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COMMENTARY

Recommended Nomenclature for the Vertebrate Alcohol Dehydrogenase Gene Family

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ABSTRACT. The alcohol dehydrogenase (ADH) gene family encodes enzymes that metabolize a wide variety of substrates, including ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid peroxidation products. Studies on 19 vertebrate animals have identified ADH orthologs across several species, and this has now led to questions of how best to name ADH proteins and genes. Seven distinct classes of vertebrate ADH encoded by non-orthologous genes have been defined based upon sequence homology as well as unique catalytic properties or gene expression patterns. Each class of vertebrate ADH shares <70% sequence identity with other classes of ADH in the same species. Classes may be further divided into multiple closely related isoenzymes sharing >80% sequence identity such as the case for class I ADH where humans have three class I ADH genes, horses have two, and mice have only one. Presented here is a nomenclature that uses the widely accepted vertebrate ADH class system as its basis. It follows the guidelines of human and mouse gene nomenclature committees, which recommend coordinating names across species boundaries and eliminating Roman numerals and Greek symbols. We recommend that enzyme subunits be referred to by the symbol "ADH" (*a*lcohol *deh*ydrogenase) followed by an Arabic number denoting the class; i.e. ADH1 for class I ADH. For genes we recommend the italicized root symbol "*ADH*" for human and "*Adh*" for mouse, followed by the appropriate Arabic number for the class; i.e. *ADH1* or *Adh1* for class I ADH genes. For organisms where multiple species-specific isoenzymes exist within a class, we recommend adding a capital letter after the Arabic number; i.e. ADH1A, ADH1B, and ADH1C for human α, β, and γ class I ADHs, respectively. This nomenclature will accommodate newly discovered members of the vertebrate ADH family, and will facilitate functional and evolutionary studies. BIOCHEM PHARMACOL **58**;3:389–395, 1999. © 1999 Elsevier Science Inc.

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ADH‡‡ (EC 1.1.1.1) of vertebrates is a cytosolic, dimeric, zinc-containing, NAD-dependent enzyme with a subunit molecular mass of 40 kDa [1]. The enzyme belongs to the large superfamily of medium-chain dehydrogenases/reductases, which also includes polyol dehydrogenases, threonine dehydrogenase, quinone oxidoreductases, and other proteins [2]. The vertebrate ADH family consists of several enzymes able to catalyze the reversible oxidation of a wide variety of endogenous and xenobiotic primary and secondary alcohols to produce the corresponding aldehydes and ketones. Two additional enzyme families that function to interconvert alcohols and aldehydes/ketones are the aldo-keto reductase family, which recently has been named AKR [3], and the short-chain dehydrogenase/reductase family [4]. The aldehyde dehydrogenase family oxidizes a wide variety of aldehydes to carboxylic acids [5].

Protein purification and gene cloning studies in various vertebrate species have led to the identification of seven distinct classes of ADH based upon sequence alignment, phylogenetic tree analyses, catalytic properties, and gene expression patterns [6–8]. Established ADH classes share less than 70% amino acid sequence identity with other ADH classes within the same organism, and some organisms have multiple ADH isoenzymes within a single class that share sequence identities greater than 80%. No single species is presently known that encodes all seven ADH classes. For instance, in the human, only ADH classes I, II,

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‡‡ *Abbreviations:* ADH, alcohol dehydrogenase.

III, IV, and V have been described, and in the mouse only ADH classes I, II, III, and IV have been reported [9] (unpublished data). Class VI ADH has been observed only in the rat and the deer mouse [10, 11], and class VII ADH has been found only in the chicken [12].

