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# A new histone variant: macroH2A2

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## Abstract

MacroH2A1 and macroH2A2 are two different histone loci with probable common genetic ancestry.

# Significance and context

X inactivation is the mechanism by which cells of female mammals achieve equivalent levels of X-chromosome gene expression to those of males, and is brought about by the silencing of all but one of their X chromosomes. X inactivation is achieved by several mechanisms - expression of the *Xist* transcript, methylation, and hypoacetylation of histones H3 and H4 - which have been shown to act synergistically. Histones are components of nucleosomes, structures known to be physically associated with particular areas of chromosomes and to directly affect their transcriptional status. Associated with, and enriched in, the inactivated X chromosome is a variant of the core histone H2A, named macroH2A. Its role is unclear but it is known that initation and propagation of X inactivation is a prerequisite, and maintenance by continuing *Xist*expression is a requirement, for association of this histone with the inactive X chromosome.

Chadwick and Willard have now discovered a second macroH2A variant that also associates with the inactive X chromosome. BLAST searches of human expressed sequence tag (EST) databases at GenBank found a sequence similar to that of macroH2A1, and after obtaining the full-length human cDNA the authors also identified a full-length mouse equivalent by a BLAST search. They then carried out subcellular localization studies of the human sequence to determine its function.

# Key results

Chadwick and Willard showed that macroH2A2 is 80% identical at the amino-acid level to macroH2A1 but maps to a different chromosome in humans. The almost identical genomic structure, determined by alignment of the cDNA with the genomic sequence, suggests recent divergence from a common ancestor. MacroH2A2 was shown to co-fractionate with nucleosomes and to co-localize with macroH2A1 in the Barr body (the inactivated X chromosome). A third histone variant, termed H2A-Bbd, that had been previously identified, was found to be depleted in the inactivated X chromosome.

# Conclusions

The authors find that the majority of histone variants are related to histone H2A, and suggest that this might reflect lower structural constraints for the H2A position in the nucleosome, as opposed to H2B or H4 which have no apparent variants. The similar structures of macroH2A1 and macroH2A2 indicate a similar, if not redundant, function. The non-random distribution of these histones led to a search for similar non-random distributions of other histones, but none was found, except for H2A-Bbd, which was found to be deficient in the inactive X chromosome. The authors point out the difficulty in explaining the means by which some histone variants are accumulated in the inactive X whereas others, which have a highly similar amino-acid sequence, are excluded or otherwise randomly distributed; but they suggest as a mechanism for X-inactivation that nucleosome conformation might affect access to the transcription machinery.

# Reporter's comments

This paper demonstrates the success of a systematic database search for similar proteins which is then confirmed by experiments in the 'wet lab'. In this case, no other variants of macroH2A1 could be found by searching the EST databases. As X inactivation occurs very early in embryonic development, and certain of these early embryonic stages may well be under-represented or even absent from EST databases, however, the possibility of other variants of these proteins cannot be excluded at this stage.

# Table of links

Human Molecular Genetics

## References

1. Chadwick BP, Willard HF: Histone H2A variants and the inactive X chromosome: identification of a second macroH2A variant. Hum Mol Genet. 2001, 10: 1101-1113. 0964-6906