report

Revised nomenclature for the mammalian long-chain acyl-CoA synthetase gene family

Douglas G. Mashek,* Karin E. Bornfeldt,† Rosalind A. Coleman,[1,*] Johannes Berger,§ David A. Bernlohr, Paul Black,†† Concetta C. DiRusso,†† Steven A. Farber,§§ Wen Guo,*** Naohiro Hashimoto,††† Varsha Khodiyar,§§§ Frans A. Kuypers,**** Lois J. Maltais,†††† Daniel W. Nebert,§§§§ Alessandra Renieri,***** Jean E. Schaffer,††††† Andreas Stahl,§§§§§ Paul A. Watkins,****** Vasilis Vasiliou,†††††† and Tokuo T. Yamamoto§§§§§§**

Departments of Nutrition and Pediatrics,* University of North Carolina, Chapel Hill, NC 27599; Department of Pathology,† University of Washington, Seattle, WA 98195; Medical University of Vienna,§ Brain Research Institute, Neuroimmunology, A-1090 Vienna, Austria; Department of Biochemistry, Molecular Biology, and Biophysics,** University of Minnesota, Minneapolis, MN 55455; Ordway Research Institute, Inc.,†† Albany, NY 12208; Department of Microbiology and Immunology,§§ Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107; Department of Medicine,*** Boston University School of Medicine, Boston, MA 01228; Tissue Stem Cell Research Team,††† Mitsubishi Kagaku Institute of Life Sciences, Machida, Tokyo 194-8511, Japan; The Human Genome Organization Gene Nomenclature Committee,§§§ Department of Biology, University College London, London NW1 2HE, UK; Children's Hospital Oakland Research Institute,**** Oakland, CA 94609; Mouse Genomic Nomenclature Committee,†††† The Jackson Laboratory, Bar Harbor, ME 04609; Department of Environmental Health and Center for Environmental Genetics,§§§§ University of Cincinnati Medical Center, Cincinnati OH 45267-0056; Medical Genetics,***** University of Siena, Policlinico Le Scotte, 53100 Siena, Italy; Department of Internal Medicine,††††† Washington University School of Medicine, St. Louis, MO 63110; Research Institute,§§§§§ Palo Alto Medical Foundation, Palo Alto, CA 94301; Kennedy Krieger Institute,****** Baltimore, MD 21205; Molecular Toxicology and Environmental Health Sciences Program,†††††† Department of Pharmaceutical Sciences, University of Colorado Health Sciences Center, Denver, CO 809262; and Center for Advanced Genome Research,§§§§§§ Institute of Development, Aging, and Cancer, Tohoku University, Sendai 981-8555, Japan

Abstract By consensus, the acyl-CoA synthetase (ACS) community, with the advice of the human and mouse genome nomenclature committees, has revised the nomenclature for the mammalian long-chain acyl-CoA synthetases. ACS is the family root name, and the human and mouse genes for the long-chain ACSs are termed *ACSL1,3–6* and *Acsl1,3–6*, respectively. Splice variants of ACSL3, -4, -5, and -6 are cataloged. Suggestions for naming other family members and for the nonmammalian acyl-CoA synthetases are made.—Mashek, D. G., K. E. Bornfeldt, R. A. Coleman, J. Berger, D. A. Bernlohr, P. Black, C. C. DiRusso, S. A. Farber, W. Guo, N. Hashimoto, V. Khodiyar, F. A. Kuypers, L. J. Maltais, D. W. Nebert, A. Renieri, J. E. Schaffer, A. Stahl, P. A. Watkins, V. Vasiliou, and T. T. Yamamoto. **Revised nomenclature for the mammalian long-chain acyl-CoA synthetase gene family. *J. Lipid Res.* 2004.** 45: **1958–1961.**

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In mammals, long-chain acyl-CoA synthetase (ACSL) catalyzes the initial step in cellular long-chain fatty acid metabolism. In this reaction, ACSL ligates fatty acids to CoA in a two-step reaction (1, 2): *1*) fatty acid + ATP → fatty acyl-AMP + pyrophosphate; *2*) fatty acyl-AMP + CoA → fatty acyl-CoA + AMP. Since the cDNA encoding ACSL was cloned in 1990 (3), five isoforms of ACSL differing in their substrate preferences, enzyme kinetics, cellular and organelle locations, and regulation have been identified and characterized in rodents and humans. Although our knowledge of the ACSL family has advanced greatly in recent years, inconsistencies regarding ACSL nomenclature have led to confusion in the scientific literature. To alleviate the confusion regarding ACSL naming and numbering, a group of researchers studying the *ACSL* genes, in coordination with the human and mouse genome nomenclature committees (HGNC and MGNC), have revised the previous nomenclature system. The purpose of this report is to present the revised and approved nomenclature for the *ACSL* gene family in humans and rodents and to en-

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[1] To whom correspondence should be addressed.
e-mail: rcoleman@unc.edu

courage scientists referencing ACSL to adhere to the new nomenclature.

