²⁺ 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 +50mV (Park & Fishman 2011, Grant 2009).

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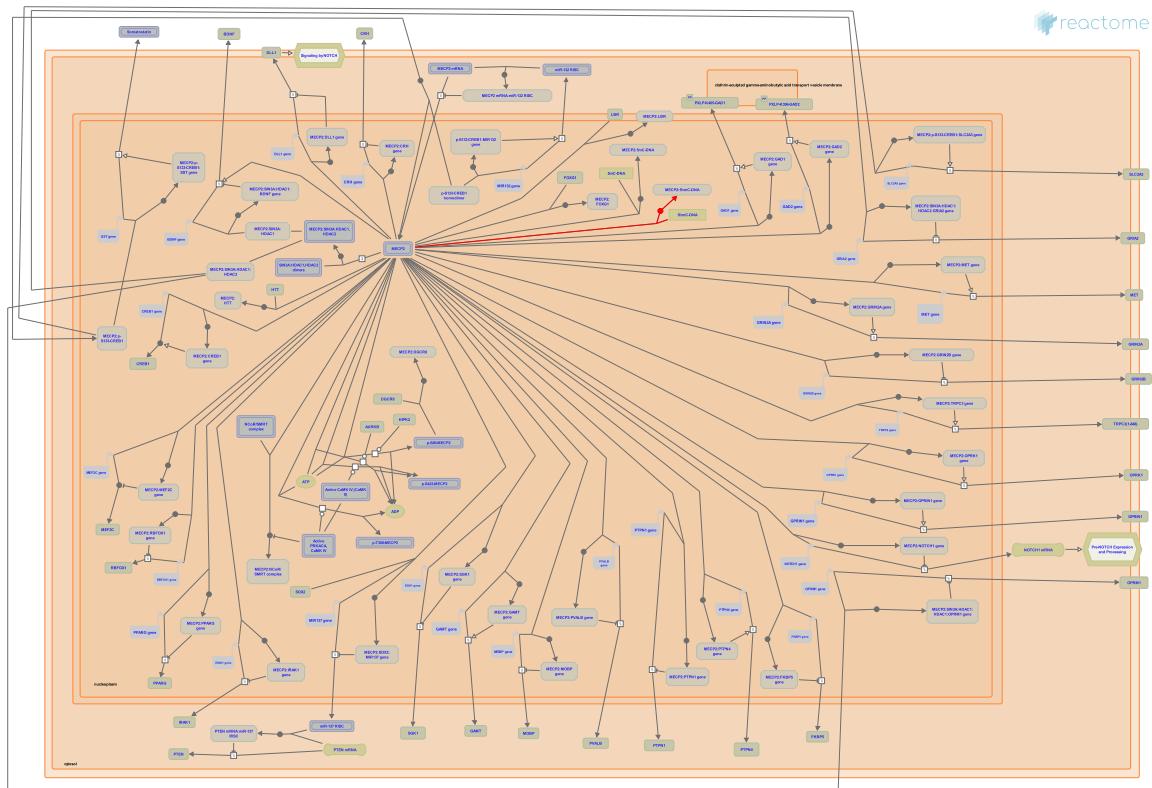
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2014-05-27	Authored	Jassal B
2014-05-27	Created	Jassal B
2015-11-09	Reviewed	Colotti G
2022-01-09	Modified	Weiser JD

2 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id
CACNA2D2	Q9NY47	SCN2A	P35498, Q15858, Q99250

7. Loss of MECP2 binding ability to 5hmC-DNA (R-HSA-9022534)



Cellular compartments: nucleoplasm.

Diseases: Rett syndrome.

Missense mutations in the methyl-CpG binding domain (MBD) of MECP2, spanning amino acids 90 to 162, negatively affect the binding ability of MECP2 to hydroxymethylated DNA (Mellen et al. 2012).

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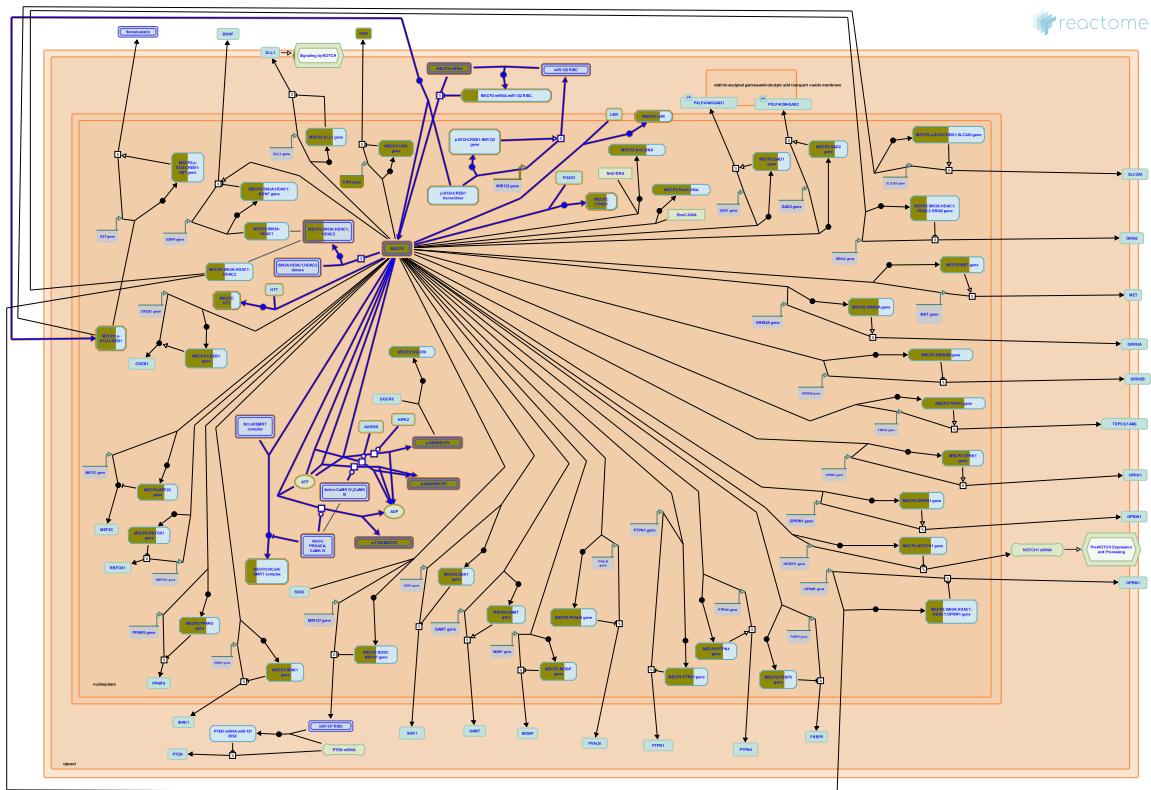
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2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

8. 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).

