Mechanism of autoinhibition and activation of the human MORC2 GHKL ATPase

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The Microrchidia (MORC) proteins are gyrase, heat-shock protein 90, histidine kinase, MutL (GHKL) ATPases that remodel chromatin to regulate epigenetic silencing. Patient mutations in human MORC2 lead to hereditary Charcot-Marie-Tooth disease, a neuromuscular disorder that causes nerve damage and muscle weakness. It has been previously proposed that MORC2 dimerisation is dependent on ATP binding to transduce epigenetic silencing at the Histone 3 Lysine 9 trimethylated (H3K9me3)-marked chromatin [1]. Here we report a cryo-electron microscopy structure of the full-length human MORC2 and reveal that it forms a dimer in the presence of the C-terminal coiled-coil domain. By comparison with the structure of the MORC2 bound to AMP-PNP – which we also report here – we show that the dimer formation is enhanced in the presence of ATP analog. Using hydrogen-deuterium exchange mass spectrometry, we also show that the CW zinc finger-like domain of MORC2 interacts with DNA, consistent with its binding to H3K9me3-marked chromatin *in vitro*. Further, mutations in the MORC2 ATPase region resulted in decreased ATP hydrolysis activity, suggestive of an autoinhibitory mechanism that prevents nucleosomes binding prior to ATP hydrolysis. Our structures together with biochemical data reveal the molecular details of DNA recognition by MORC2 ATPase and how ATP is orientated for dimerisation. This work reveals key molecular activities of MORC2 that might apply to other MORC family members in eukaryotic organisms.

[1] Douse, C. H., Bloor, S., Liu, Y., Shamin, M., Tchasovnikarova, I. A., Timms, R. T., Lehner, P. J. & Modis, Y. (2018). *Nat. Commun.* **9**, 651.