Mystery of Rett timing explained in MeCP2 binding

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For decades, scientists and physicians have puzzled over the fact that infants with the postnatal neurodevelopmental disorder Rett syndrome show symptoms of the disorder from one to two years after birth.

In a report in the *Proceedings of the National Academy of Sciences*, Dr. Huda Zoghbi and her colleagues from Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, unravel the mystery by looking at when and how the causal gene involved (methyl-CpG binding protein 2 or MECP2) binds to methylated cytosine over the course of brain development.

Using mice in which the MeCP2 protein is tagged with a fluorescent green protein, they determined genome-wide MeCP2 binding profiles in the adult animal brain. In addition to the expected finding of MeCP2 binding to methylated cytosine with guanine (CG) with high affinity, they also found that MeCP2 binds to cytosine when it is followed by either adenine, cytosine or thymine instead of guanine (non-CG methylation or "mCH").

"This pattern is unique to the maturing and adult nervous system," said Zoghbi. She noted that genes that accumulate non-CG methylation after birth are preferentially dysregulated in mouse of models of diseases associated with the lack of, or elevations, of the MeCP2 protein.

"This suggests that MeCP2 binds to newly established methylated cytosine followed by any base other than a guanine as neurons mature to

enact its function of regulating gene expression," said Zoghbi

The study provides insight into the molecular mechanism that governs MeCP2 and also gives a rationale for why the symptoms occur at least a year after birth.

More information: MeCP2 binds to non-CG methylated DNA as neurons mature, influencing transcription and the timing of onset for Rett syndrome, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1505909112

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