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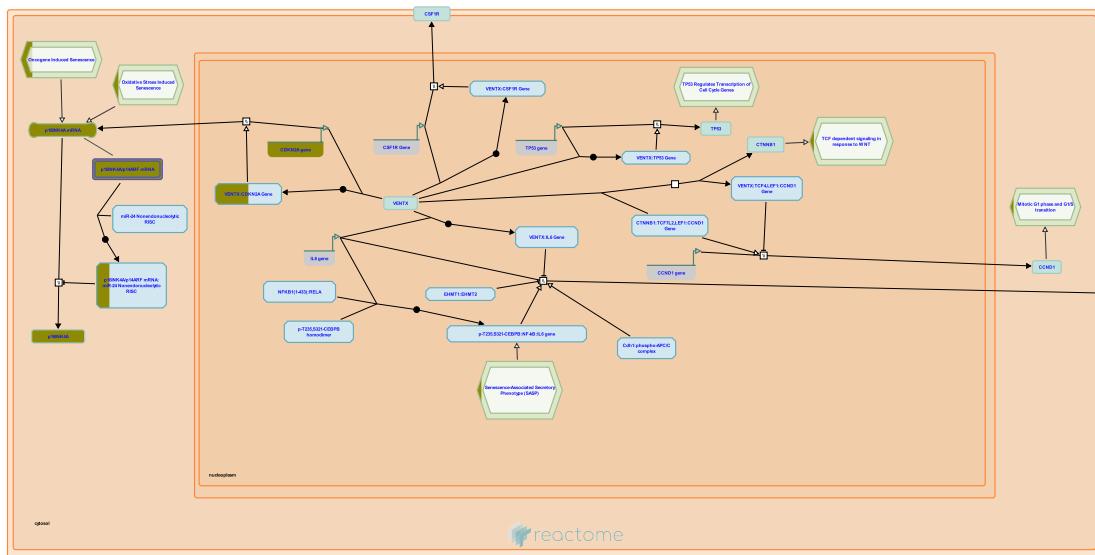
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-11-26	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id
MECP2	P51608-1, P51608-2

Input	Ensembl Id
MECP2	ENST00000303391, ENST00000453960

9. Transcriptional Regulation by VENTX (R-HSA-8853884)



The VENTX (also known as VENT homeobox or VENTX2) gene is a member of the homeobox family of transcription factors. The ortholog of VENTX was first described in Xenopus where it participates in BMP and Nanog signaling pathways and controls dorsoventral mesoderm patterning (Onichtchouk et al. 1996, Scerbo et al. 2012). The zebrafish ortholog of VENTX is also involved in dorsoventral patterning in the early embryo (Imai et al. 2001). Rodents lack the VENTX ortholog (Zhong and Holland 2011). VENTX is expressed in human blood cells (Moretti et al. 2001) and appears to play an important role in hematopoiesis. The role of VENTX in hematopoiesis was first suggested based on its role in mesoderm patterning in Xenopus and zebrafish (Davidson and Zon 2000). VENTX promotes cell cycle arrest and differentiation of hematopoietic stem cells and/or progenitor cells (Wu, Gao, Ke, Giese and Zhu 2011, Wu et al. 2014). Ventx suppression leads to expansion of hematopoietic stem cells and multi-progenitor cells (Gao et al., J. Biol. Chem., 2012). VENTX induces transcription of cell cycle inhibitors TP53 (p53) and p16INK4A and activates tumor suppressor pathways regulated by TP53 and p16INK4A (Wu, Gao, Ke, Hager et al. 2011), as well as macrophage colony stimulating factor receptor (CSF1R) (Wu, Gao, Ke, Giese and Zhu 2011) and inhibits transcription of cyclin D1 (CCND1) (Gao et al. 2010) and Interleukin-6 (IL6) (Wu et al. 2014). ChIP-seq showed that EGR3 transcription factor directly binds to the promoter of IL6 and IL8 genes (Baron VT et al., BJC 2015). While VENTX expression may suppress lymphocytic leukemia (Gao et al. 2010), high levels of VENTX have been reported in acute myeloid leukemia cells, with a positive effect on their proliferation (Rawat et al. 2010). Another homeobox transcription factor that regulates differentiation of hematopoietic stem cells is DLX4 (Bon et al. 2015). Studies on colon cancer showed that VentX regulates tumor associated macrophages and reverts immune suppression in tumor microenvironment (Le et al. 2018). MEK1 is required for Xenopus Ventx2 asymmetric distribution during blastula cell division. Ventx2 inhibition by MEK1 is required for embryonic cell commitment (Scerbo et al., eLife, 2017). VENTX induces TP53-independent apoptosis in cancer cells (Gao H, Oncotarget, 2016). During Xenopus embryonic development, VENTX ortholog regulates transcription of the sox3 gene (Rogers et al. 2007) as well as the early neuronal gene zic3 (Umair et al. 2018).

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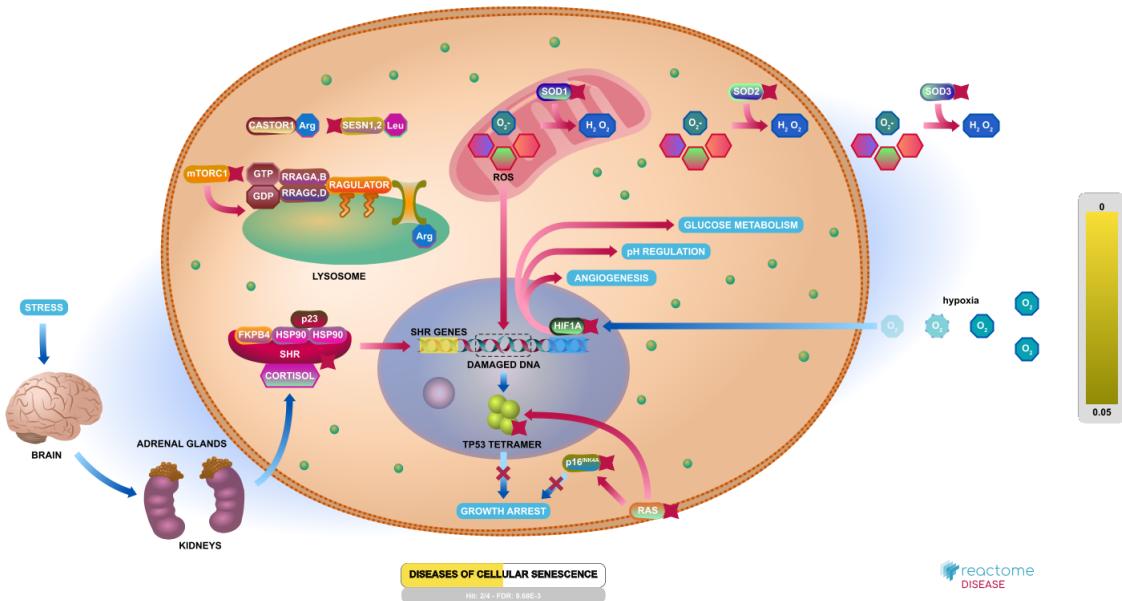
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2019-10-18	Reviewed	Vegi NM
2019-11-01	Edited	Orlic-Milacic M
2021-11-27	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id
CDKN2A	P42771

Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755

10. Diseases of cellular response to stress (R-HSA-9675132)



Cells are subject to external and internal stressors, such as foreign molecules that perturb metabolic or signaling processes, cellular respiration-generated reactive oxygen species that can cause DNA damage, oxygen and nutrient deprivation, and changes in temperature or pH. The ability of cells and tissues to respond to stress is essential to the maintenance of tissue homeostasis (Kultz 2005) and dysregulation of cellular response to stress is involved in disease.

So far, we have captured diseases of cellular senescence.

Impaired cellular senescence contributes to malignant transformation and cancer development by enabling continuous proliferation of damaged cells. On the other hand, presence of an excessive number of senescent cells that are not cleared by the immune system promotes tissue inflammation and creates a microenvironment suitable for growth of neighboring malignant cells. In addition to cancer, senescence is also involved in other age-related diseases such as atherosclerosis, osteoarthritis, chronic obstructive lung disease, and diabetes (Childs et al. 2015, He and Sharpless 2017, Hamsanathan et al. 2019, Faget et al. 2019, Gorgoulis et al. 2019, Rhinn et al. 2019). Senotherapy is a new field of pharmacology that aims to therapeutically target senescence to improve healthy aging and age-related diseases (Schmitt 2017, Gorgoulis et al. 2019).

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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
2020-08-25	Modified	Matthews L

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

Input	UniProt Id
CDKN2A	P42771, Q8N726

11. Diseases of Cellular Senescence ([R-HSA-9630747](#))



Diseases: cancer.

Cellular senescence plays an important role in normal aging, as well as in age-related diseases. Impaired cellular senescence contributes to malignant transformation and cancer development. Presence of an excessive number of senescent cells that are not cleared by the immune system, however, promotes tissue inflammation and creates a microenvironment suitable for growth of neighboring malignant cells. Besides cancer, senescence is also involved in atherosclerosis, osteoarthritis and diabetes (Childs et al. 2015, He and Sharpless 2017).

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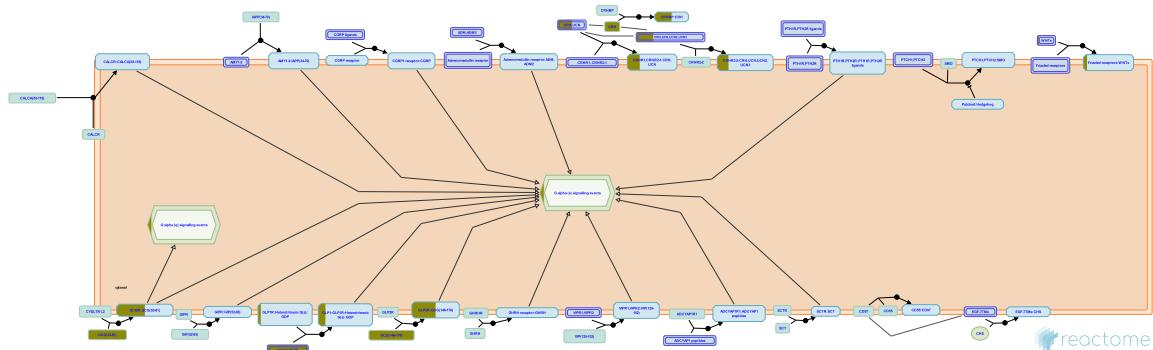
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2019-05-07	Edited	Orlic-Milacic M
2019-06-03	Reviewed	Nathan V, Hayward NK
2019-06-11	Modified	Orlic-Milacic M

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

Input	UniProt Id
CDKN2A	P42771, Q8N726

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



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

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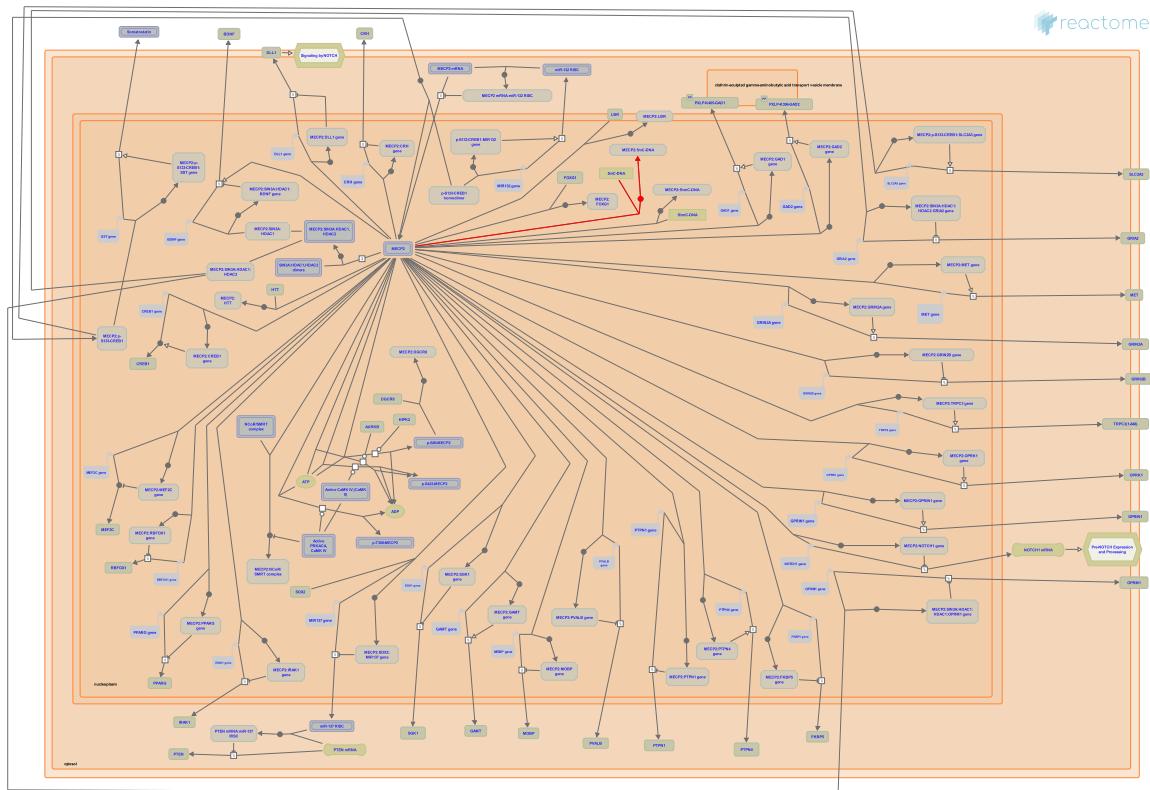
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2008-07-14	Created	Jassal B
2009-05-29	Reviewed	D'Eustachio P
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
CRH	P06850	GCG	P01275
GNB2	P62879	WNT4	O96014, P56705

