report

# A revised nomenclature for mammalian acyl-CoA thioesterases/hydrolases

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**Abstract Acyl-CoA thioesterases, also known as acyl-CoA hydrolases, are a group of enzymes that hydrolyze CoA esters such as acyl-CoAs (saturated, unsaturated, branched-chain), bile acid-CoAs, CoA esters of prostaglandins, etc., to the corresponding free acid and CoA. However, there is significant confusion regarding the nomenclature of these genes. In agreement with the HUGO Gene Nomenclature Committee and the Mouse Genomic Nomenclature Committee, a revised nomenclature for mammalian acyl-CoA thioesterases/hydrolases has been suggested for the 12 member family. The family root symbol is ACOT, with human genes named ACOT1–ACOT12, and rat and mouse genes named Acot1–Acot12. Several of the ACOT genes are the result of splicing events, and these splice variants are cataloged.—**Hunt, M. C., J. Yamada, L. J. Maltais, M. W. Wright, E. J. Podesta, and S. E. H. Alexson. **A revised nomenclature for mammalian acyl-CoA thioesterases/hydrolases. *J. Lipid Res.* 2005.** 46: **2029–2032.**

**Supplementary key words** fatty acid metabolism • coenzyme A • peroxisomes

Acyl-CoA thioesterases (EC 3.1.2.1. and EC 3.1.2.2.) are enzymes that catalyze the hydrolysis of CoA esters of various molecules to the free acid plus CoA (1, 2). These enzymes have also been referred to in the literature as acyl-CoA hydrolases, acyl-CoA thioester hydrolases, and palmitoyl-CoA hydrolases. The reaction carried out by these enzymes is as follows:

$$\text{CoA ester} + H_2O \rightarrow \text{free acid} + \text{coenzyme A} \qquad \textit{(Eq. 1)}$$

These enzymes are distinct from long-chain acyl-CoA synthetases in that they hydrolyze the CoA-activated molecule to the free acid and CoA, whereas long-chain acyl-CoA synthetases ligate fatty acids to CoA, to produce the CoA ester (3). Although the functions for many of the acyl-CoA thioesterases in this gene family are not fully understood, they are considered to regulate intracellular levels of CoA esters, the corresponding free acid, and coenzyme A and, in turn, cellular processes involving these compounds. Over the years, several different groups have identified and cloned unrelated acyl-CoA thioesterases, which has led to many inconsistencies regarding the nomenclature in the literature. In view of this, we have put together the revised and approved nomenclature for the acyl-CoA thioesterase gene family in human, mouse, and rat to avoid confusion in this field (**Table 1**). This nomenclature has been devised in cooperation with the HUGO Gene Nomenclature Committee and the Mouse Genomic Nomenclature Committee and proposes the use of *ACOT* as the root symbol for the acyl-CoA thioesterase gene family. Therefore, it is recommended and hoped that the new nomenclature of ACOT will be accepted and used by all scientists.

## NOMENCLATURE

Acyl-CoA thioesterases are referred to in the literature as acyl-CoA hydrolases, but as the reaction carried out by these enzymes is the cleavage of a thioester bond, we believe that the name acyl-CoA thioesterase, gene symbol *ACOT-*, is more appropriate for the nomenclature of these enzymes.

The substrate specificity for these enzymes is rather diverse, with some members hydrolyzing long-chain saturated and unsaturated acyl-CoAs (4–9), whereas others hydrolyze a broad variety of CoA-activated substrates, in-

*Manuscript received 3 June 2005 and in revised form 20 June 2005.*

*Published, JLR Papers in Press, July 1, 2005.*
*DOI 10.1194/jlr.E500003-JLR200*

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TABLE 1. Revised nomenclature for the acyl-CoA thioesterase (ACOT/Acot) gene family

