Possible roles of conserved non-coding sequences and CpG islands in transcriptional regulation of Hox loci

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Motivation

The mechanism of transcriptional regulation of human Hox clusters is mostly unknown, mainly because the non-coding regions involved in the regulation of these genes are functionally uncharacterized. The purpose of this work is to identify potentially important regulatory regions of human Hox genes. First, we searched for the CNSs (termed “conserved non-coding sequences”) in the Hox genes between Homo sapiens and Fugu rubripes. Since the CNSs identified have remained almost unchanged for about 450 Myr, it is possible that these CNSs may play a critical role, such as a possible promoter, in regulation of Hox genes. Moreover, we tried to locate the CpG islands that have spread over all Hox loci, because the presence of CpG islands in the Hox loci can be frequently associated with the location of transcription start sites. The CpG islands can be also the target of specific histone modifications by which the chromatin structure can be remodeled by switching it from an active to a silent form or vice versa. Thus, it is possible that an evolutionary change of these CpG islands can affect strongly the functional availability of the CNSs, possibly through structural changes of chromatin, for the transcriptional regulation of Hox gene clusters.

Methods

In the present study, we used the tool “Vista Browser” to retrieve the CNSs that were obtained from the pre-computed sequence alignments of non-coding regions between Human and Fugu. We also used the tool “Realigner” to make global alignments of possible promoter regions to examine their sequence conservation. The map of predicted bona fide CpG islands was retrieved from the USCS Genome Browser. For the expression profile data, we used a qRT-PCR database of the GNP (Genome Network Project).

Results

When the nucleotide sequences of the Hox gene clusters were compared between human and fugu, we found that there are a high number of both CNSs and CpG islands in the non-coding regions of each corresponding Hox locus. Moreover, we found that there are two kinds of interesting correlations: one is a negative correlation between the occurrence frequencies of CNSs and CpG islands and the degree of sequence conservation in the entire 5’ flanking regions of Hox loci, and the other is a positive correlation in occurrence frequencies between the CNSs and the CpG islands. The latter correlation observed is of particular interest not only because this observation was made for the first time, but also because it implies direct or indirect interaction between possible promoter sequences and chromatin structures. It eventually leads us to the future perspective that a possible mechanism of transcriptional regulation of Hox genes may be proposed, when functional identification of CNSs can be appropriately made in relation to the promoter activities and when a functional role of CpG islands can be reasonably identified in relation to the chromatin structures.

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