# 2016-2017 Research and Design Model


**Hartford Union High School SMART Team**

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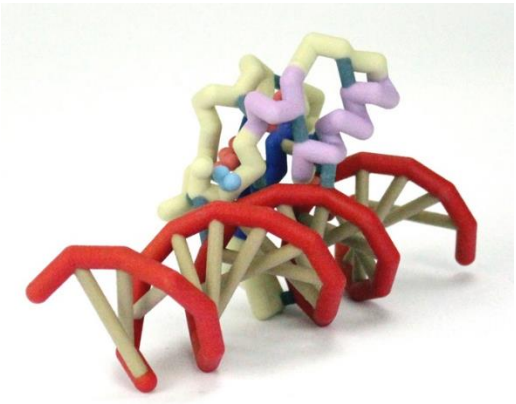
## The Role of MeCP2 Mutations in a Reg-Rett-Able Syndrome

**PDB:** 5BT2


**Primary Citation:** Ballestar, E., Yusufzai, T. M., & Wolffe, A. P. (2000, May 26). Effects of Rett Syndrome Mutations of the Methyl-CpG Binding Domain of the Transcriptional Repressor MeCP2 on Selectivity for Association with Methylated DNA. *Biochemistry, 39*(24), 7100-7106. doi:10.1021/bi0001271


**Format:** Alpha carbon backbone

**RP:** Zcorp with plaster



**Description:**

Rett Syndrome affects about one in every 10,000 to 15,000 births. It is a genetic neurodevelopmental disorder that mainly occurs in females. Affected males die in infancy because the syndrome exhibits an X-linked dominant pattern of inheritance. Rett Syndrome is caused by mutations in the X-linked Methyl CpG binding protein 2 (MeCP2) coding gene. MeCP2 is necessary for epigenetic regulation of gene expression. This protein represses transcription by acting as a molecular bridge between methylated DNA and a complex of co-repressor proteins including histone deacetylases and Sin3A. Mutations of MeCP2 cause overexpression of several genes during brain development. MeCP2 is a 52-kDa protein with two functional domains: the transcriptional repressor domain (TRD) and the methyl-CpG binding domain (MBD). Within the MBD, mutations of Arg106, Arg133, Phe155, and Thr158 result in a decreased binding affinity of MeCP2 to methylated DNA: 2-fold for mutated Thr158 and 100-fold for the remaining mutated amino acids. The MBD has three beta sheets with Thr158 located on the c-terminal end. Here, hydrophilic residues interact specifically with the methylated DNA. The Hartford Union High School SMART (Students Modeling A Research Topic) Team designed a model of MeCP2 using 3D printing technology to represent the MBD-methylated DNA complex. The model highlights the amino acids involved in the interaction between MeCP2 and methylated DNA. Modeling the structure of MeCP2 allows for a more detailed understanding of the interaction between MeCP2 and DNA. This information will be crucial for designing treatments or interventions to improve the quality of life for Rett syndrome patients.

**Specific Model Information:**

- Beta sheets are colored darkslateblue
- Alpha helix is colored thistle
- Hydrogen bonds are colored tan
- Struts are colored gray
- Mutated side chains for 106, 133, and 155 are colored salmon.
- Mutated side chain for 158 is skyblue.
    - This side chain is colored differently than the other mutated side chains because it shows reduced binding affinity by 2-fold instead of by 100-fold.
- DNA is colored firebrick
- The remainder of the backbone is colored lemonchiffon.
- Magnets have been added to the 4 manual struts between MeCP2 and the DNA to demonstrate where MeCP2 interacts with the DNA groove. These are at the following locations:

    [DT]30:C.P #1169 to [THR]160:A.CA #552 15.025 -6.742 -26.822
    [5CM]33:C.P #1245 to [VAL]136:A.CA #357 7.479 9.279 -18.805
    [DA]6:B.P #674 to [LYS]130:A.CA #306 3.271 -1.045 -9.33
    [DG]9:B.P #736 to [GLY]114:A.CA #184