13. 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).

References

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Edit history

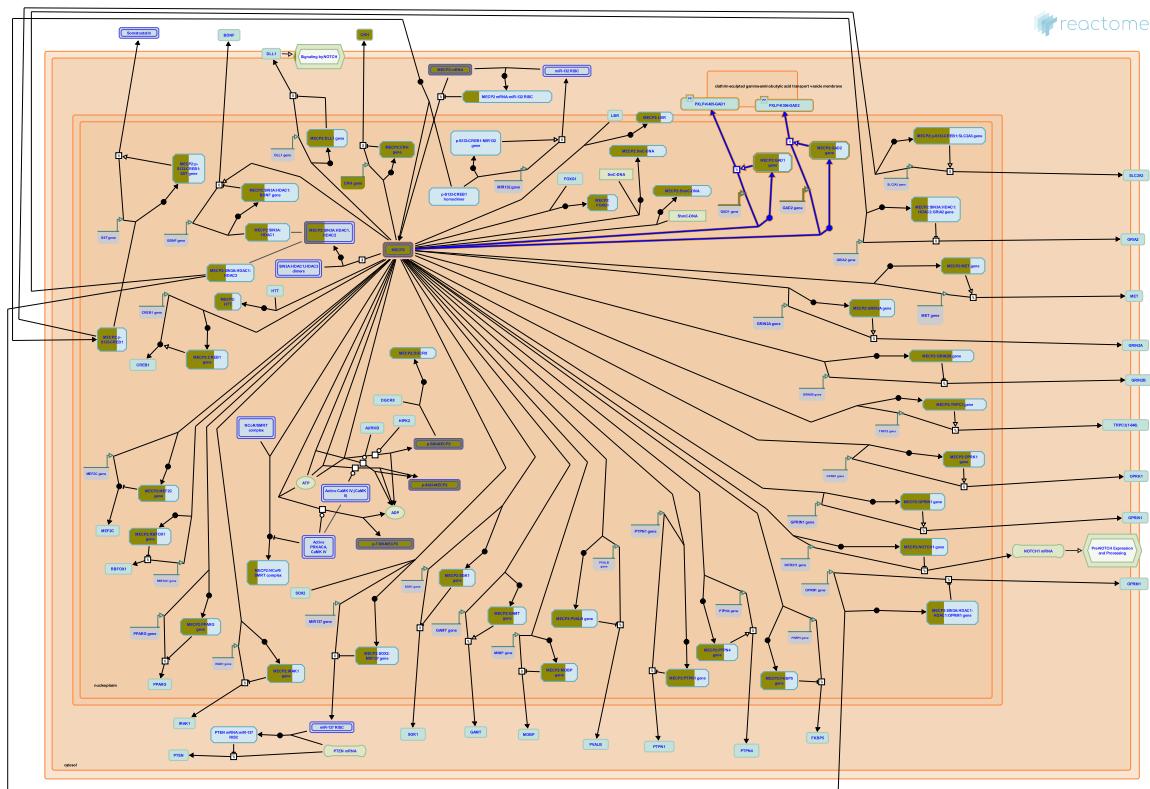
Date	Action	Author
2017-09-25	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M

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

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

14. MECP2 regulates transcription of genes involved in GABA signaling (R-HSA-9022927)



MECP2 regulates expression of several genes involved in GABA (gamma-aminobutyric acid) signaling. Transcription of GAD1 (GAD67) and GAD2 (GAD65) genes is directly positively regulated by MECP2. GAD1 and GAD2 are components of the glutamic acid decarboxylase complex involved in production of the neurotransmitter GABA. Mice lacking Mecp2 from GABA-releasing neurons have decreased GABA levels and exhibit multiple Rett syndrome features (Chao et al. 2010).

Mecp2 deletion in mouse GABAergic parvalbumin-expressing (PV) cells, cortical interneurons playing a key role in visual experience-induced ocular dominance plasticity, does not result in Rett-like phenotype, other than defects in motor coordination and motor learning. While functions of the visual cortex are preserved in mice lacking Mecp2 in GABAergic PV cells, the visual input-induced spiking responses are decreased. Mecp2 loss impairs maturation of membrane functions of cortical GABAergic PV cells. Mecp2 may be needed for PV cell-mediated cortical GABA inhibition. Mecp2-deficient cortical PV cells show reduced mRNA levels of several genes involved in GABA signaling, such as Parvalbumin, Gad2, Calretinin, Gabra1 and Gabra2, as well as reduced levels of Glu3, a glutamate receptor subunit, and Kv3.1, a potassium channel (He et al. 2014).

