EAST EUROPEAN SCIENCE JOURNAL

#8 (36), 2018 część 2

Wschodnioeuropejskie Czasopismo Naukowe
(Warszawa, Polska)
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#8 (36), 2018 part 2

East European Scientific Journal
(Warsaw, Poland)
The journal is registered and published in Poland. The journal is registered and published in Poland.
Articles in all spheres of sciences are published in the journal. Journal is published in **English, German, Polish and Russian.**

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Format - A4, color printing
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Wydrukowano w «Aleje Jerozolimskie 85/21, 02-001 Warszawa, Polska»

Wschodnioeuropejskie Czasopismo Naukowe

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THE ORDER OF DUPLICATION OF HUMAN ALDH ENCODING GENE

Summary: Human aldehyde dehydrogenase (ALDH) causes oxidation of acetaldehyde to acetate. Humans have 18 genes encoding the ALDH enzymes. The order of duplication of human ALDH encoding gene was not completely detected. In this work ALDH encoding gene was analyzed by phylogenetic methods. Genetic distances of paralogs and order of duplication of human ALDH encoding gene were detected.

Key words*: human, aldehyde dehydrogenase (ALDH); encoding genes; enzymes, paralogs*

Introdaction.

In humans the primary pathway of ethanol metabolism involves oxidation to acetaldehyde by the enzyme alcohol dehydrogenase (ADH) [1, 3]. The acetaldehyde then is further oxidized by the enzyme aldehyde dehydrogenase (ALDH) to acetate, which is either excreted in the urine or reincorporated into intermediary metabolism as acetyl-CoA. The hydrogen atoms that are released during these reactions are used to generate a compound called reduced nicotinamide dinucleotide (NADH), with two NADH molecules produced per molecule of acetate generated.

The resulting NADH and acetate are thought to provide both the excess reducing equivalents and excess acetyl-CoA that are needed as starting material for fatty acid synthesis, which results in the development of fatty liver disease if high amounts of alcohol are ingested over time. Both ADH and ALDH exist in different variants with different levels of activity, therefore resulting in different rates of ethanol metabolism [4, 9].

The executed research is devoted to estimation of divergence between sequences of human aldehyde dehydrogenase (ALDH) encoding gene [5, 6]. The acetaldehyde produced by the action of one or more ADH enzymes must be oxidized efficiently by one or more ALDH enzymes in order for the cell/tissue to maintain non-toxic levels of this reactive molecule. Even transient elevation of acetaldehyde can provoke aversive reactions in people whose ALDH activity is reduced either genetically or pharmacologically.

Unlike the human ADH genes, the ALDH genes are not localized to a single chromosome [14]. Humans have 18 genes encoding for members of the ALDH enzyme superfamily [6]. Three of these — ALDH1A1, ALDH1B1, and ALDH2 — are most relevant to acetaldehyde oxidation. The three ALDH enzymes encoded by these genes share more than 68 percent amino acid sequence identity; all three enzymes function in the cell as homotetramers [18]. The ALDH1A1 enzyme is found in the cytosol, whereas both ALDH1B1 and ALDH2 are produced in the nucleus but have leader sequences that direct them to cell components called mitochondria, where they exert their functions in the mitochondrial interior (i.e., the matrix) [6]. Of the three isoenzymes, ALDH2 seems to carry out the most of the oxidation of ethanol-derived acetaldehyde, as demonstrated by the effects of its inhibition by activated forms of the medication disulfiram and by the effects of a functional polymorphism commonly found in East Asian populations (ALDH2*2), in which a critical glutamate is substituted by a lysine residue at position 504 of the precursor protein (487 of the mature protein) (ALDH2-Lys504; rs671). With both disulfiram and the ALDH2*2 enzyme, ALDH2 activity is severely compromised, resulting in increased levels of acetaldehyde, which enters the systemic circulation and initiates the commonly observed facial flushing syndrome [9].

In vitro kinetic analyses also are consistent with the key role of ALDH2, demonstrating that the ALDH2 isoenzyme has the highest catalytic efficiency for acetaldehyde oxidation. The ALDH2*2 allele is relatively common in East Asia (frequencies of 12 to 41 percent), where it has a very strong effect on risk for alcoholism [9].

Thus, people who carry one copy of the inactive allele are strongly protected against alcoholism (odds ratio from 0.5 to 0.12 and homozygotes are almost completely protected [13]. The study of the human genome and latest identification of mutations in

ALDH genes associated with changing of ALDH enzyme activity have led to the identification of many disease associations, such as cataracts (ALDH1A1, ALDH3A1, ALDH18A1), seizures (ALDH7A1), hyperprolinaemia (ALDH4A1), heart disease (ALDH2), alcohol sensitivity (ALDH1A1, ALDH1B1, ALDH2), certain cancers (ALDH2) and a broad array of other metabolic and developmental abnormalities [2, 7, 8, 10].

