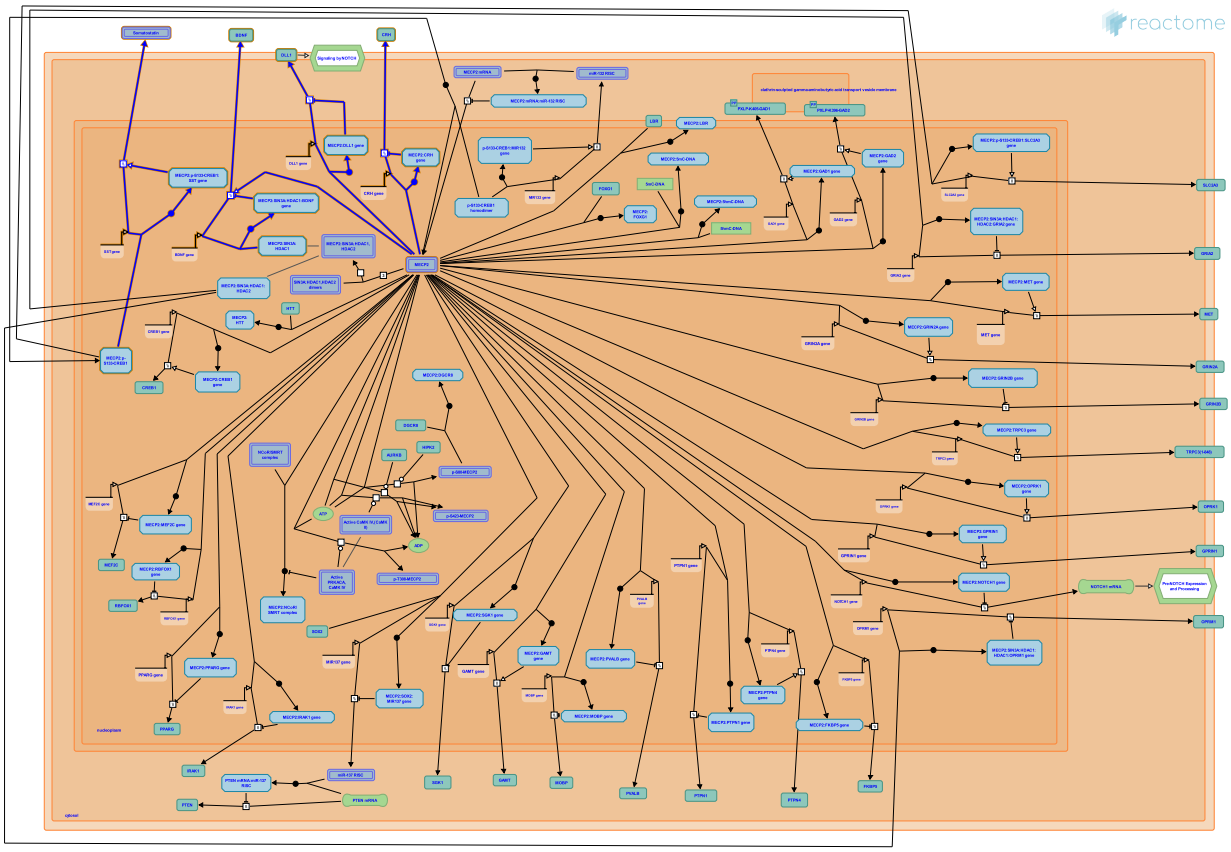
MECP2 regulates transcription of neuronal ligands



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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

