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Ilda D'Annessa, Anna Gandaglia, Elena Brivio, Gilda Stefanelli, Angelisa Frasca, Nicoletta Landsberger, Daniele Di Marino

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Tyr120Asp mutation alters domain flexibility and dynamics of MeCP2 DNA Binding Domain leading to impaired DNA interaction: atomistic characterization of a Rett syndrome causing mutation.

Ilda D’Annessa¹, Anna Gandaglia², Elena Brivio², Gilda Stefanelli², Angelisa Frasca³
Nicoletta Landsberger²,³*, Daniele Di Marino⁴*

¹Istituto di Chimica del Riconoscimento Molecolare, CNR, Milan, Italy, ²San Raffaele Rett Research Unit, San Raffaele Scientific Institute, Milan, Italy, ³Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy, ⁴Department of Informatics, Institute of Computational Science, Università della Svizzera Italiana, Lugano, Switzerland

ABSTRACT
Mutations in the X-linked MECP2 gene represent the main origin of Rett syndrome, causing a profound intellectual disability in females. MeCP2 is an epigenetic transcriptional regulator containing two main functional domains: a methyl-CpG binding domain (MBD) and a transcription repression domain (TRD). Over 600 pathogenic mutations were reported to affect the whole protein; almost half of missense mutations affect the MBD. Understanding the impact of these mutations on the MBD structure and interaction with DNA will foster the comprehension of their pathogenicity and possibly genotype/phenotype correlation studies. Herein, we use molecular dynamics simulations to obtain a detailed view of the dynamics of WT and mutated MBD in the presence and absence of DNA. The pathogenic mutation Y120D is used as paradigm for our studies. Further, since the Y120 residue was previously found to be a phosphorylation site, we characterize the dynamic profile of the MBD also in the presence of Y120 phosphorylation (pY120). We found that addition of a phosphate group to Y120 or mutation in aspartic acid affect domain mobility that samples an alternative conformational space with respect to the WT, leading to impaired ability to interact with DNA. Experimental assays showing a significant reduction in the binding affinity between the mutated MBD and the DNA confirmed our predictions.

* to whom correspondence should be addressed
Daniele Di Marino,
Università della Svizzera Italiana.
Via Giuseppe Buffi 13, Lugano, Switzerland.
Email: daniele.di.marino@usi.ch

Nicoletta Landsberger,
University of Milan, 20090 Segrate Milano, Italy.
Email: nicoletta.landsberger@unimi.it
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