References

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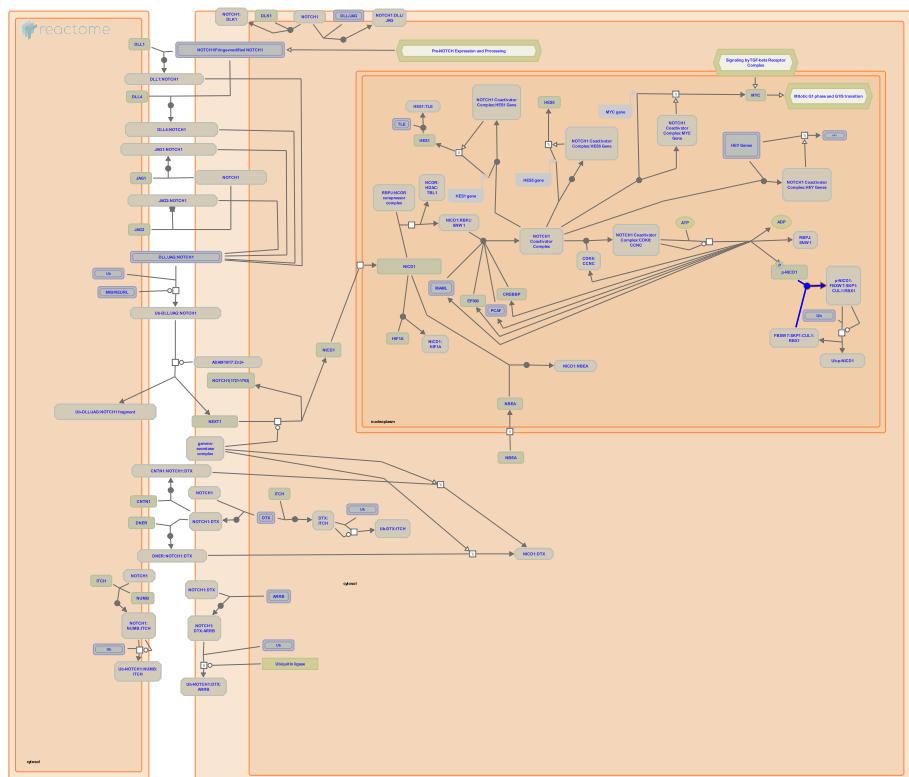
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Date	Action	Author
2017-09-26	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

15. Loss of Function of FBXW7 in Cancer and NOTCH1 Signaling (R-HSA-2644607)



Diseases: cancer.

Loss of function mutations found in FBXW7 in T-cell acute lymphoblastic leukemia are predominantly dominant negative missense mutations that target one of the three highly conserved arginine residues in the WD repeats of FBXW7 (Thompson et al. 2007, O'Neil et al. 2007). These three arginine residues are part of the FBXW7 substrate binding pocket and each one of them contacts the phosphorylated threonine residue in the conserved substrate phosphodegron region (Orlicky et al. 2003). Specifically, FBXW7 interacts with the PEST domain of NOTCH1 upon phosphorylation of the PEST domain by CDK8 (Fryer et al. 2004). FBXW7 mutants are therefore unable to bind and promote ubiquitination of the NOTCH1 intracellular domain (NICD1), leading to prolonged NICD1 transcriptional activity (Thompson et al. 2007, O'Neil et al. 2007).

References

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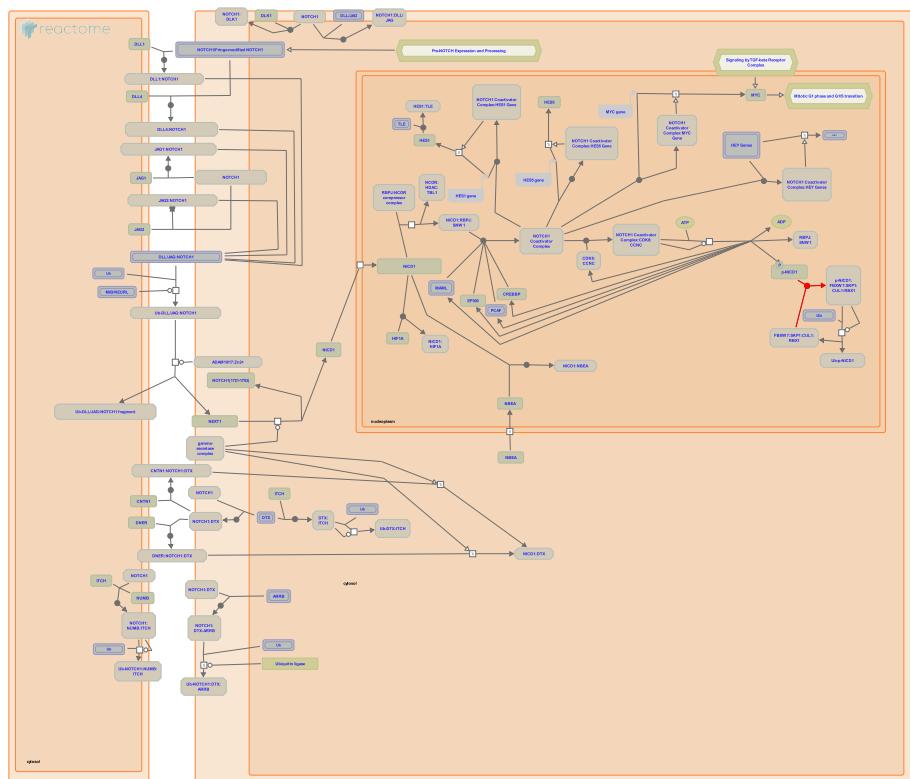
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Date	Action	Author
2012-11-22	Created	Orlic-Milacic M
2013-01-04	Authored	Orlic-Milacic M
2013-01-09	Edited	Jassal B
2013-02-10	Reviewed	Haw R
2013-02-11	Modified	Orlic-Milacic M

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

Input	UniProt Id
FBXW7	Q969H0-1, Q969H0-4

16. FBXW7 Mutants and NOTCH1 in Cancer (R-HSA-2644605)



Diseases: cancer.

FBXW7 (FBW7) is a component of the SCF (SKP1, CUL1, and F-box protein) ubiquitin ligase complex SCF-FBW7 which is involved in the degradation of NOTCH1 (Oberg et al. 2001, Wu et al. 2001, Fryer et al. 2004). Loss of function mutations in FBXW7 are frequently found in T-cell acute lymphoblastic leukemia (Akhoondi et al. 2007, Thompson et al. 2007, O'Neil et al. 2007) and are mutually exclusive with NOTCH1 PEST domain mutations (Thompson et al. 2007, O'Neil et al. 2007).