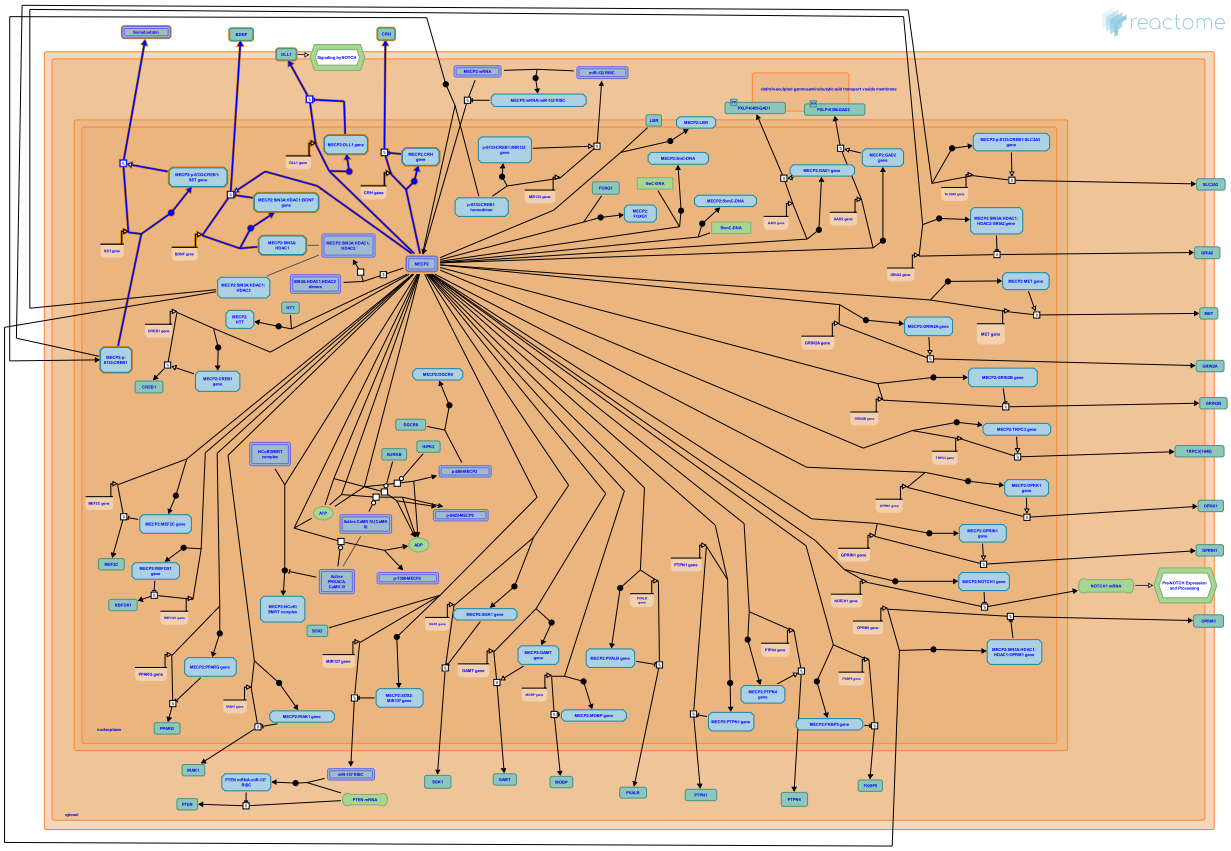
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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

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

MECP2 regulates transcription of neuronal ligands ↗

Stable identifier: 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).

Literature references

Mandel-Brehm, C., Samaco, RC., Zoghbi, HY., McGill, BE., Shaw, CA., McGraw, CM. (2012). Crh and Oprm1 mediate anxiety-related behavior and social approach in a mouse model of MECP2 duplication syndrome. *Nat. Genet., 44*, 206-11. ↗

Carson, JP., Bundle, SF., Zoghbi, HY., McGill, BE., Yaylaoglu, MB., Thaller, C. (2006). Enhanced anxiety and stress-induced corticosterone release are associated with increased Crh expression in a mouse model of Rett syndrome. *Proc. Natl. Acad. Sci. U.S.A., 103*, 18267-72. ↗

Zhong, X., Jin, P., Chau, KF., Masliah, J., Kong, G., Chi, J. et al. (2014). Cell cycle-linked MeCP2 phosphorylation modulates adult neurogenesis involving the Notch signalling pathway. *Nat Commun, 5*, 5601. ↗

Qin, J., Jung, SY., Wong, ST., Zoghbi, HY., Shaw, C., Chahrour, M. et al. (2008). MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science, 320*, 1224-9. ↗

Gangadaran, S., Lakowski, TM., KhorshidAhmad, T., Cortes, C., Namaka, M., Acosta, C. (2016). Transcriptional Regulation of Brain-Derived Neurotrophic Factor (BDNF) by Methyl CpG Binding Protein 2 (MeCP2): a Novel Mechanism for Re-Myelination and/or Myelin Repair Involved in the Treatment of Multiple Sclerosis (MS). *Mol. Neurobiol., 53*, 1092-107. ↗

