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Xist comparative genomics

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Abstract

The primary sequence of *Xist* seems not to be important for *Xist* to function in X-chromosome inactivation.

Significance and context

The untranslated RNA transcript of the XIST gene is required for X-chromosome inactivation in mammalian cells. To discover conserved regions that might be crucial for function, *XIST* sequences in four species of the genetically well-characterized vole were examined and compared to each other, and to mouse and human XIST.

Key results

The structure of the *Xist* gene in voles, including 5' and 3' regions, was found to be very similar to that in the mouse. The location of the major *Xist*promoter site in the vole was confirmed as the P1 promoter, analogous to the P1 site in mouse and humans. Nuclease protection assays and 3' RACE showed specific termination sites and several different transcript lengths.

Using the 'Percent Identity Plot', or PIP, program, the authors then identified and analyzed conserved genomic sequences. They found a high degree of similarity between sequences from all four vole species, but also insertion of species-specific repeat elements in upstream regions and in the 3' region of the gene. Sequence similarity between mouse and vole was relatively low, with no extended regions of high similarity, although there were short homologous regions in the promoter and in some exons and introns. Vole and human sequences showed an even lower level of homology, restricted to promoter and transcribed regions, and the regions of high homology between human and vole varied from those found between mouse and vole, suggesting that this conservation of sequence is not biologically significant.Two regions of high similarity interrupted by unrelated sequence were found upstream of the *Xist* gene in rodents, for which the authors predicted promoter activity and a gene, possibly in antisense relative to *Xist*. The mouse putative early promoter P0 mapped within this region but no vole homolog for this was found.

A feature of the upstream region common to all species was the enrichment of various repeats, also seen at the 3' end, which fits with a hypothesis that *Xist* tandem repeats are involved in X-inactivation by binding regulatory molecules in a cooperative way. Tandem repeat regions are well conserved in the human and mouse XIST genes, and have now also been seen in voles, most notably in the 5' region.

Conclusions

Vole *Xist* gene structure is similar to that of the mouse, being transcribed from the P1 promoter with several transcript variants. Poor *Xist* sequence conservation was observed between vole and human, and between vole and mouse, the latter being considered surprising because of the relatively recent divergence of these two. There were similar rates of mutation in exons and introns, suggesting low evolutionary pressure to retain the primary sequence. Thus the repetitive nature of the sequence seems to be more important than the sequence itself. Regions surrounding the *Xist* gene were found to be saturated with repeats, lending weight to the hypothesis that long interspersed repeats (LINEs), in which the X chromosome is enriched, may amplify the X-inactivation signal. The results suggested that other repeats may also be involved in spreading the signal.

Reporter's comments

This paper is an example of how the importance of repeat elements in the regulation of gene expression is becoming increasingly apparent.

Table of links

Genome Research

References

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