References

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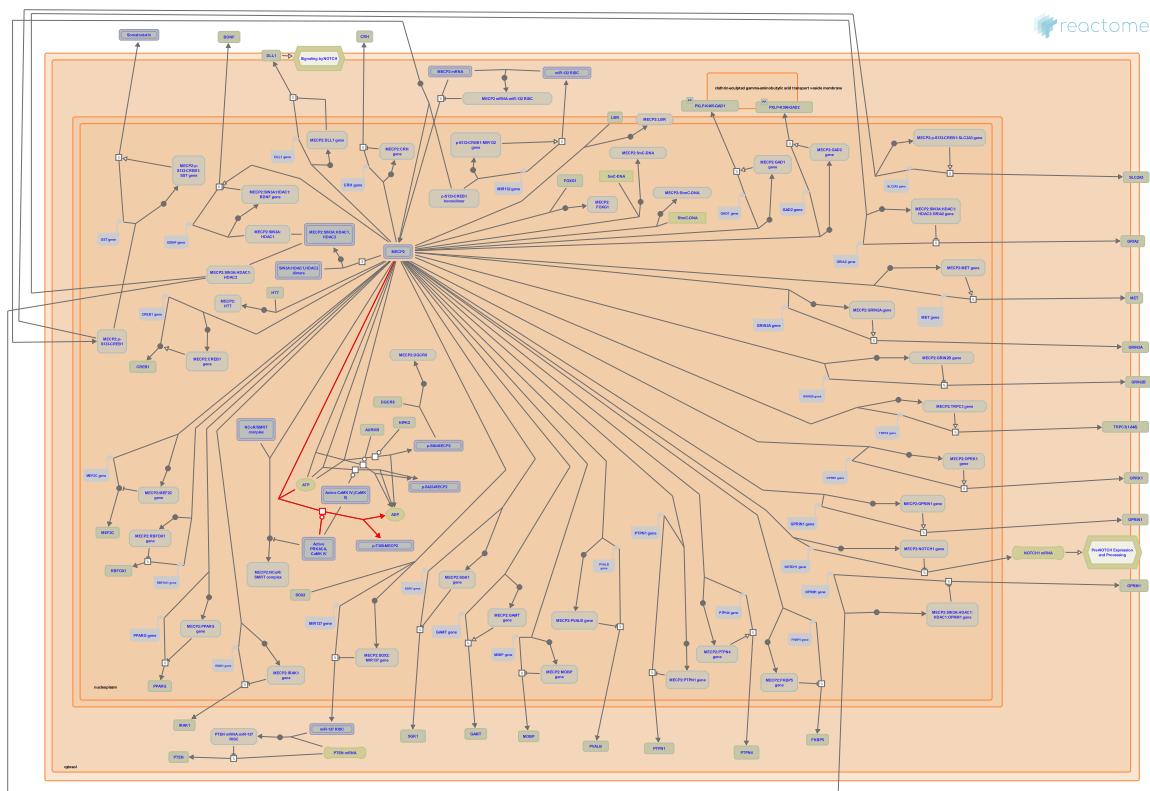
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2013-01-04	Authored	Orlic-Milacic M
2013-01-09	Edited	Jassal B
2013-02-10	Reviewed	Haw R
2015-02-09	Modified	Wu G

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

Input	UniProt Id
FBXW7	Q969H0-1, Q969H0-4

17. Loss of phosphorylation of MECP2 at T308 (R-HSA-9022535)



Cellular compartments: nucleoplasm.

Diseases: Rett syndrome.

Missense mutations of methyl-CpG-binding protein 2 (MECP2) in the vicinity of its threonine T308 phosphorylation site can negatively affect the ability of MECP2 to be phosphorylated at T308 in response to neuronal membrane depolarization (neuronal activity) (Ebert et al. 2013).

References

Kastan NR, Greenberg ME, Ekiert R, Bird AP, Lyst MJ, Hu LS, ... Robinson ND (2013). Activity-dependent phosphorylation of MeCP2 threonine 308 regulates interaction with NCoR. *Nature*, 499, 341-5. [\[CrossRef\]](#)

Edit history

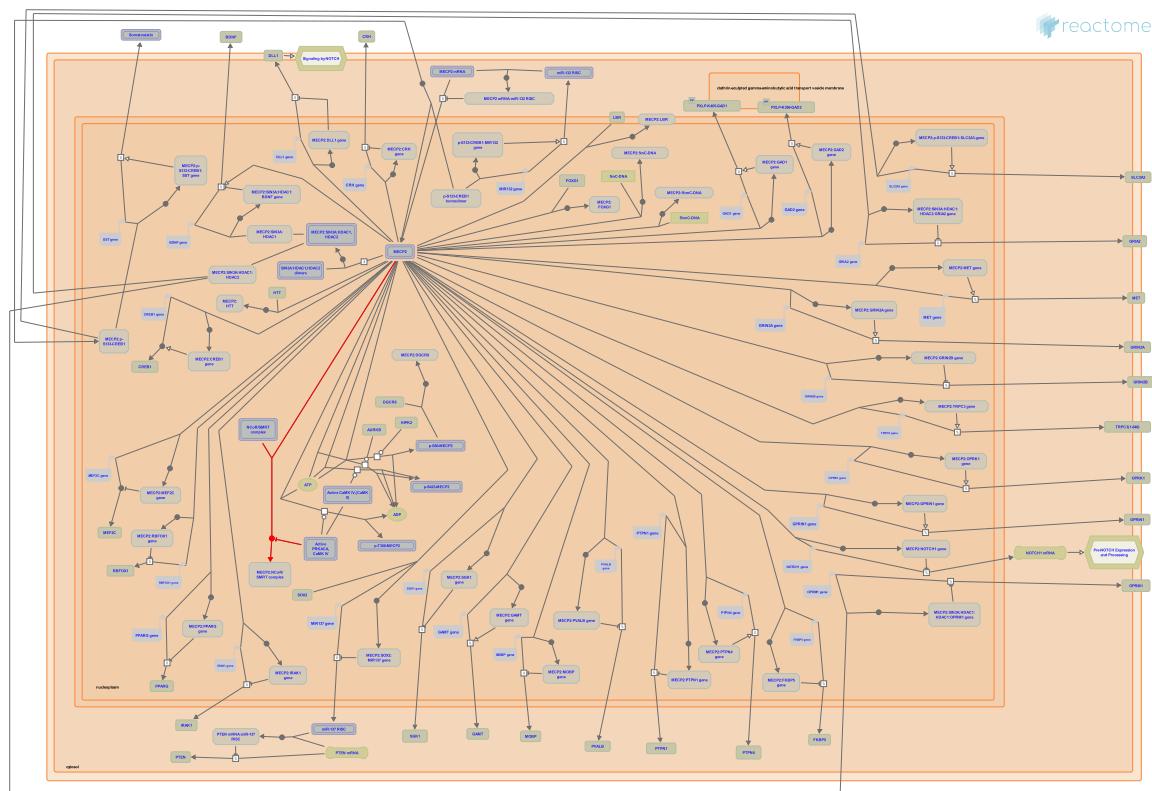
Date	Action	Author
2017-09-25	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

Input	UniProt Id
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18. Loss of MECP2 binding ability to the NCoR/SMRT complex (R-HSA-9022537)



Cellular compartments: nucleoplasm.