Editions

2017-10-02	Authored	Orlic-Milacic, M.
2018-08-07	Reviewed	Christodoulou, J., Krishnaraj, R.
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MECP2:SIN3A complex binds the promoter of the BDNF gene ↗

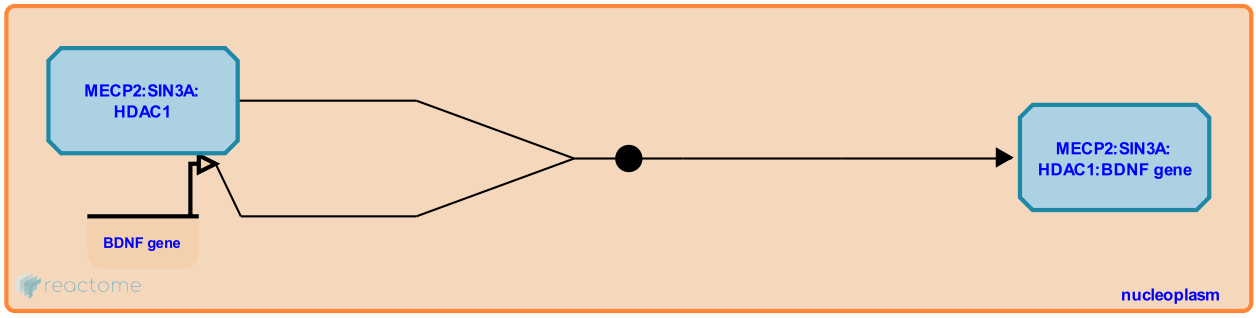
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9006050

Type: binding

Compartments: nucleoplasm

Inferred from: Mecp2:Sin3a complex binds the Bdnf gene promoter (Mus musculus)



Based on studies in mice, the complex of MECP2, SIN3A and HDAC1 binds one of several alternative promoters of the brain-derived neurotrophic factor (BDNF) gene, the promoter in front of the BDNF exon IV (Martinowich et al. 2003). This promoter is homologous to the promoter in front of the rat Bdnf exon III, which was also shown to be occupied by Mecp2 (Chen et al. 2003).

Followed by: BDNF gene transcription

Literature references

West, AE., Greenberg, ME., Griffith, EC., Chen, WG., Jaenisch, R., Lin, Y. et al. (2003). Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science, 302*, 885-9. ↗

Fouse, S., Wu, H., Sun, YE., Fan, G., He, F., Martinowich, K. et al. (2003). DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. *Science, 302*, 890-3. ↗

Editions

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BDNF gene transcription ↗

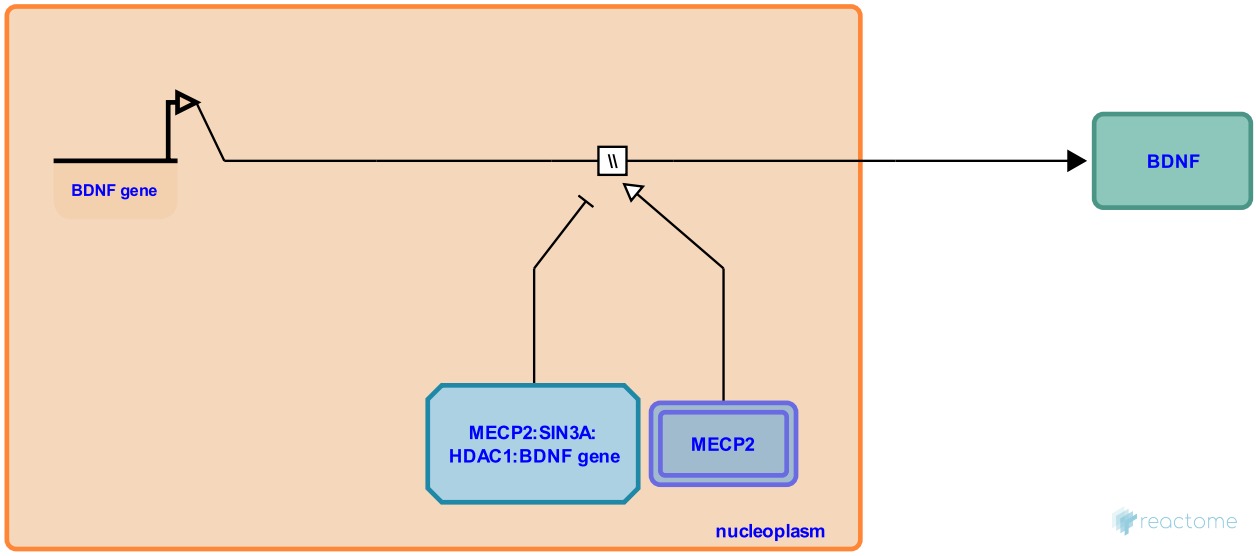
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9006122

