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

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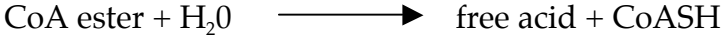
Abstract

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 coenzyme A. There is however significant confusion regarding the nomenclature of these genes. In agreement with the HUGO Gene Nomenclature Committee (HGNC) and the Mouse Genomic Nomenclature Committee (MGNC), 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 ACOT1-12, and rat and mouse named Acot1-12. Several of the ACOT genes are the result of splicing events and these splice variants are catalogued.

Introduction

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 coenzyme A (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:



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 CoASH 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 this short article, with the revised and approved nomenclature for the acyl-CoA thioesterase gene family in human, mouse and rat, to help avoid confusion in this field. This nomenclature has been carried out in co-operation with the HUGO Gene Nomenclature Committee (HGNC) and the Mouse Genomic Nomenclature Committee (MGNC) and proposes the use of *ACOT* as the root symbol for the acyl-CoA thioesterase gene family. It is therefore 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, it is considered that the name acyl-CoA thioesterase, gene symbol *ACOT*-, is more appropriate to 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), while others hydrolyze a broad variety of CoA-activated substrates including bile acids, branched-chain fatty acids, prostaglandins etc (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) while the mouse and rat symbols are lowercase except for the first letter (e.g. Acot1, Acot2 etc). Gene and allele symbols are italicized while protein symbols are nonitalicized capitalized 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) *ACOT1*, (gDNA) *ACOT1*, (cDNA) *ACOT1*.

Gene clusters/families

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 (ACOT3-6) (6). The proteins resulting from these genes are all encoded for by three exons. In human, however, there are 4 distinct genes on chromosome 14q24.3 that encode two cytosolic enzymes (ACOT1 and ACOT6), one mitochondrial (ACOT2) and one peroxisomal enzyme (ACOT4) (14). ACOT1, 2 and 4 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, which 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 carboxyterminal –SKV, which is a variant of the peroxisomal type 1 targeting signal of –SKL, which targets proteins to peroxisomes (17). Database analysis shows that ACOT2 in fact contains 62 extra amino acids at its N-terminal end, which function as a mitochondrial targeting sequence that targets the protein to mitochondria (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 hormonal regulation of steroidogenesis had been described (19).

One gene that has caused much confusion is the *ACOT8*. This gene was cloned from several species and the protein characterized. In human, the ACOT8 was identified as hACTEIII (20) and hTE (21), as a protein that interacted with and activated the HIV-1 Nef protein. Later this gene was identified and characterized as a peroxisomal acyl-CoA thioesterase YJR019C or 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 10*, this subfamily comprises two genes in mouse. These two mitochondrial proteins are 95% identical to each other (9). One gene is encoded on chromosome XF3, while the second gene is encoded on chromosome 15B1. 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. Acot 3, ACOT7/Acot7 and Acot11 (6,23,24).

Acot3, ACOT7/Acot7 and ACOT11 variants

Acot3 and ACOT11

In the case of *Acot3*, two splice variants have been identified in mouse, which result in two almost identical proteins, one of which contains 11 extra amino acids in 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 *_v2*) were identified, whereas only one variant was identified in mouse which is most similar to *ACOT11_v2* (24).

ACOT7/Acot7 variants

The human *ACOT7* gene comprises at least thirteen exons, of which the first four exons (1a-1d) can be used as alternative first exons. Three patterns of splicing occur at exon X located between exons 7 and 8 that contain an internal 3'-splice acceptor site. Thus, it gives rise theoretically to twelve transcript variants through a mechanism of alternative exon use. So far, seven kinds of ACOT7 variants (*ACOT7_v1* to *v7*) have been demonstrated (23). *ACOT7_v1* to *v4* have unique sequences derived from the respective exon 1's 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 to 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 thioesterses/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 help to reduce confusion in this field. It is recommended that any newly identified *ACOT*/*Acot* family members should be given the next available number in the *ACOT* system and refer to the website (http://www.gene.ucl.ac.uk/nomenclature/genefamily/acot.html)

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Table I: Revised nomenclature for the acyl-CoA thioesterase (ACOT/Acot) gene family

Approved nomenclature (chromosome location)			Previous nomenclature & Aliases	Accession No. Gene & protein sequences		
Human	Rat	Mouse		Human	Rat	Mouse
ACOT 1 (14q24.3)	Acot1 (6q31)	Acot1 (12 D3)	CTE-I, LACH2, ACH2	DQ082754	Y09334 NM_031315	Y14004 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) (variant 5:2)		XM_234399 XP_234399	variant 1 AY563097 NP_599007 variant 2 AY563098
ACOT4 14q24.3	Acot4 (6q31)	Acot4 (12 D3)	PTE-Ib, Pte2b	NM_152331	XM_234398 XP_234398	NM_134247
	Acot5 (6q31)	Acot5 (12 D3)	PTE-Ic			AY563099 NM_145444
ACOT6	Acot6 (6q31)	Acot6 (12 D3)	PTE-Id	DQ082756		AY999300

Approved nomenclature (chromosome location)			Previous nomenclature & Aliases	Accession No. Gene & protein sequences		
Human	Rat	Mouse		Human	Rat	Mouse
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

Approved nomenclature (chromosome location)			**Previous nomenclature & Aliases**	**Accession No. Gene & protein sequences**		
Human	Rat	Mouse		Human	Rat	Mouse
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 variant 2 AF416922	XM-233269	AF416923
ACOT 12 (5q14.1)	Acot12 (2q12)	Acot12 (13 C3)	CACH-1, MGC105114 mCACH-1, CACH	AB078619 Q8WYK0	NM_130747	AB078618

Please also refer to 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.