Diseases: Rett syndrome.

Missense mutations in the transcriptional repression domain of methyl-CpG-binding protein 2 (MECP2) can negatively affect binding of MECP2 to the nuclear receptor co-repressor (NCoR/SMRT) complex (Lyst et al. 2013, Ebert et al. 2013).

References

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Kastan NR, Greenberg ME, Ekiert R, Bird AP, Lyst MJ, Hu LS, ... Robinson ND (2013). Activity-dependent phosphorylation of MeCP2 threonine 308 regulates interaction with NCoR. *Nature*, 499, 341-5. [🔗](#)

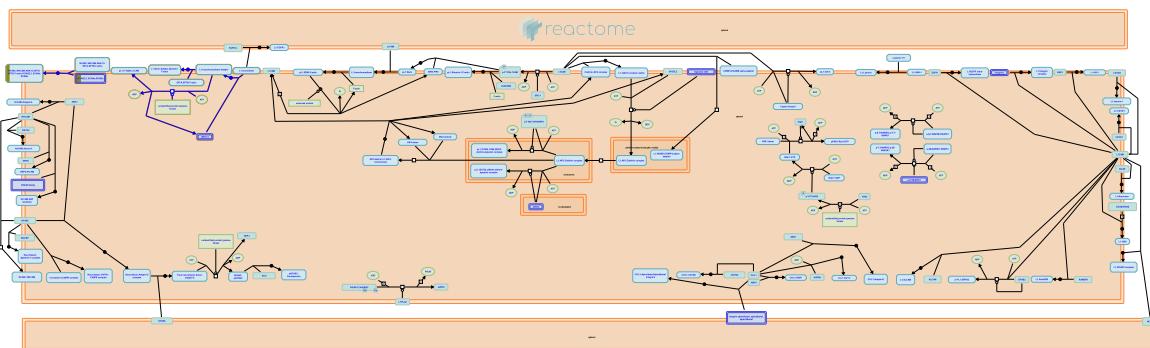
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Date	Action	Author
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

19. 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.

References

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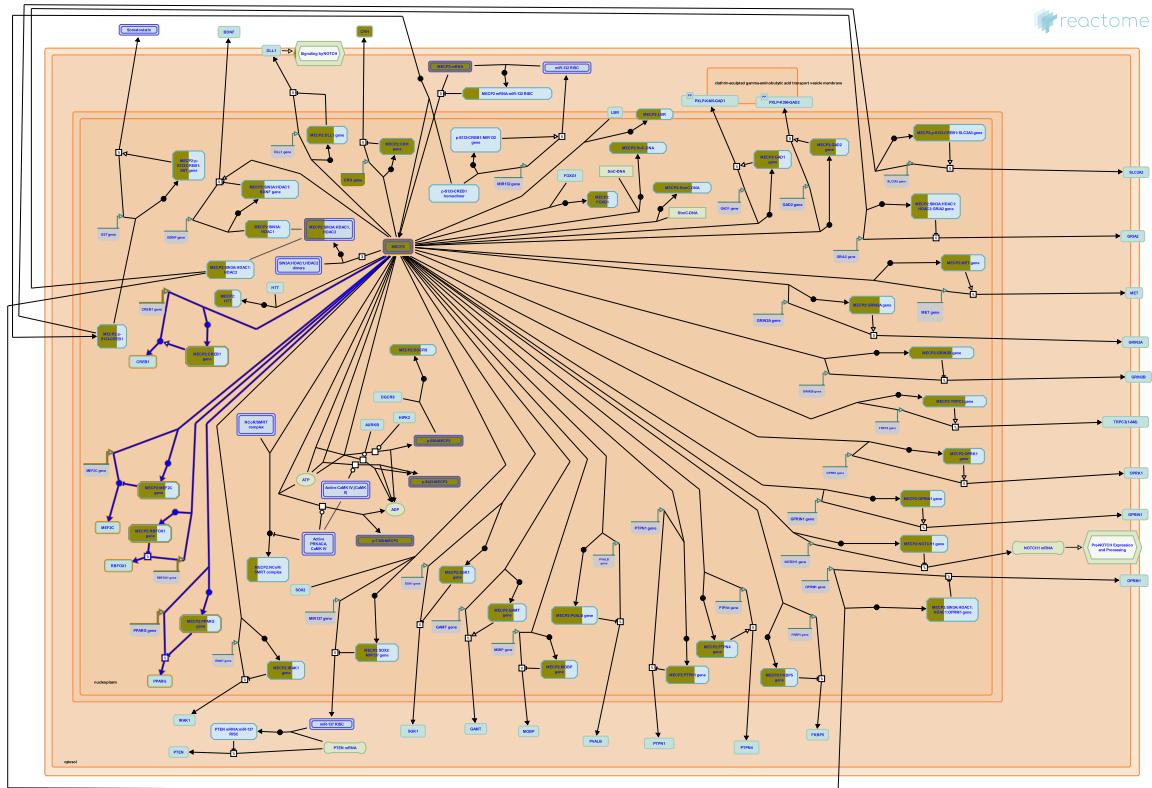
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Date	Action	Author
2008-07-30	Edited	Garapati P V
2008-07-30	Authored	Garapati P V
2009-10-27	Created	Garapati P V
2010-02-16	Reviewed	Maness PF
2021-11-25	Modified	Weiser JD

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

Input	UniProt Id
SCN2A	P35498, Q15858, Q99250

20. MECP2 regulates transcription factors (R-HSA-9022707)



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).

