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PALEOENVIRONMENT. THE STONE AGE

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THE IMPORTANCE OF CHANGES TO MICRORNA IN THE EVOLUTION OF *HOMO NEANDERTHALENSIS* AND *HOMO DENISOVA**

MicroRNA (hereafter, miRNA) genes have an important role in the transcriptional regulation of protein-coding genes, modulation of embryonic development, differentiation of embryonic stem cells, tissue formation and other processes. In this paper, we present an integrated study of the fastest evolving miRNAs in Homo neanderthalensis and Homo denisova, whose genomes have recently been sequenced. It has been demonstrated by the analysis of the functions of genes targeted by these miRNAs and changes in the secondary structures of their precursors that mutations in miRNA genes may have played a major role in the evolution of H. neanderthalensis and H. denisova, especially in the development and function of their brains.

Keywords: *Homo neanderthalensis, Homo denisova, miRNA, molecular evolution.*

The nuclear genomes of *Homo neanderthalensis* (*H. n.*) (Green et al., 2010), the first representative of archaic humans who became known as early as the mid-1800s, and *Homo denisova (H. d.)* (Reich et al., 2010), the archaic human who lived 50–45 ka ago according to the carbon dating of fossils found in Denisova Cave in the Altai, were sequenced in 2010 (Derevianko, 2011). The analysis of the genome of *H. d.*, who spread over Southern Siberia and Central Asia identifies them as one of the early human populations directly involved in the origins of modern humans, both anatomically and genetically (Ibid.). Numerous materials obtained from field and laboratory studies, provide evidence that *H. d.* alone created one of the most prominent Upper Paleolithic cultures in Eurasia, which developed for several millennia in parallel with cultures associated with European Neanderthals and Cro-Magnons and was purely autochthonous (Ibid.).

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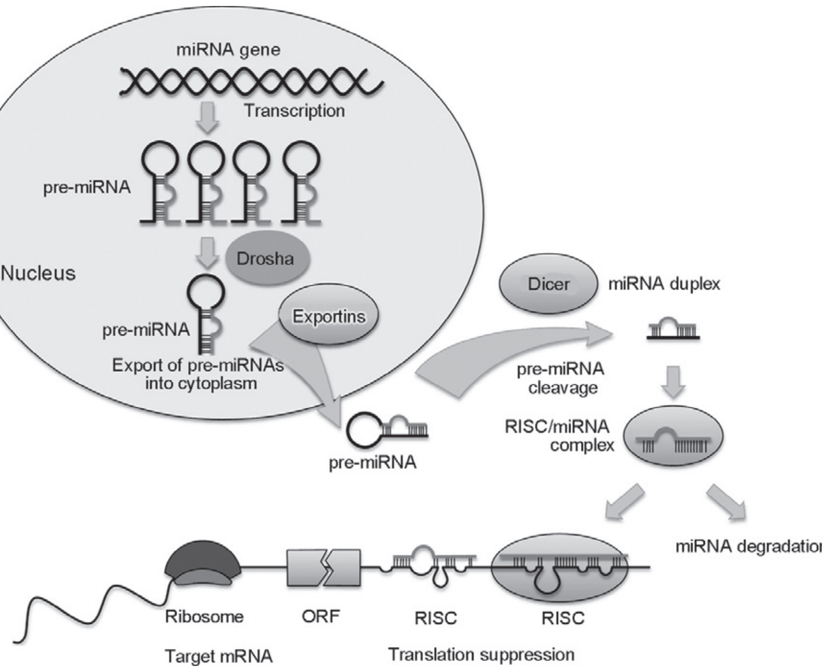

Fig. 1. Generalized canonical pattern of miRNA maturation.

The comparative analysis of the *H. n., H. d.* and *Homo sapiens sapiens* (*H. s. s.*) genomes estimates their split about 0.8 Ma ago (Reich et al., 2010). It is not clear, however, which gene systems were affected by directional selection in the Neanderthals and Denisovans. In an attempt to address this problem, we have made a computer-aided comparison between the *H. s. s.* genome and the *H. n.* and *H. d.* genomes with a focus on the structural and functional organization of the miRNAs they encode. The rationale for such a comparison is as follows (Hu et al., 2011; Somel et al., 2011): (1) the association between the fastest evolutionary changes in the diverging hominids and the changes in gene encoding transcription factors and miRNAs is becoming more and more obvious; (2) it has recently been demonstrated that mutations that occurred in miRNA genes at the time when anatomically modern humans emerged may be associated with changes in the development and function of the central nervous system. The results of our analysis suggest that the *H. n.* and *H. d.* genomes have accumulated differences in some miRNAs, including those regulating the expression of genes functioning in the tissues of the nervous system, uterus, testes, immune system and others, since these two species split.

Modern data on miRNA maturation

A molecule of the miRNA precursor (pre-miRNA) encoded by the corresponding gene is ~80 nucleotides long and forms a hairpin-like secondary structure, which appears as a duplex that ends in a loop*. As a rule, in the beginning, the pre-miRNA is recognized by the protein complex DGCR8/Drosha, then the enzyme Drosha cuts off a distal part of the RNA hairpin stem, then the RNA hairpin with a truncated stem is taken to the cytoplasm with the use of the protein Exportin-5 and binds to the enzyme Dicer, which cuts off the loop (Treiber T., Treiber N., Meister, 2012) (Fig. 1). At the end of the process, a miRNA duplex ~20 nucleotides in length is formed, with one of the strands normally appearing as a mature miRNA (Ibid.; Yang, Lai, 2011). There are many alternative ways of miRNA maturation. For example, it can occur directly from intron** sequences in protein-coding genes (Yang, Lai, 2011). The sequence of a mature miRNA and sometimes its complementary sequence (miRNA*) influence the expression of protein-coding genes by complementary binding to a messenger RNA (mRNA) as part of the RNA-protein complex RISC (RNA-Induced Silencing Complex), thus suppressing translation and/or initiating degradation of the mRNA (Treiber T., Treiber N., Meister, 2012; Yang, Lai, 2011). The efficiency of pre-miRNA cleavage by the protein

*A secondary structure of RNA forms when various RNA regions interact complementarily (that is, their nucleotides meet as follows: A with U and G with C). The complementary regions in the secondary structure resemble the stem of a hairpin (a helix composed of two RNA strands) and alternate with unpaired fragments (loops).

**An intron is the region of a protein-coding gene that contains no information on the amino acid sequence of the protein.