NOMENCLATURE

The HGNC and MGNC have chosen ACS as the family root name: synthetase, rather than ligase or synthase, was selected for the activity and acyl-CoA for the product. Synthetase refers to a reaction that uses ATP and forms an acyl-AMP intermediate. Despite the fact that the best known substrates are fatty acids, the entire spectrum of natural and xenobiotic substrates used by ACSL and other ACS subfamilies is not fully known, but it certainly encompasses substrates that are not fatty acids. For example, xenobiotic carboxylic acids (4) and bile acids (5) are substrates. Thus, the use of acyl-CoA is preferred because it does not limit ACS substrates to fatty acids.

The ACS family includes enzymes that prefer short-, medium-, long-, or very long-chain fatty acids as substrates. Although related family members exhibit considerable overlap in their use of fatty acids of similar chain lengths, differences in the amino acid sequences of the AMP/ATP and fatty acid binding motifs distinguish subfamilies previously designated as acetyl-CoA synthetase, medium-chain acyl-CoA synthetase, long-chain acyl-CoA synthetase, very long-chain acyl-CoA synthetase, bubblegum (lipidosin), and scFat2p (6). Earlier studies used the term LACS (long-chain ACS) to distinguish ACS isoforms that act on long-chain fatty acids; however, the revised nomenclature recommends a hierarchical approach with ACS as the root symbol followed by a letter to specify the length of fatty acid acted upon. The HGNC and MGNC have approved the ACSL mammalian gene nomenclature.

As standard guidelines for human and rodent gene nomenclature, the human symbols are entirely capitalized (e.g., *ACSS*, *ACSM*, *ACSL*) and the rodent symbols are lowercase with the exception of the first letter (e.g., *Acss*, *Acsm*, *Acsl*) (7). The HGNC recommends that gene and allele symbols be italicized and protein symbols be represented in nonitalicized fonts. Italics need not be used in gene catalogs. Proteins are shown in uppercase letters. To distinguish between mRNA, genomic DNA, and cDNA, the relevant prefix should be written in parentheses: (mRNA) *ACSL1*, (gDNA) *ACSL1*, (cDNA) *ACSL1*.

ORTHOLOGY

Improper designation of *ACSL1*, the first cloned human ACSL family member, has caused considerable confusion. Although two separate genes were originally reported to encode FACL1 (fatty acid-CoA ligase) and FACL2 (8, 9), it was subsequently discovered that *FACL1* and *FACL2* are the same gene. Therefore, the revised nomenclature system now identifies *FACL1/FACL2* as human *ACSL1*. As a consequence of the original human nomenclature, the previously reported *FACL2* was not orthologous to rodent *ACS2*. To correct this problem, the former rodent *ACS2* has been redesignated as *Acsl6* because it shares highest sequence identity with human *ACSL6* [originally characterized as *LACS5* (10)], as shown in **Table 1**. Hence, according to the revised nomenclature system, there is no *ACSL2* in humans or in rodents.

SPLICE VARIANTS

The *ACSL3*, *ACSL4*, *ACSL5*, and *ACSL6* genes encode mRNAs and proteins that have splice variants. The human *ACSL3* gene encodes two transcripts with varying 5′ untranslated regions, ACSL3 variant 1 (*ACSL3_v1*) and

TABLE 1. Revised nomenclature for the long-chain acyl-CoA synthetase gene family

Approved Nomenclature (Chromosome Location)			Previous Nomenclature and Aliases	Gene and Protein Sequences		
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Human	Rat	Mouse		Human	Rat	Mouse
ACSL1 (4q34-q35)	Acsl1 (16q11)	Acsl1 (8 B1.1)	FACL1, FACL2, LACS, LACS1, ACS1, LACS2	NM_001995, NP_001986	NM_012820, NP_036952	NM_007981, NP_032007
ACSL3 (2q34-q35)	Acsl3 (9q33)	Acsl3 (1 C4)	FACL3, ACS3, PRO2194	variant 1 / variant 2: NM_004457 / NM_203372 NP_004448 / NP_976251.1	NM_057107, NP_476448	XM_129894, XP_129894
ACSL4 (Xq22.3-q23)	Acsl4 (Xq14)	Acsl4 (X F1)	FACL4, ACS4, LACS4, MRX63	variant 1 / variant 2: NM_004458 / NM_022977 NP_004449 / NP_075266	NM_053623, NP_446075	NM_019477, NP_062350
ACSL5 (10q25.1-q25.2)	Acsl5 (1q55)	Acsl5 (19 D2)	FACL5, ACS2, ACS5	variant 1 / variant 2 / variant 3: NM_016234 / NM_203379 / NM_203380 NP_057318 / NP_976313 / NP_976314	NM_053607, NP_446059	BC031544, AAH31544
ACSL6 (5q31)	Acsl6 (10q22)	Acsl6 (11 B1.3)	FACL6, ACS2, LACS2, LACS5, KIAA0837	variant 1 / variant 2: NM_015256 / AB020644 NP_056071 / BAA74860	variant 1 / variant 2: NM_130739 / — NP_570095 / AY625254	variant 1 / variant 2: NM_144823 / AY167035 NP_659072 / AAO38689