Type: omitted

Compartments: nucleoplasm

Inferred from: Bdnf gene expression (Mus musculus)



Binding of MECP2 to the promoter of the BDNF gene represses BDNF transcription in unstimulated neurons, tying BDNF expression with neuronal membrane depolarization (Chen et al. 2003, Martinowich et al. 2003). BDNF encodes Brain-derived neurotrophic factor. MECP2-mediated recruitment of the histone deacetylase (HDAC) containing SIN3A co-repressor complex is thought to induce histone deacetylation at the BDNF promoter, invoking BDNF gene silencing (Martinowich et al. 2003).

Surprisingly, MECP2 deficiency in Rett syndrome results in an overall decreased expression of BDNF (Klein et al. 2007, Chahrour et al. 2008, Fyffe et al. 2008). One proposed mechanism is indirect, through the loss of MECP2-mediated repression of REST and RCOR1 (CoREST) genes, as REST and RCOR1 act as repressors of BDNF transcription from promoter 1 (Abuhatzira et al. 2007). Previously, it was reported that the CoREST complex also represses transcription of Bdnf from the Mecp2-binding murine promoter 4 (corresponding to human MECP2-binding BDNF promoter 3) (Ballas et al. 2005).

For detailed review of dual regulation of BDNF transcription by MECP2, please refer to Li and Pozzo-Miller 2014, and KhorashidAhmad et al. 2016.

Deficit in Bdnf expression in Mecp2 null mice results in downregulation of Igf1 expression through a microRNA-dependent pathway regulated by Bdnf signaling. Induction of signaling by the beta2-adrenegic receptor can restore Igf1 expression in Mecp2 null mice (Mellios et al. 2014).

Preceded by: MECP2:SIN3A complex binds the promoter of the BDNF gene

Literature references

West, AE., Greenberg, ME., Griffith, EC., Chen, WG., Jaenisch, R., Lin, Y. et al. (2003). Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science, 302*, 885-9. ↗

Impey, S., Mandel, G., Lioy, DT., Klein, ME., Goodman, RH., Ma, L. (2007). Homeostatic regulation of MeCP2 expression by a CREB-induced microRNA. *Nat. Neurosci., 10*, 1513-4. ↗

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2017-10-02	Authored	Orlic-Milacic, M.
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MECP2 binds CRH gene promoter ↗

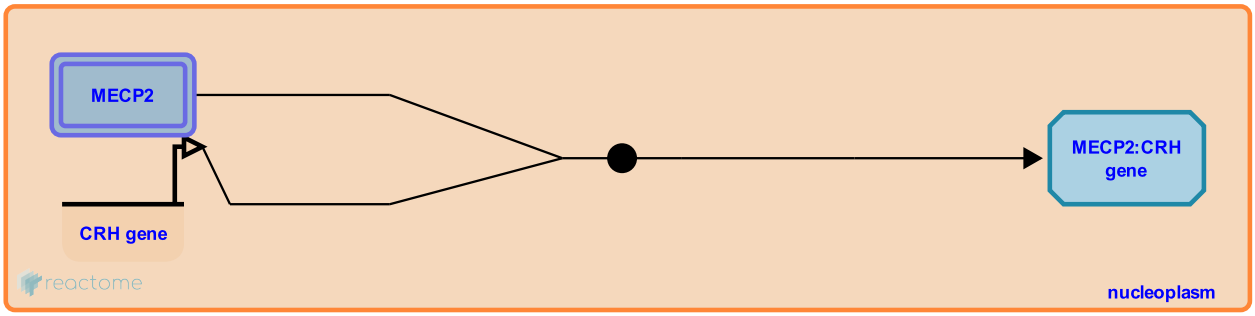
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9017983

