## MECP2

From Wikipedia, the free encyclopedia

<table>
<thead>
<tr>
<th>Available structures</th>
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<td><strong>PDB</strong> 1qk9, 1ub1</td>
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<table>
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<th>Identifiers</th>
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<tr>
<td><strong>Symbols</strong> MECP2; RTS; AUTSX3; DKFZp686A24160; MRX16; MRX79; PPMX; RTT</td>
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<table>
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<th>External IDs</th>
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<tr>
<td>OMIM: 300005 MGI: 99918 HomoloGene: 3657 GeneCards: MECP2 Gene</td>
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<th>Gene Ontology</th>
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<tr>
<td><strong>Molecular function</strong> • DNA binding • transcription corepressor activity</td>
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<td><strong>Cellular component</strong> • nucleus</td>
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| **Biological process** • negative regulation of transcription from RNA polymerase II promoter • transcription • regulation of transcription, DNA-
RNA expression pattern

More reference expression data

Orthologs

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MECP2 (methyl CpG binding protein 2 (Rett syndrome)) is a gene[1] that provides instructions for making its protein product, MECP2, also referred to as MeCP2.[2] MECP2 appears to be essential for the normal function of nerve cells. The protein seems to be particularly important for mature nerve cells, where it is present in high levels. The MeCP2 protein is likely to be involved in turning off ("repressing" or "silencing") several other genes. This prevents the genes from making proteins when they are not needed. Recent work has shown that MeCP2 can also activate other genes.[3] The MECP2 gene is located on the long (q) arm of the X chromosome in band 28 ("Xq28"), from base pair 152,808,110 to base pair 152,878,611.

DNA methylation is the major modification of eukaryotic genomes and plays an essential role in mammalian development. Human proteins MECP2 (this protein), MBD1, MBD2, MBD3, and MBD4 comprise a family of nuclear proteins related by the presence in each of a methyl-CpG binding domain (MBD). Each of these proteins, with the exception of MBD3, is capable of binding specifically to methylated DNA. MECP2, MBD1 and MBD2 can also repress transcription from methylated gene promoters. In contrast to other MBD family members, MECP2 is X-linked and subject to X inactivation. MECP2 is dispensable in stem cells. MECP2 gene mutations are the cause of some cases of Rett syndrome, a progressive neurologic developmental disorder and one of the most common causes of mental retardation in females.[4]

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Function

MeCP2 protein is found in all cells in the body, including the brain, acting as a transcriptional repressor and activator, depending on the context. However, the idea that MeCP2 functions as an activator is relatively new and remains controversial. In the brain, it is found in high concentrations in neurons and is associated with maturation of the central nervous system (CNS) and in forming synaptic contacts.

Mechanism of action

The MeCP2 protein binds to forms of DNA that have been methylated. The MeCP2 protein then interacts with other proteins to form a complex that turns off the gene. Methylation is a chemical alteration made to a "cytosine" (C) when it occurs in a particular DNA sequence, "CpG". Many genes have CpG islands, which frequently occur near the beginning of the gene. MECP2 does not bind to these islands in most cases, as they are not methylated. The expression of a few genes may be regulated through methylation of their CpG island, and MECP2 may play a role in a subset of these. Researchers have not yet determined which genes are targeted by the MeCP2 protein, but such genes are probably important for the normal function of the central nervous system. However, the first large-scale mapping of MECP2 binding sites in neurons found that only 6% of the binding sites are in CpG islands, and that 63% of MECP2-bound promoters are actively expressed and only 6% are highly methylated, indicating that MECP2's main function is something other than silencing methylated promoters.

Once bound, MeCP2 will condense the chromatin structure, form a complex with histone deacetylases (HDAC), or block transcription factors directly. More recent studies have demonstrated that MeCP2 may also function as a transcriptional activator, through recruiting the transcription factor CREB1. This was an unexpected finding which suggests that MeCP2 is a key transcriptional regulator with potentially dual roles in gene expression. In fact, the majority of genes that are regulated by MeCP2 appear to be activated rather than repressed. However, it remains controversial whether MeCP2 regulates these genes directly or whether these changes are secondary in nature. Further studies have shown MeCP2 may be able to bind directly to unmethylated DNA in some instances. MeCP2 has been implicated in regulation of imprinted genes and loci that include UBE3A and DLX5.

