HUMAN DISEASE

Bound to repeat

A new mechanism for variable penetrance has been uncovered by a study of the genomic binding of ATRX, a SWI/SNF family member that causes a human developmental disorder. This study also suggests intriguing links among non-B DNA structures, histone variant deposition and gene expression.

Mutations in *ATRX* cause ATR-X syndrome, which is characterized by developmental abnormalities and α-thalassaemia. ATRX interacts with heterochromatic repeats, ribosomal DNA repeats and telomeres, but little is known about its binding genome-wide. Law and colleagues performed ATRX chromatin immunoprecipitation followed by sequencing and used analytical modifications that enabled them to interrogate repeat sequences. In human and mouse cells they found that ATRX predominantly binds G- and CpG-rich tandem repeats and promoter sequences.

Using cell lines from patients with ATR-X syndrome, the authors showed that *ATRX* mutations cause dysregulation of genes near ATRX tandem repeat binding sites. For example, *ATRX* mutations cause downregulation of the α-globin genes — leading to α-thalassaemia — and peaks of ATRX binding occur at G-rich repeats near these genes. Tandem repeats can be highly polymorphic, and Law *et al.* showed a correlation between the size of a repeat that is normally bound by ATRX near the α-globin genes and the severity of α-thalassaemia. Thus, repeat polymorphism explains variable penetrance in ATR-X syndrome and possibly in other genetic traits.

The authors also showed that many tandem repeats bound by ATRX can form G-quadruplexes. It is possible that the basis of gene dysregulation is the failure to resolve such structures, which is perhaps linked to ATRX's role in histone 3.3 deposition.

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ORIGINAL RESEARCH PAPER Law, M. J. *et al.* ATR-X syndrome protein targets tandem repeats and influences allele-specific expression in a size-dependent manner. *Cell* **143**, 367–378 (2010)