This table is a modified version of that posted on the Human Genome Nomenclature Committee website (http://www.gene.ucl.ac.uk/nomenclature/genefamily/acs.html). The final nomenclature for the other ACS subfamilies is still under consideration.

ACSL3_v2 (Table 1). Both transcripts encode the same ACSL3 protein. Human ACSL3 is homologous to rat and mouse ACSL3. Likewise, human ACSL4 is homologous to rat and mouse ACSL4. In humans, two splice variants of ACSL4 have been demonstrated (11). Compared with *ACSL4_v1*, *ACSL4_v2* contains an earlier in-frame start codon that encodes a hydrophobic N terminus that is 41 amino acids longer. Human ACSL5, which is homologous to rat and mouse ACSL5, has three splice variants. *ACSL5_v1* encodes a protein with a 56 amino acid longer N terminus (ACSL5a) compared with the protein encoded by both *ACSL5_v2* and *ACSL5_v3*, which encode the same shorter protein (ACSL5b). Splice variants of *ACSL6* have been identified in humans and rodents (unpublished observations). The *ACSL6_v1* and *ACSL6_v2* transcripts of human *ACSL6* differ in amino acid residues 306–331 because they are encoded by exon 14 and exon 13, respectively, as a result of alternative exon use.

The numerous examples of *ACSL* genes encoding multiple proteins having different N-terminal and/or internal regions suggest that additional splice variants will be identified. The HGNC recommends that new variants of *ACSL1–6* or *Acsl1–6* should be named splice variants of a gene (e.g., *ACSL5_v4*) if they use some of the same exons as an existing ACSL isoform (http://www.gene.ucl.ac.uk/nomenclature/guidelines.html). For genes with multiple promoters, the alternative promoters are designated by the addition of the lowercase letters "pr" (e.g., symbol: *ACSL6_pr1*; name: long-chain acyl-CoA synthetase 6, promoter 1). Proteins translated from mRNA splice variants may be distinguished by lowercase suffixes (e.g., ACSL5a and ACSL5b).

OTHER ACS FAMILY MEMBERS

It should be noted that proteins of the family previously named very long-chain ACS (VLCS) (6) are also known as fatty acid transport proteins (FATPs). These are included in the superfamily of proteins encoded by members of the solute carrier gene family, whose currently approved gene symbols are *SLC27A1–6* (12). The VLCS/FATPs also have acyl-CoA synthetase enzymatic activity (13–16). Thus, these proteins may play a dual role in the transport and esterification of their substrates.

Some amino acid sequences are shared between ACSL subfamily members and other enzymes, such as acetyl-CoA synthetase, bubblegum, and scFat2p, and related proteins (6). As yet, a standardized nomenclature has not been formulated for these other enzymes or for the yeast and bacterial ACS families. Each member of the extended ACS family has the ATP/AMP binding motif that is a hallmark of adenylate-forming enzymes as well as a fatty acid binding motif defined in the bacterial homolog FadD (17).

CONCLUSIONS

Previous publications have used a multitude of names for members of the ACSL family, which has led to confusion among investigators. Implementation of the revised nomenclature proposed here for the mammalian ACSL gene family will reduce disparities and render our literature more accessible to us as well as to those outside the field.

The use of *ACSS* and *ACSM* root symbols for the acetyl-CoA and medium-chain acyl-CoA synthetases, respectively, should also be considered. The VLCS/FATP/*SLC27A1–6* and the bubblegum/lipidosin subfamily members use as substrates long-chain and very long-chain fatty acids and/or bile acids; thus, it is not yet clear what prefix should be used to designate these enzymes. Further consultation is needed among scientists who study these proteins. We propose that those working on ACS genes in other organisms also consider adopting a similar nomenclature.

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