Structure

MeCP2 is part of a family of methyl-CpG-binding domain proteins (MBD), but possesses its own unique differences which help set it apart from the group. It has two functional domains:

- a methyl-cytosine-binding domain (MBD) composed of 85 amino acids; and
The MBD domain forms a wedge and attaches to the methylated CpG sites on the DNA strands. The TRD region then reacts with SIN3A to recruit histone deacetylases (HDAC). There are also unusual, repetitive sequences found at the carboxyl terminus. This region is closely related to the fork head family, at the amino acid level.

Role in disease

Rett syndrome is caused by mutations in the MECP2 gene. Several types of mutations have been identified in people with Rett syndrome. These mutations include changes in single base pairs (the building material of DNA), insertions or deletions of DNA in the gene, and changes that affect how the gene is processed into a protein. Mutations in the gene alter the structure of the MeCP2 protein or lead to reduced amounts of the protein. As a result, the protein is unable to bind to DNA or turn other genes on or off. Genes that are normally repressed by MeCP2 remain active and continue to make large amounts of particular proteins when they are not needed. Other genes that are normally activated by MeCP2 remain inactive and thus unable to make protein products. This defect probably disrupts the normal functioning of nerve cells, leading to the signs and symptoms of Rett syndrome.

This disease is mainly found in girls with a prevalence of around 1 in every 10,000. Patients are born with very hard to find signs of a disorder, but after about six months to a year and half, speech and motor function capabilities start to decrease. This is followed by seizures, growth retardation and cognitive and motor impairment. This is a X-linked dominant disease that is found predominatley affecting the paternal X chromosome. It has been linked to male lethality, due to its prevalence in females, but in rare cases some males can also be affected by Rett Syndrome.

Mutations in the MECP2 gene have also been identified in people with several other disorders affecting the central nervous system. For example, MECP2 mutations are associated with some cases of moderate to severe X-linked mental retardation. Mutations in the gene have also been found in males with severe brain dysfunction (neonatal encephalopathy) who live only into early childhood. In addition, several people with features of both Rett syndrome and Angelman syndrome (a condition characterized by mental retardation, problems with movement, and inappropriate laughter and excitability) have mutations in the MECP2 gene. Lastly, MECP2 mutations or changes in the gene’s activity have been reported in some cases of autism (a developmental disorder that affects communication and social interaction).

More recent studies reported genetic polymorphisms in the MeCP2 genes in patients with systemic lupus erythematosus (SLE). SLE is a systemic autoimmune disease that can affect multiple organs. MeCP2 polymorphisms have been reported so far in European-derived and Asian lupus patients.

The genetic loss of MECP2 has been identified as changing the properties of cells in the locus ceruleus the exclusive source of noradrenergic innervation to the cerebral cortex and hippocampus.
Researchers have concluded that "Because these neurons are a pivotal source of norepinephrine throughout the brainstem and forebrain and are involved in the regulation of diverse functions disrupted in Rett syndrome, such as respiration and cognition, we hypothesize that the locus ceruleus is a critical site at which loss of MECP2 results in CNS dysfunction."[16]

**[edit] Interactions**

MECP2 has been shown to interact with SKI protein[17] and Nuclear receptor co-repressor 1.[17] In neuronal cells the MECP2 mRNA is thought to interact with miR-132, which silences the expression of the protein. This forms part of a homeostatic mechanism that could regulate

**References**

Further reading


1qk9: THE SOLUTION STRUCTURE OF THE DOMAIN FROM MECP2 THAT BINDS TO METHYLATED DNA

1ub1: Solution structure of the matrix attachment region-binding domain of chicken MeCP2