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PARALOGS AND ORDER OF DUPLICATION OF HUMAN ALCOHOL DEHYDROGENASE ENCODING GENES

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ПАРАЛОГИ И ПОРЯДОК ДУПЛИКАЦИИ ГЕНОВ АЛКОГОЛЬДЕГИДРОГЕНАЗЫ ЧЕЛОВЕКА
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Путем филогенетического анализа нуклеотидных последовательностей с помощью метода максимального правдоподобия определен порядок дупликации гомологов генов алкогольдегидрогеназы человека — *ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6* и *ADH7.* По результатам филогенетического анализа построена дендрограмма. Проведена оценка эволюционной дивергенции между последовательностями исследуемых генов.

Ключевые слова: алкогольдегидрогеназа, филогенетический анализ, дупликация, ген.

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By phylogenetic analysis of nucleotide sequences the order of duplication of homologues of human alcohol dehydrogenase genes *ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6* and *ADH7* was determined by Maximum Likelihood method. A dendrogram was constructed according to result of conducted phylogenetic analysis. Evaluation of the evolutionary divergence between sequences of the studied genes was made.

Key words: alcohol dehydrogenase, phylogenetic analysis, duplication, gene.

The executed research is devoted to estimation of evolutionary divergence between sequences of human alcohol dehydrogenase (ADH) encoding genes. Humans have seven ADHs that can carry out the first step in alcohol metabolism. The genes encoding these enzymes all are localized on chromosome 4 in a head-to-tail array about 370 kb long. The enzymes produced from these genes all differ slightly in their activities. There are seven paralogs of ADH; the first ADH1 enzyme has got three subunits A, B and C [1; 6]. The *ADH1A*, *ADH1B*, and *ADH1C* genes1 produce closely related proteins that function as homo- and heterodimers; their kinetic properties, tissue localization, and developmental expression all support major roles in oxidative ethanol metabolism in the liver. The *ADH4* gene is expressed almost exclusively in the liver, where it contributes significantly to ethanol oxidation at higher levels of consumption. The product of the ubiquitously expressed *ADH5* gene is the

glutathione-dependent formaldehyde dehydrogenase (also known as nitrosoglutathione reductase [GSNOR]). The physiological substrates for ADH5 (α-ADH) are compounds (i. e., adducts) formed during the reaction between glutathione and formaldehyde and between glutathione and nitric oxide. The main functions of this enzyme are to oxidize formaldehyde to formic acid and to terminate nitric oxide signaling. The human ADH5 enzyme is nonsaturable with ethanol as a substrate, unless medium-chain fatty acids are present in the assay, and was originally thought to contribute little to ethanol oxidation [1]. However, its relatively high maximal velocity, coupled with its ubiquitous expression pattern and the high concentrations of ethanol found in gastric tissues, has led some researchers to suggest that it plays a significant role in first-pass metabolism.

Although the *ADH6* gene has been identified, there are as yet no physiological data on the functions of the ADH6 enzyme. The *ADH7* gene has a limited expression pattern and mainly is found in endothelial cells, such as those lining the esophageal and stomach tissues, as well as during embryonic development when it may contribute to the metabolism of retinol, a form of vitamin A [3]. In adults, *ADH7* has been implicated in the first-pass metabolism of ethanol taking place in the gastroesophageal tissues, before the ethanol is delivered to the liver via the portal vein.

The aim of this work was to detect the order of duplication of ADH encoding genes.

Material and Methods

The analysis involved seven nucleotide sequences from EMBL [4]. Codon positions included were 1st + 2nd + 3 rd + Noncod-
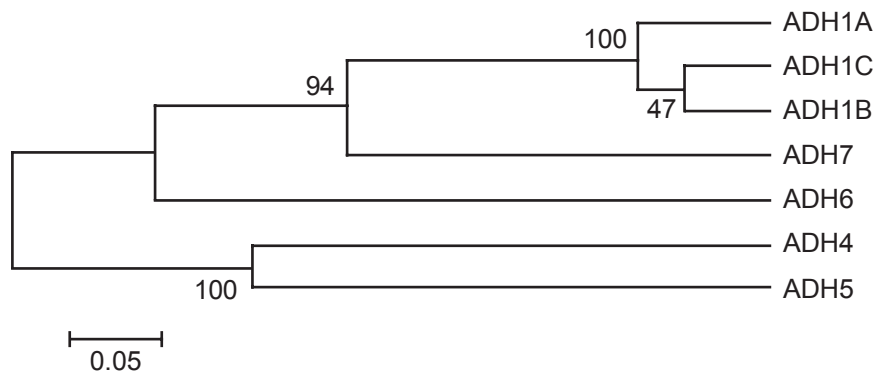

Fig. 1. Molecular phylogenetic analysis by Maximum Likelihood method. Numbers at the knotes are the bootstrap analysis indicators (the existence of a branch is significant at the value of ≥ 70)

ing. All positions containing gaps and missing data were eliminated. There were a total of 1085 positions in the final dataset. The evolutionary history was inferred by using the Maximum Likelihood method based on the Tamura-Nei model. The percentage of trees in which the associated taxa clustered together is shown next to the branches. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach, and then selecting the topology with superior log likelihood value. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. Evolutionary analyses were conducted in MEGA5 [5]. The reliability of the inferred tree was detected by bootstrap test. Reli-

able result was considered at 70 and more [2].

Results and Discussion

The order of ADH duplication is shown in fig. 1.

The estimation of evolutionary divergence between ADH sequences has been accomplished and is shown in table 1.

The tree with the highest log likelihood (-5711.0071) is shown (fig. 1). The number of base substitutions per site from between sequences are shown (table 1). Analyses were conducted using the Maximum Composite Likelihood model. There were studied seven nucleotide sequences in the analysis. Codon positions included were 1st + 2nd + 3rd + Noncoding. All positions containing gaps and missing data were eliminated. A total of 1085 positions were taken into final dataset. Evolutionary analyses were conducted in MEGA5 [5].

Table 1

Estimates of Evolutionary Divergence between ADH Sequences

ADH1A,,
ADH1B,0.048,,
ADH1C,0.059,0.046,,
ADH4,0.463,0.462,0.459,,
ADH5,0.466,0.457,0.458,0.423,,
ADH6,0.42,0.42,0.417,0.489,0.486,,
ADH7,0.351,0.35,0.358,0.521,0.467,0.431,,

In conclusion seven different ADHs that metabolize ethanol have been identified. The products of these genes assemble into dimers in different combinations as well as the genes encoding these enzymes exist in different variants (i. e., alleles).

Ключові слова: алкогольдегідрогеназа, філогенетичний аналіз, дуплікація, ген.

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