Type: binding

Compartments: nucleoplasm

Inferred from: Mecp2 binds Crh gene promoter (Mus musculus)



Based on studies in mice, MECP2 binds to the promoter of the CRH gene, encoding corticotropin-releasing hormone (corticoliberin) (McGill et al. 2006, Samaco et al. 2012). MECP2 preferentially binds to the CRH promoter with a repressive dimethylation of histone H3 (McGill et al. 2006).

Followed by: CRH gene expression is repressed by MECP2

Editions

2017-10-02	Authored	Orlic-Milacic, M.
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CRH gene expression is repressed by MECP2 ↗

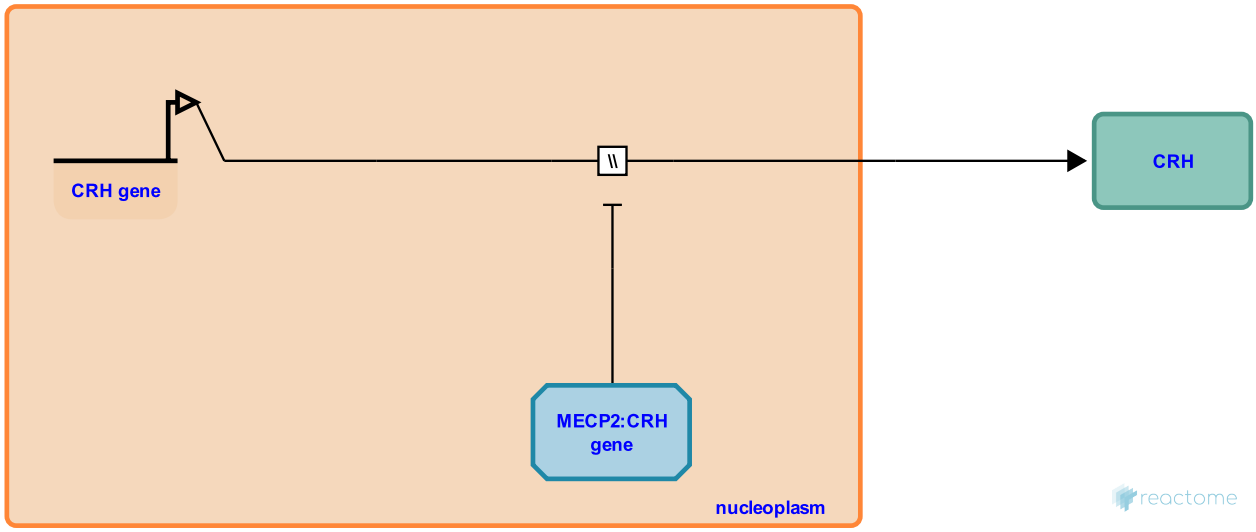
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9017988

Type: omitted

Compartments: nucleoplasm, extracellular region

Inferred from: Crh gene expression is repressed by Mecp2 (Mus musculus)



Based on studies in mice, MECP2 represses transcription from the CRH gene promoter (McGill et al. 2006). Mice with the loss of function of Mecp2 exhibit overexpression of Crh (McGill et al. 2006). Surprisingly, mice with Mecp2 gene duplication, which serve as a model for the MECP2 duplication syndrome, also overexpress Crh (Samaco et al. 2012).

Preceded by: MECP2 binds CRH gene promoter

Editions

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MECP2:CREB1 binds SST gene promoter ↗