ADH amino acid sequence comparisons from multiple vertebrate species indicate divergence from a common ancestor during early vertebrate evolution [13, 14]. This ancestor is evidently class III ADH, which is the only ADH of the medium-chain dehydrogenase/reductase superfamily found also in lower animals, plants, yeast, and bacteria [6, 15]. Class III ADH gene duplications throughout evolution have given rise independently to ADHs specific for vertebrate animals, invertebrate animals, plants, or microorganisms [6, 16]. Class III ADH functions as a glutathione-dependent formaldehyde dehydrogenase in the oxidative elimination of formaldehyde; for example, upon reaction of formaldehyde with glutathione to produce *S*-hydroxymethylglutathione, class III ADH oxidizes the hydroxymethyl group to a formyl group to produce *S*-formylglutathione, which is then the substrate for a hydrolase that regenerates glutathione and produces formate [17, 18]. Class III ADH does not function in ethanol or retinol oxidation [19], but several other classes of vertebrate ADH that have evolved from it have evidently acquired this ability. Thus, much of the analysis of vertebrate ADH function has focused upon the role of these enzymes in ethanol metabolism, particularly as it pertains to human alcohol abuse [20–23], as well as the role of ADH in retinol metabolism for production of the ligand retinoic acid, which controls a nuclear receptor signaling pathway [12, 24–29]. In addition, ADH functions in the metabolism of hydroxysteroids [12, 30], aldehydes produced by lipid peroxidation [24, 31], and compounds derived from dopamine and norepinephrine degradation [32, 33].

ADH NOMENCLATURE

The early identification of multiple ADHs in the horse [34, 35], human [36], mouse [37], and rat [38] led to species-specific nomenclatures that were useful at the time, but have resulted in many non-orthologous ADHs having the same protein and/or gene names, and many orthologous ADHs having different names. An ADH nomenclature was proposed recently based upon the class system that relies primarily upon amino acid sequence homology and secondarily upon catalytic properties or expression patterns to identify orthologs [39]. The nomenclature proposed here is essentially an extension of that idea with the addition of a set of protein and gene names that provide the same name for the same protein/gene in different species as well as the elimination of the use of Roman numerals and Greek symbols, as recommended by the International Nomenclature Workshop [40]. It is recommended that the enzyme "*a*lcohol *deh*ydrogenase" be referred to by the symbol "ADH" followed by an Arabic number rather than a Roman numeral denoting the class. Thus, class I ADH is named ADH1. For multiple isoenzymes within a class, we recommend adding a capital letter after the Arabic number rather than Greek symbols. Thus, the three human class I ADHs previously called ADHα, ADHβ, and ADHγ are named ADH1A, ADH1B, and ADH1C, respectively. For genes, we recommend the italicized root symbol "*ADH*" for human and "*Adh*" for mouse and rat, followed by the appropriate Arabic number for the class, and a letter if necessary for multiple isoenzymes within a class. Thus, the three human class I ADH genes are named *ADH1A*, *ADH1B*, and *ADH1C*, and the single mouse, rat, and deermouse class I ADH genes are named *Adh1*. The new names conform to the guidelines provided by the Human Genome Organization Nomenclature Committee [41], the International Committee on Standardized Genetic Nomenclature for Mice [42], and the Rat Genome Database (http://ratmap.gen.gu.se/). The gene nomenclature for other vertebrate organisms is not addressed here.

The new ADH gene and protein nomenclature for humans and several rodent species, along with the old names, is shown in Table 1. As indicated, ADH1 (class I ADH) consists of three isoenzymes encoded by unique genes in the human, but only one enzyme and gene in the mouse, rat, and deer mouse. Mammalian ADH2 (class II ADH), ADH3 (class III ADH), ADH4 (class IV ADH), ADH5 (class V ADH), and ADH6 (class VI ADH) are each encoded by only one gene in all mammalian species where they have been demonstrated to exist, except the rabbit which has two forms of ADH2 [43]. ADH7 (class VII ADH) has not been identified yet in mammals. DNA sequences of pseudogenes have been reported for human and mouse ADH3 [44, 45] as well as mouse ADH1 [46]. We recommend that the human ADH3 pseudogene presently named *ADH5P1* in the Human Genome Database be renamed *ADH3P1*, and the mouse ADH3 pseudogene presently named *Adh5-ps1* in the Mouse Genome Database be renamed *Adh3-ps1*. The current name for the mouse ADH1 pseudogene (*Adh1-ps1*) in the database does reflect the correct class of ADH and should be maintained. These names follow the guidelines established for human and mouse pseudogene nomenclature [41, 42].

