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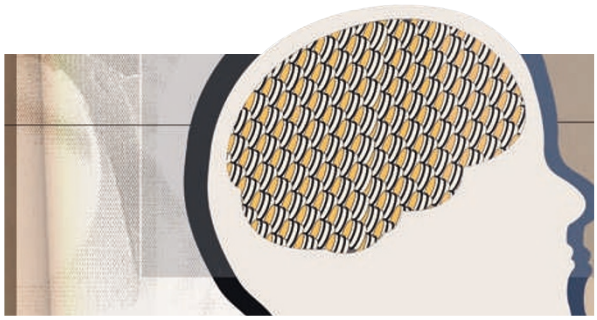

GENES AND DISEASE

Chromatin on the brain

Several proteins that modulate chromatin structure have been implicated in human developmental disorders, some of which share phenotypic features. Now the finding that three of these disease-associated proteins interact at a subset of imprinted genes suggests overlapping molecular mechanisms in syndromes that affect brain development.

The α-thalassaemia mental retardation, X-linked syndrome (ATR-X) is caused by mutations in the *ATRX* gene, which encodes a chromatin-remodelling factor. Depletion of ATRX in mouse cells disrupts sister-chromatid cohesion during mitosis, so Kernohan and colleagues investigated whether ATRX might interact with the protein complex that controls this process, cohesin. Indeed, ATRX and cohesin subunits co-immunoprecipitated in the mouse forebrain, independently of mitosis. In addition, in the forebrain the ATRX–cohesin complex was found to be associated with MECP2, a methyl-CpG-binding protein.

Intriguingly, MECP2 and cohesin, like ATRX, are mutated in disorders that have neurodevelopmental phenotypes — Rett syndrome (RTT) and Cornelia de Lange syndrome (CdLS), respectively. How might this complex of chromatin-associated proteins function in brain development?

Allele-specific chromatin immunoprecipitation revealed that ATRX, MECP2 and subunits of cohesin are enriched at the maternal *H19* imprinting-control region. In humans and mice, *ATRX* mutations cause aberrant DNA methylation at repetitive elements, but the authors found no change in methylation at *H19* in a forebrain-specific *Atrx*-knockout mouse; instead, histone acetylation and methylation were altered. During embryogenesis, *Atrx* knockout in the forebrain did not affect *H19* expression, nor expression of the neighbouring imprinted gene, insulin-like growth factor 2 (*Igf2*); however, postnatally, *H19* and *Igf2* were upregulated. This was due to increased expression of the maternal allele, which is normally repressed after birth, not reactivation of the silent paternal allele. Recently, cohesin and MECP2 have been implicated in chromosomal looping, and Kernohan *et al.* found that other imprinted genes have increased expression in postnatal forebrain in the absence of ATRX. Therefore, they speculate that the ATRX–MECP2–cohesin complex is involved in *trans*-regulation of a previously reported network of imprinted genes. Repression of these genes might be required for normal brain maturation, which could explain phenotypic similarities in ATR-X, RTT and CdLS.

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ORIGINAL RESEARCH PAPER Kernohan, K. D. *et al.* ATRX partners with cohesin and MeCP2 and contributes to developmental silencing of imprinted genes in the brain. *Dev. Cell* **18**, 191–202 (2010)

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