References

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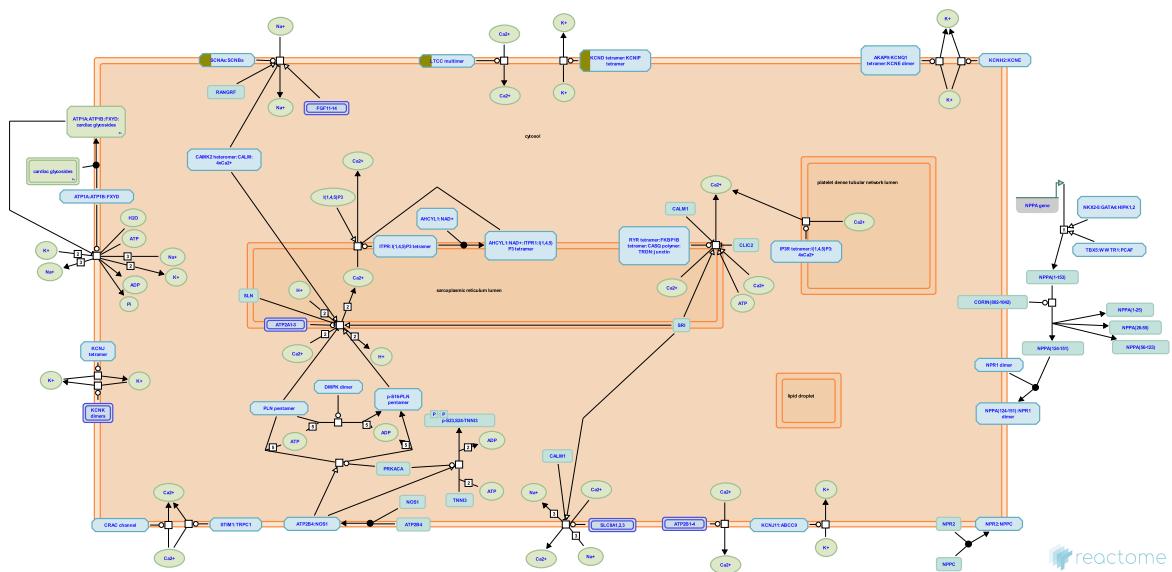
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Date	Action	Author
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

21. 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).

References

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Grant AO (2009). Cardiac ion channels. *Circ Arrhythm Electrophysiol*, 2, 185-94.

Edit history

Date	Action	Author
2014-05-27	Edited	Jassal B
2014-05-27	Authored	Jassal B
2014-05-27	Created	Jassal B
2015-11-09	Reviewed	Colotti G
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CACNA2D2	Q9NY47	KCNIP1	Q9NZI2	SCN2A	P35498, Q15858, Q99250

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



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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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

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

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

Loss of function of MECP2
in Rett syndrome



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.

References

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Edit history

Date	Action	Author
2017-05-11	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

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



reactome

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).

References

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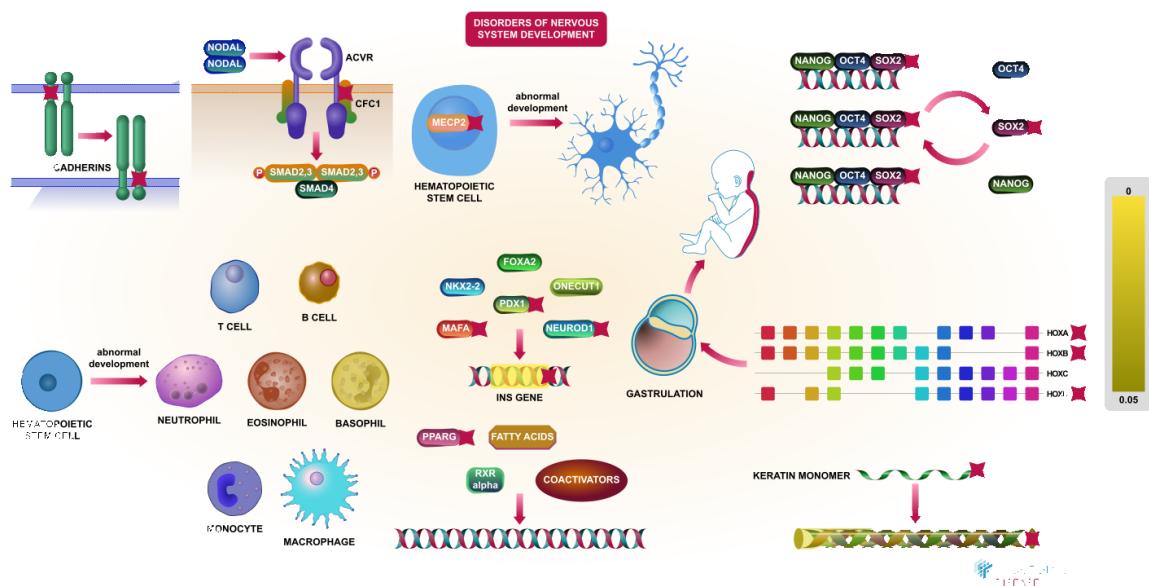
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Date	Action	Author
2017-05-11	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2018-09-05	Modified	Shorser S

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

25. 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).

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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

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

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.

46 of the submitted entities were found, mapping to 65 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BSN	Q9UPA5	CACNA2D2	Q9NY47	CBX6	O95503
CDKN2A	P42771, P42772, Q8N726	CECR1	Q9NZK5	CRH	P06850
CSGALNACT1	Q8TDX6	DDC	P20711	DSCAML1	Q8TD84
EPB41L3	Q9Y2J2	FASN	P49327	FBXW4	P57775
FBXW7	Q969H0-1, Q969H0-4	GCG	P01275	GLYCTK	Q8IVS8
GNB2	P62879	GPC6	Q9Y625	GRIA3	P42263
HERC2	O95714	KCNIP1	Q9NZI2	KLHL3	Q9UH77
LSAMP	Q13449	MECP2	P51608-1, P51608-2	MED19	A0JLT2
MINK1	Q8N4C8	MLL4	O14686, Q9UMN6	MMP15	P51511
NINL	Q9Y2I6	NPC1L1	Q9UHC9-2	NPHP4	O75161
PCSK2	P16519	PDK4	Q16654	PHKA2	P46019
PI4KA	P42356	PLXNA1	Q9UIW2	PLXNA3	P51805
POLG	P27958	RRP36	Q96EU6	SCARB1	Q8WTV0-2
SCN2A	P35498, Q15858, Q99250	SLC6A19	Q695T7	SMPD1	P17405
SPG7	Q9UQ90	UTY	O14607	WDR59	Q6PJI9
WNT4	O96014, P56705				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755	CRH	ENSG00000147571	FASN	ENSG00000169710
GCG	ENSG00000115263	MECP2	ENST00000303391, ENST00000453960	MINK1	ENSG00000141503
WNT4	ENSG00000162552				

7. Identifiers not found

These 32 identifiers were not found neither mapped to any entity in Reactome.

ATCAY	C11orf41	C19orf63	C4orf44	CBFA2T2	CCDC64	CELSR3	CPLX2
DIP2A	EFR3B	FAM117A	FAM160A2	FEV	FEZ1	GPR64	H6PD
HCP5	KIAA0195	KIAA1244	KIAA1324	LOC100130899	NAV3	PCDHB5	PLEKHH3
SEPN1	SLC39A11	SNX29	SPEF2	STK36	TARBP1	TPRG1L	ZFR2