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A common thread links multiple human cognitive disorders

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A new study reveals that a common underlying mechanism is shared by a group of previously unrelated disorders which all cause complex defects in brain development and function. Rett syndrome (RTT), Cornelia de Lange syndrome (CdLS) and Alpha-Thalassemia mental Retardation, X-linked syndrome (ATR-X) have each been linked with distinct abnormalities in chromatin, the spools of proteins and DNA that make up chromosomes and control how genetic information is read in a cell.

Now, research, published by Cell Press in the February 16th issue of the journal *Developmental Cell,* helps to explain why these different chromatin abnormalities all interfere with proper gene expression patterns necessary for normal development and mature brain function.

"Although clearly distinct from one another, human developmental disorders that are linked with chromatin dysfunction often share similar cognitive clinical features," explains senior study author, Dr. Nathalie Bérubé from the University of Western Ontario. "Whether the overlapping cognitive symptoms are due to underlying interlinked molecular mechanisms is still poorly understood." Her work now demonstrates that chromatin proteins defective in RTT, CdLS, and ATR-X syndromes are all associated with each other - and are required for one another's function - at certain "imprinted genes" in the developing mouse brain. Imprinted genes are a relatively rare type of gene that carries different information depending on whether it is inherited from the mother or the father. The results support the conclusion that ATRX (the chromatin protein that is defective in ATR-X syndrome) and its binding

partners regulate expression of imprinted genes, and likely other genes required for normal brain development, by controlling chromatin structure.

"Our findings provide the first glimpse of the cooperation between ATRX and multiple other disease proteins in the regulation of common gene targets, perhaps explaining similarities between the associated human syndromes," says Dr. Bérubé. "The failure to properly suppress genes that are essential during embryonic development, but potentially detrimental in the mature brain, might contribute to cognitive deficiencies characteristic of RTT, CdLS and ATR-X syndromes. Further studies are needed to gain a better understanding of the specific role of these chromatin proteins and the molecular pathogenesis of the associated human disorders."

Provided by Cell Press