The order of duplication of human ALDH encoding gene has not been completely detected yet [17]. The purpose of this study was to detect the order of duplication of human ALDH encoding gene and genetic distances between their paralogs.

Material and methods.

The sequences were taken from KEGG GENES Database and National Centre of Biotechnology Information [15, 16]. Each gene sequences were aligned by ClustalW algorithm [11]. The evolutionary history was inferred by using the Maximum Likelihood method based on the Tamura-Nei model. The tree with the highest log likelihood (-19135.3636) is shown. 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. The analysis involved 19 nucleotide sequences. Codon positions included were 1st+2nd+3rd+Noncoding. All positions containing gaps and missing data were eliminated. There were a total of 961 positions in the final dataset. Evolutionary analyses were conducted in MEGA5. The reliability of the inferred tree was detected by bootstrap test [12]. Reliable result was considered at 70 and more.

The order of duplication and genetic distances of human ALDH encoding gene are shown in figure.

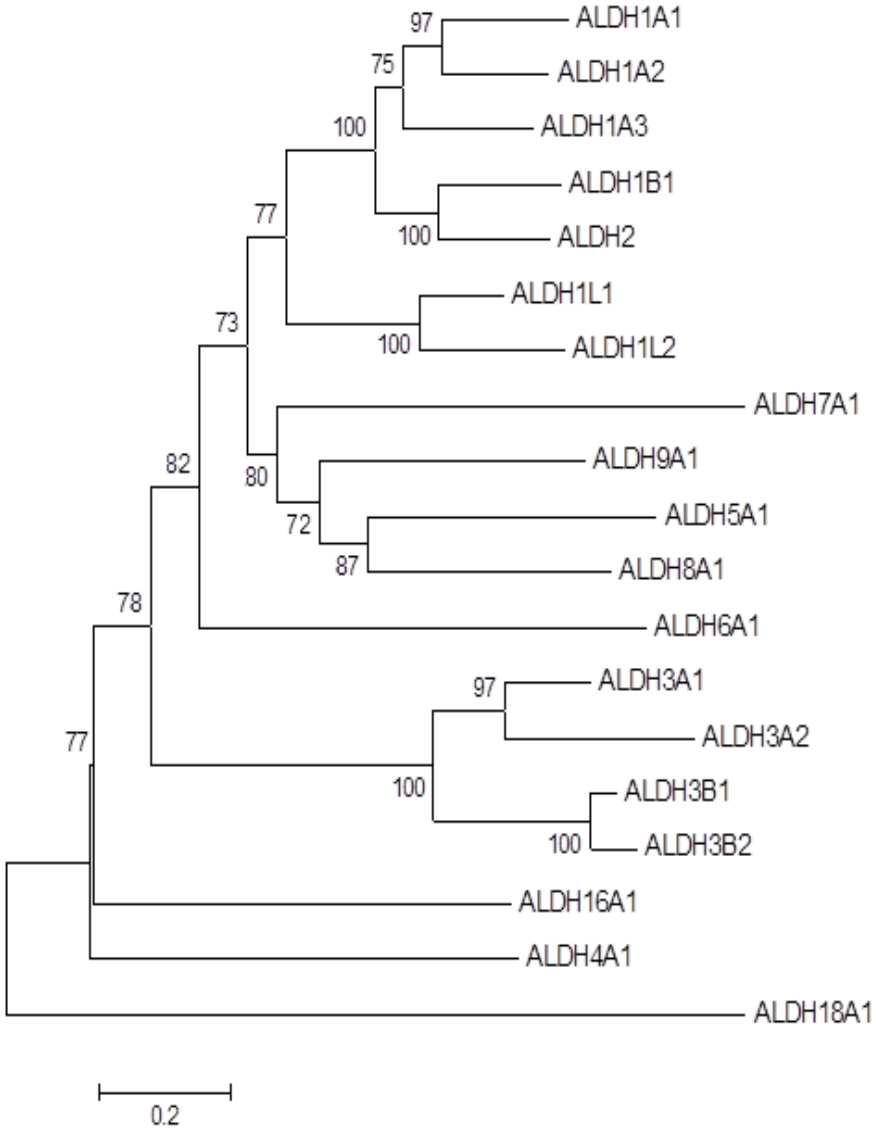

Figure. The order of duplication and genetic distances of human ALDH encoding gene analyzed by Maximum Likelihood method. Numbers at the knots are the bootstrap analysis indicators (the existence of a branch is significant at the value of ≥ 70). The scale displays the length of the branches (substitutions per position).

Results and discussion.

Phylogenetic tree based on duplication of human ALDH encoding gene consists of one branch with ALDH18A1 encoding gene and one clade with other paralogs of ALDH encoding gene. The obtained tree constructed according to bootstrap test is reliable and authentic.

In conclusion different human ALDH encoding genes, their paralogs, order of duplication and genetic distances have been identified and successfully calculated. The products of the studied genes assemble into dimers in different combinations which consequently determine the different vast properties of host organism metabolism.

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