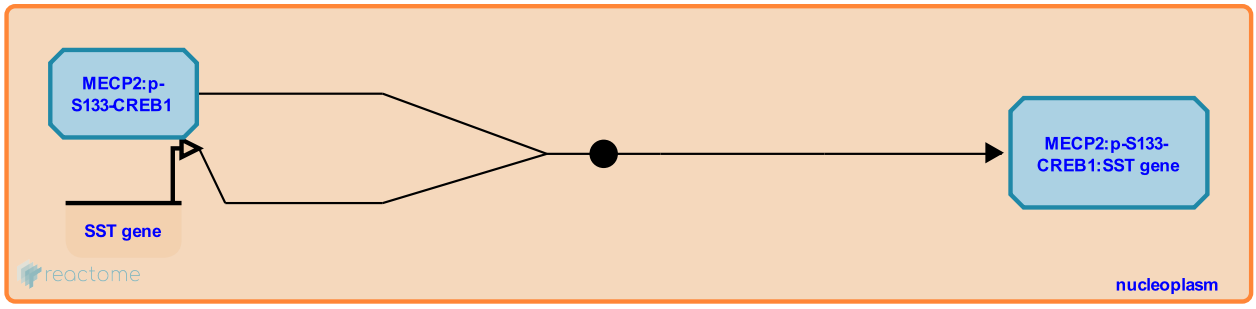
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9021919

Type: binding

Compartments: nucleoplasm

Inferred from: Mecp2:Creb1 binds Sst gene promoter (Mus musculus)



Based on studies in mice, the complex of MECP2 and CREB1 binds the promoter region of the STT gene, encoding somatostatin (Chahrour et al. 2008).

Followed by: SST gene expression is stimulated by MECP2 and CREB1

Editions

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SST gene expression is stimulated by MECP2 and CREB1 ↗

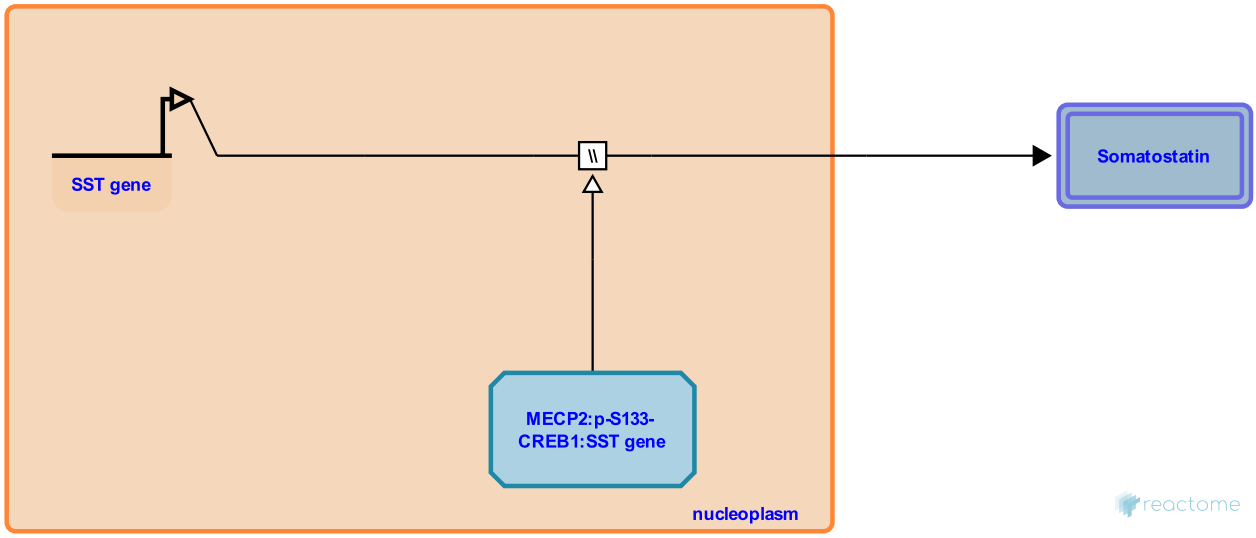
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9021935

Type: omitted

Compartments: nucleoplasm, extracellular region

Inferred from: Sst gene expression (Mus musculus)



Based on studies in mice, transcription of the SST gene, encoding somatostatin, is synergistically stimulated by MECP2 and CREB1, which form a complex at the SST promoter (Chahrour et al. 2008).

Preceded by: MECP2:CREB1 binds SST gene promoter

Editions

2017-10-02	Authored	Orlic-Milacic, M.
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2018-08-08	Edited	Orlic-Milacic, M.

