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Human *TSIX*- an evolutionary relic?

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Abstract

Analysis of the human *TSIX* transcript shows it to be a truncated and probably non-functional evolutionary relic

Significance and context

X-inactivation in female mammals is the means by which they compensate for having an additional X chromosome relative to males. The mechanisms of silencing extra X chromosomes are not known, but current thinking is that an RNA transcript originates from the *XIST* (X-inactive specific transcript) gene located in the X-inactivation center of one X chromosome, and this results in the silencing of that chromosome - unless its expression is blocked. In mice, this block has been suggested to be provided by the antisense RNA transcript of *Xist* - namely *Tsix* - which originates at a point downstream of the *Xist* locus and extends all the way back over the gene to cover the promoter.

Key results

Transcripts from the human *XIST* region were studied by inserting concatamerized human *XIST* genomic regions into mouse embryonic stem cells and observing transcription directly in these cells and also in the chimeric mice derived from them. Migeon *et al.* found a human transcript that could be the counterpart of the mouse *Tsix*, but with crucial differences. Analysis of its sequence has thrown up some fascinating insights into the mechanisms of X-inactivation and specifically into the action of the mouse antisense *Tsix* transcript. Briefly, only one antisense transcript from around the human *XIST* region was detected, arising from a point downstream of the *XIST* gene and extending upstream but not as far as its murine counterpart, and not covering the promoter region of the human *XIST* gene. Furthermore, a GC-rich region is missing from the 5' end of this antisense gene, a region whose counterpart in the mouse is differentially methylated. Finally, a massive rearrangement of the region downstream of the *XIST* gene was revealed in humans compared to mice.

Conclusions

The major conclusions drawn by Migeon *et al*. are that a functional human *TSIX* transcript probably did exist once upon a time, but that some kind of major X-chromosome rearrangement event(s) severely truncated the 5' end of the antisense gene. This resulted directly or indirectly in the loss of the imprintable CpG island, while also breaking up another postulated gene, the human version of the mouse testis-specific factor *Tsx*, into several pieces and scattering them around the X chromosome. Migeon *et al*. suggest that the human *TSIX* gene cannot get imprinted, that it is expressed after the X-inactivation event, and that its transcript does not interact with the *XIST* promoter, so that it may be a nonfunctioning relic. They argue that, together with other data, this provides evidence for the existence of other as-yet undiscovered factors involved in X-inactivation in humans.

Reporter's comments

The paper includes an excellent and highly readable discussion, with a full overview of the most recent work to date. As far as the implications for mouse X-inactivation are concerned, my reading of this paper is that mouse *Tsix* may reinforce non-random X-inactivation in some of its tissues by the differential imprinting of a CpG island in exon 2 of the *Tsix* gene, and that it suppresses *Xist* gene expression by interacting directly with the promoter - but it is not sufficient on its own to have a role in random X-inactivation.

Table of links

American Journal of Human Genetics

References

1. Migeon BR, Chowdhury AK, Dunston JA, McIntosh I: Identification of *TSIX*, encoding an RNA antisense to human*XIST*, reveals differences from its murine counterpart: implications for Xinactivation. Am J Hum Genet. 2001, 69: 951-960. 0002-9297