Using this nomenclature, we recommend names for the various vertebrate ADH proteins for which existing sequence data have placed them within a certain class (Table 2). Orthologs for ADH1, ADH2, ADH3, ADH4, and ADH6 have been found, whereas ADH5 has been observed only in humans and ADH7 only in chickens. Multiple isoenzymes found for ADH1 (human, horse, baboon, monkey, and lizard), ADH2 (rabbit), and ADH3 (codfish and shark) are designated by a capital letter following the Arabic number. The designations for these isoenzymes are based on conversion of previously existing Greek symbols to capital letters (i.e. human αβγ, baboon βγ, and monkey α), use of previously existing capital letter designations (i.e. horse E and S), conversion of previously existing number designations to capital letters (i.e. rabbit II-1 and II-2), or conversion of previously existing lower case letters to

TABLE 1. New and old nomenclatures for human and rodent ADH proteins and genes*

Organism	Class I	Class II	Class III	Class IV	Class V	Class VI	Class VII
New nomenclature							Not yet found in mammals
Human							
Protein	ADH1A ADH1B ADH1C	ADH2	ADH3	ADH4	ADH5		
Gene	*ADH1A* *ADH1B* *ADH1C*	*ADH2*	*ADH3*	*ADH4*	*ADH5*		
Pseudogene			*ADH3P1*				
Mouse							
Protein	ADH1	ADH2	ADH3	ADH4			
Gene	*Adh1*	*Adh2*	*Adh3*	*Adh4*			
Pseudogene	*Adh1-ps1*		*Adh3-ps1*				
Rat							
Protein	ADH1	ADH2	ADH3	ADH4		ADH6	
Gene	*Adh1*	*Adh2*	*Adh3*	*Adh4*		*Adh6*	
Deer mouse							
Protein	ADH1					ADH6	
Gene	*Adh1*					*Adh6*	
Old nomenclature							
Human							
Protein	α β γ	π	χ	σ or μ	Class V		
Gene	*ADH1* *ADH2* *ADH3*	*ADH4*	*ADH5*	*ADH7*	*ADH6*		
Pseudogene			*ADH5P1*				
Mouse							
Protein	A_2	Class II	B_2	C_2			
Gene	*Adh-1*	?	*Adh-2*, *Adh5*	*Adh-3*, *Adh7*			
Pseudogene	*Adh1-ps1*		*Adh5-ps1*				
Rat							
Protein	ADH-3	Class II	ADH-2	ADH-1		Class VI	
Gene	?	?	?	?		?	
Deer mouse							
Protein	A_2					Class VI	
Gene	*Adh-1*					*Adh-2*	

* References for ADH sequences: human [44, 47–60]; mouse [9, 45, 46, 61–63] and unpublished data; rat [10, 64–67]; and deer mouse [11].

capital letters (i.e. lizard a and b, codfish h and l, shark a and b). Since the existence of multiple isoenzymes within certain ADH classes is species-specific, and since such isoenzymes may serve species-specific functions, the naming of these forms using capital letters is species-specific. The letter designation is not intended to identify isoenzyme orthologs across species. Instead, orthologs are identified simply by the number designation following the symbol ADH.

For many organisms, additional ADHs not described here are known to exist by enzyme activity assays, but lack sequence data to place them definitively within a class. We recommend that those enzymes which have catalytic properties and tissue distribution profiles of a certain known class be referred to as ADH1-like, ADH2-like, etc. until sequence data exist to identify them for certain. A good example is the deer mouse, which by starch gel analysis appears to have ADH3-like and ADH4-like enzyme activities [11], but no sequence data for these two activities. The establishment of additional classes (i.e. ADH8, ADH9, etc. if necessary) should be undertaken with great care only when complete amino acid sequence data and other properties indicate a substantial difference from the existing classes.