| Approved Nomenclature (Chromosome Location) | | | Previous Nomenclature and Aliases | Accession Number Gene and Protein Sequences | | |
|---|---|---|---|---|---|---|
| Human | Rat | Mouse | | Human | Rat | Mouse |
| ACOT1 (14q24.3) | Acot1 (6q31) | Acot1 (12 D3) | CTE-I, LACH2, ACH2 | DQ082754 | Y09334<br>NM_031315 | Y14004<br>NM_012006 |
| ACOT2 (14q24.3) | Acot2 (6q31) | Acot2 (12 D3) | MTE-I, PTE2, ARTISt/p43 | DQ082755 | AB010429 | NM_134188 |
| | Acot3 (6q31) | Acot3 (12 D3) | PTE-Ia, Pte2a (variant 5:1) | | XM_234399 | variant 1, AY563097 |
| | | | | | XP_234399 | NP_599007 |
| | | | (variant 5:2) | | | variant 2, AY563098 |
| ACOT4 (14q24.3) | Acot4 (6q31) | Acot4 (12 D3) | PTE-Ib, Pte2b | NM_152331 | XM_234398<br>XP_234398 | NM_134247 |
| | Acot5 (6q31) | Acot5 (12 D3) | PTE-Ic | | | AY563099<br>NM_145444 |
| ACOT6 | Acot6 (6q31) | Acot6 (12 D3) | PTE-Id | DQ082756 | | AY999300 |
| ACOT7 (1p36.31-p36.11) | Acot7 (5q36) | Acot7 (4 E2) | BACH, CTE-II, ACT, ACH1, BACHa | variant 1, NM_007274 | Y09332 | AB049821 |
| | | | MTE-II, LACH1, BACHb | variant 2, AB074417 BAC20176.1 | D88891 | AB088411 BAC20217.1 |
| | | | BACHc | variant 3, AB074418 BAC20177.1 | | AB088412 BAC20218.1 |
| | | | BACHd | variant 4, AB074419 BAC20178.1 | | |
| | | | BACHa/X | variant 5, AB074415 BAC20174.1 | | |
| | | | BACHa/Xi | variant 6, AB074416 BAC20175.1 | | |
| | | | 50 kDa BACH | variant 7 | | AB207243 |
| ACOT8 (20q12-q13.1) | Acot8 (3q42) | Acot8 (2 H3) | PTE-2, Pte1, hTE, hACTEIII, PTE1 | NP_005460.2 NM_005469 | AF452100 AAL66289.1 | NM_133240 NP_573503.1 |
| ACOT9 (Xp22.11) | Acot9 (Xq22) | Acot9 (X F3) | MT-ACT48, act48.1, Acate2, U8, MTE-2, CGI-16, p48 | AF132950 | BC085822 AAH85822 | AJ238893 |
| | | Acot10 (15 A3) | MT-ACT48, act48.2, Acate3 | | | AJ238894 |
| ACOT11 (1p32.3) | Acot11 (5q34) | Acot11 (4 C7) | BFIT, BFIT1, Them1, MGC25974, KIAA0707, BFIT2 | variant 1, AF416921<br>variant 2, AF416922 | XM-233269 | AF416923 |
| ACOT12 (5q14.1) | Acot12 (2q12) | Acot12 (13 C3) | CACH-1, MGC105114, mCACH-1, CACH | AB078619 Q8WYK0 | NM_130747 | AB078618 |

Please see the Human Genome Nomenclature Committee website (http://www.gene.ucl.ac.uk/nomenclature/genefamily/acot.html) for further information on the ACOT/Acot gene family.

cluding bile acids, branched-chain fatty acids, prostaglandins (Acot8) (10, 11), or acetyl-CoA (12, 13).

According to human, mouse, and rat gene nomenclature guidelines, human symbols are entirely capitalized (e.g., ACOT1, ACOT2, etc.), whereas the mouse and rat symbols are lowercase except for the first letter (e.g., Acot1, Acot2, etc.). Gene and allele symbols are italicized, whereas protein symbols are nonitalicized uppercase letters. 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) *ACOT1*, (gDNA) *ACOT1*, (cDNA) *ACOT1*.

## GENE CLUSTERS/FAMILIES

The mouse has six distinct genes (previously called type-I acyl-CoA thioesterases), all located in a cluster within 120 kb on mouse chromosome 12 D3 (6, 14). These six gene products result in one protein localized in cytosol (ACOT1) (4), one protein in mitochondria (ACOT2) (15), and four proteins in peroxisomes (ACOT3–ACOT6) (6). The proteins resulting from these genes are all encoded by three exons. In human, however, there are four distinct genes on chromosome 14q24.3 that encode two cytosolic enzymes (ACOT1 and ACOT6), one mitochondrial enzyme (ACOT2), and one peroxisomal enzyme (ACOT4) (14). ACOT1, ACOT2, and ACOT4 open reading frames are encoded by three distinct exons. However, the *ACOT6* gene in human encodes a protein that is shorter than the other ACOT proteins, and translation appears to start at a methionine at the end of exon 2. The human gene family contains one expressed pseudogene, encoded on chromosome 19, that is an intronless gene and contains many in-frame stop codons. In the case of *ACOT2*, this cDNA has previously been cloned as a peroxisomal acyl-CoA thioesterase (PTE2) (16). ACOT2 contains a C-terminal −SKV, which is a variant of the peroxisomal type 1 targeting signal of

−SKL, which targets proteins to peroxisomes (17). Database analysis shows that, in fact, ACOT2 contains 62 extra amino acids at its N-terminal end, which function as a mitochondrial targeting sequence that targets the protein to mitochondria (M. C. Hunt et al., unpublished results). ACOT2, in addition to being identified as a mitochondrial acyl-CoA thioesterase (15), was also identified as a phosphoprotein called ARTISt involved in steroid synthesis (18). Recently, ACOT2 involvement in a novel pathway of arachidonic acid release in the hormonal regulation of steroidogenesis was described (19).