MECP2 binds DLL1 gene promoter ↗

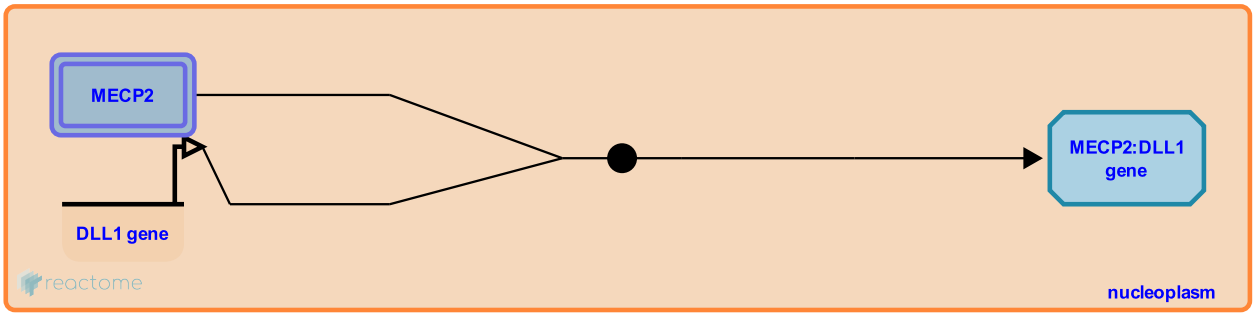
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9023348

Type: binding

Compartments: nucleoplasm

Inferred from: Mecp2 binds Dll1 gene promoter (Mus musculus)



Based on studies in mice, MECP2 binds the promoter of DLL1 gene, encoding NOTCH ligand Delta 1. Binding of MECP2 to the DLL1 gene promoter is inhibited by AURKB-mediated phosphorylation of MECP2 at serine residue S423 (Li et al. 2014).

Followed by: DLL1 gene expression is inhibited by MECP2

Editions

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DLL1 gene expression is inhibited by MECP2 ↗

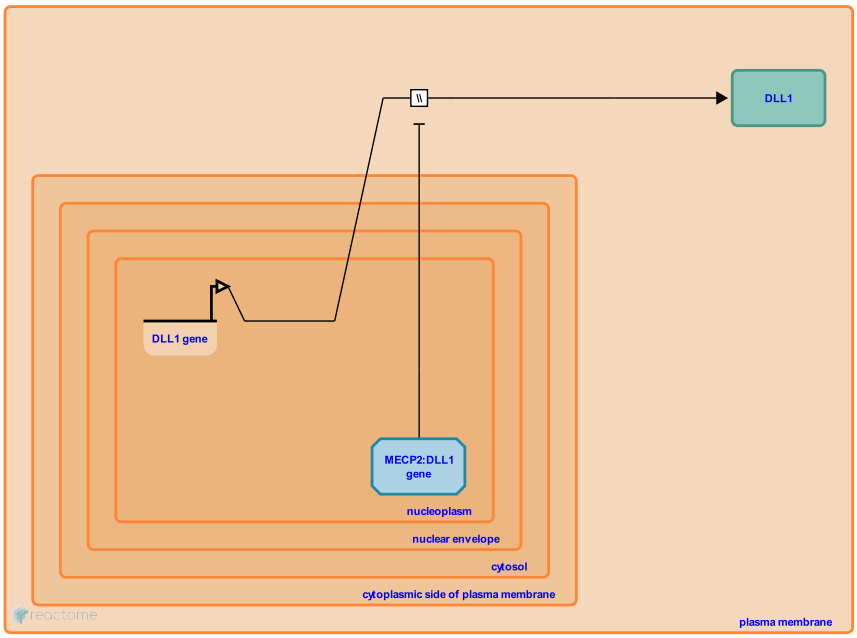
Location: MECP2 regulates transcription of neuronal ligands

Stable identifier: R-HSA-9023351

Type: omitted

Compartments: plasma membrane, nucleoplasm

Inferred from: Dll1 gene expression is inhibited by Mecp2 (Mus musculus)



Based on studies in mice, increased MECP2 occupancy of the DLL1 gene promoter, encoding NOTCH ligand Delta 1, correlates with decreased transcription of DLL1. MECP2 therefore inhibits DLL1 transcription (Li et al. 2014).

Preceded by: MECP2 binds DLL1 gene promoter

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2017-10-02	Authored	Orlic-Milacic, M.
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