Several polymorphic variants of human ADH1 exist that are encoded as alleles from the same gene as reviewed previously [39]. A new nomenclature covering these variants is recommended (Table 3). The commonly studied β_1, β_2, and β_3 variants, which differ in their efficiency for ethanol oxidation, are now named ADH1B1, ADH1B2, and ADH1B3, respectively. The variants γ_1 and γ_2 are now named ADH1C1 and ADH1C2, respectively. No α variants have been reported. The gene names are italicized versions of these protein names with an asterisk preceding the allele number designation (i.e. *ADH1B*1*, *ADH1B*2*, etc.) as recommended by the Human Genome Organiza-

TABLE 2. Proposed nomenclature of known vertebrate ADHs*

Organism	Class I	Class II	Class III	Class IV	Class V	Class VI	Class VII
Human	ADH1A ADH1B ADH1C	ADH2	ADH3	ADH4	ADH5		
Mouse	ADH1	ADH2	ADH3	ADH4			
Rat	ADH1	ADH2	ADH3	ADH4		ADH6	
Deer mouse	ADH1					ADH6	
Horse	ADH1E ADH1S		ADH3				
Baboon	ADH1B ADH1C						
Monkey	ADH1A						
Rabbit	ADH1	ADH2A ADH2B	ADH3				
Gopher	ADH1						
Chicken	ADH1		ADH3				ADH7
Quail	ADH1						
Ostrich	ADH1	ADH2					
Kiwi	ADH1						
Alligator	ADH1						
Cobra	ADH1						
Lizard	ADH1A ADH1B		ADH3				
Frog	ADH1			ADH4			
Codfish	ADH1		ADH3H ADH3L				
Shark			ADH3A ADH3B				
Hagfish			ADH3				

* References for ADH sequences: human, mouse, rat, and deer mouse provided in Table 1; horse [68, 69]; baboon [70, 90] and unpublished data; monkey [71]; rabbit [43, 72]; gopher [73]; chicken [74, 75]; quail [76]; ostrich [77, 78]; kiwi [79]; alligator [80]; cobra [81]; lizard [82, 83]; frog [8, 13]; codfish [84, 85]; shark [86]; and hagfish [87].

tion Nomenclature Committee [41]. This nomenclature will ensure that all these variants are properly identified as closely related forms of ADH1.

The three closely related subunits (including polymorphic variants) of human ADH1 can hybridize to form all possible homodimers and heterodimers. We recommend that such dimeric forms be designated with a slash between the subunit names. A few examples are as follows: ADH1B1/B1, ADH1B1/B2, and ADH1B2/B2; for brevity, these can also be referred to as B1B1, B1B2, and B2B2, respectively, which replaces the previous names $\beta_1\beta_1$, $\beta_1\beta_2$, and $\beta_2\beta_2$, respectively. Likewise, homodimers and heterodimers of the two closely related subunits of horse ADH1 should be referred to as ADH1E/E, ADH1E/S, and ADH1S/S, or for brevity EE, ES, and SS, respectively.

Overall, this nomenclature allows easy identification of vertebrate ADH protein/gene orthologs, facilitates recognition of ADH class distinctions and isozyme distinctions, and accounts for expansion of the family in the future. The last point may become critical relatively soon since it is quite possible that human and mouse genome sequencing efforts will identify several new ADHs.

TABLE 3. New and old nomenclatures for human ADH1 polymorphic variants*

	Protein	Gene
New	ADH1A	*ADH1A*
	ADH1B1	*ADH1B*1*
	ADH1B2	*ADH1B*2*
	ADH1B3	*ADH1B*3*
	ADH1C1	*ADH1C*1*
	ADH1C2	*ADH1C*2*
Old	α	*ADH1*
	β_1	*ADH2*1*
	β_2	*ADH2*2*
	β_3	*ADH2*3*
	γ_1	*ADH3*1*
	γ_2	*ADH3*2*

* References for sequences: α [49]; β_1 [50]; β_2 [88]; β_3 [89]; γ_1 [51]; and γ_2 [51].

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