One gene that has caused much confusion is *ACOT8*. This gene was cloned from several species and the protein characterized. In human, ACOT8 was identified as hACTEIII (20) and hTE (21), a protein that interacted with and activated the human immunodeficiency virus-1 Nef protein. Later, this gene was identified and characterized as a peroxisomal acyl-CoA thioesterase (YJR019C and PTE1 from yeast and human, respectively) (22). The cDNA was also cloned from mouse as PTE-2, the major acyl-CoA thioesterase in mouse peroxisomes (10), and subsequently characterized in rat as rat PTE (11).

In the case of *Acot9* and *Acot10*, this subfamily comprises two genes in mouse. These two mitochondrial proteins are 95% identical to each other (9). One gene is encoded on chromosome X F3, and the second gene is encoded on chromosome 15 B1. In human and rat, there appears to be only one gene, *ACOT9/Acot9*, on chromosome X.

## SPLICE VARIANTS

Some of the *ACOT/Acot* genes identified to date undergo splicing events, which result in several different proteins with different cellular localizations (e.g., Acot3, ACOT7/Acot7, and Acot11) (6, 23, 24).

### Acot3 and ACOT11

In the case of *Acot3*, two splice variants have been identified in mouse that result in two almost identical proteins, one of which contains 11 extra amino acids at the N-terminal end, with the remaining 421 amino acids being identical (6). The function of these 11 amino acids is not known, and they do not function as a mitochondrial targeting signal. However, the two splice variants differ in their tissue expression. In human, two splice variants of *ACOT11* (*ACOT11_v1* and *ACOT11_v2*) have been identified, whereas only one variant has been identified in mouse, which is most similar to *ACOT11_v2* (24).

### ACOT7/Acot7 variants

The human *ACOT7* gene comprises at least 13 exons, of which the first 4 (1a–1d) can be used as alternative first exons. Three patterns of splicing occur at exon X, located between exons 7 and 8, which contain an internal 3′ splice acceptor site. This gives rise theoretically to 12 transcript variants through the mechanism of alternative exon use. To date, seven ACOT7 variants (*ACOT7_v1* to *ACOT7_v7*) have been demonstrated (23). *ACOT7_v1* to *ACOT7_v4* have unique sequences derived from their respective exon 1s and share the same sequence corresponding to exons 2–9. Compared with the protein encoded by *ACOT7_v1* (ACOT7a), *ACOT7_v2* and *ACOT7_v3* encode 42 and 12 amino acid longer proteins (ACOT7b and ACOT7c, respectively) that contain mitochondrial targeting signals at their N termini. *ACOT7_v5* and *ACOT7_v6* have the same sequence as *ACOT7_v1* except for having exon X-derived insertions that create premature stop codons by frame shift. Human ACOT7 is homologous to rat and mouse ACOT7. In addition to *Acot7_v1–Acot7_v3*, *Acot7_v7* was identified in mice. *Acot7_v7* has a 5′ extended sequence of *Acot7_v1*, which contains an earlier in-frame start codon that encodes an ACOT7g protein 41 amino acids longer than ACOT7a (25).

Proteins translated from mRNA variants may be distinguished by lowercase suffixes (e.g., ACOT7a and ACOT7b).

## CONCLUSIONS

Decades of research into acyl-CoA thioesterases/hydrolases has led to a disparity in the nomenclature system used by scientists. It is hoped that this new nomenclature for mammalian *ACOT* genes will reduce confusion in this field. It is recommended that any newly identified *ACOT/Acot* family members be given the next available number in the *ACOT* system by referring to the website at http://www.gene.ucl.ac.uk/nomenclature/genefamily/acot.html

This project was supported by Svenska Sällskapet för Medicinsk Forskning, Åke Wibergs Stiftelse, Hjärt-Lungfonden, Lars Hiertas Minne, Fredrik och Ingrid Thurings Stiftelse, Ruth och Richard Julins Stiftelse, Stiftelsen Professor Nanna Svartz Fond, the National Network for Cardiovascular Research (Sweden), the Swedish Research Council, FP6 European Union Project "Peroxisome" (LSHG-CT-2004-512018), the Japanese MEXT.HAIT-EKU-2001, and National Institutes of Health Grant HG-00330 (L.J.M.).

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