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*review*

# Adoption of PERILIPIN as a unifying nomenclature for the mammalian PAT-family of intracellular lipid storage droplet proteins

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**Abstract The PAT family of proteins has been identified in eukaryotic species as diverse as vertebrates, insects, and amebazoa. These proteins share a highly conserved sequence organization and avidity for the surfaces of intracellular, neutral lipid storage droplets. The current nomenclature of the various members lacks consistency and precision, deriving more from historic context than from recognition of evolutionary relationship and shared function. In consultation with the Mouse Genomic Nomenclature Committee, the Human Genome Organization Genomic Nomenclature Committee, and conferees at the 2007 FASEB Conference on Lipid Droplets: Metabolic Consequences of the Storage of Neutral Lipids, we have established a unifying nomenclature for the gene and protein family members. Each gene member will incorporate the root term *PERILIPIN* (*PLIN*), the founding gene of the PAT family, with the different genes/proteins numbered sequentially.**—Kimmel, A. R., D. L. Brasaemle, M. McAndrews-Hill, C. Sztalryd, and C. Londos. **Adoption of PERILIPIN as a unifying nomenclature for the mammalian PAT-family of intracellular lipid storage droplet proteins. *J. Lipid Res.* 2010.** 51: **468–471.**

**Supplementary key words** perilipin • adipocyte differentiation-related protein • adipophilin • tail-interacting protein of 47 kDa

PAT derives from names of three proteins, PERILIPIN, ADRP, and TIP47, with each having highly related N-terminal sequences and common affinity for intracellular neutral lipid storage droplets (1). Of these, PERILIPIN comes closest to incorporating a biological connection into its name (2). The PERILIPIN appellation is, also, without alternative.

PERILIPIN was originally identified as the most highly phosphorylated protein in lipolytically-activated adipocytes (3) and was subsequently shown to localize specifically to the surfaces of intracellular neutral lipid storage droplets [LSDs (2, 4)]. Although perilipin mRNA and protein expression is largely restricted to adipocytes (5) and steroidogenic cells (6), when ectopically expressed, it is exclusively found on LSDs, regardless of cell type (7–9). Indeed, the name "perilipin" derives from περι λιποσ, "surrounding lipid".

ADRP (10), adipocyte differentiation-related protein, is now appreciated to be a misnomer (11). Although *ADRP* mRNA is upregulated during the differentiation of cultured preadipocytes (10, 11), ADRP protein is rapidly degraded during differentiation and is undetected in mature adipocytes (11, 12). Although additional studies showed that ADRP is expressed in most other cell types (11, 13), when human ADRP was later found to associate tightly with lipid droplet surfaces, human ADRP was named adipophilin (14). Unfortunately, the term "adipophilin" inaccurately implies a specific association with adipose tissue. Further confusion of the acronym "ADRP" with autosomal dominant retinitis pigmentosa (adRP) led to another often-used designation, ADFP.

TIP47 (15), also referred to as PP17 (16), was identified by two groups in separate functional studies. TIP47, tail-interacting protein of 47 kDa, was found in a yeast two-hybrid screen for proteins that interacted with the C-terminal

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tail of the mannose 6-phosphate receptor (M6PR), hence the alternative terminology, M6PR binding protein 1 (MP-6PRBP1). Functional studies suggested linkage as a cargo sorting protein for M6PR trafficking between endosomes and the trans-Golgi network (15). Other workers interested in defining and characterizing placental tissue markers identified the same protein as Placental Protein 17, PP17 (16). This group also characterized several TIP47/PP17 splice variants. The close sequence similarity of ADRP and TIP47 prompted a reexamination of the subcellular distribution of TIP47 (17–19). Like perilipin and ADRP, TIP47 is now a recognized member of the PAT protein family that binds to LSDs.

Based upon sequence similarities and functional associations with LSDs, two additional PAT proteins are documented in mammals, S3-12 (20, 21) and PAT1/LSDP5/OXPAT/MLDP (1, 22–24).

The genes for the five PAT proteins share a common underlying structural organization and are acknowledged to define a novel gene family (see **Table 1**). Moreover, the genes for TIP47, LSDP5, and S3-12 reside within a 200 kb region of murine chromosome 17, with *Lspd5* and *S3-12* separated by <2kb.

## NOMENCLATURE

Researchers within the lipid droplet field have debated nomenclature confusion regarding the multiple names of the various PAT proteins. Formal reexamination of PAT nomenclature was initiated at the FASEB Summer Research Conference–Lipid Droplets: Metabolic Consequences of the Storage of Neutral Lipids, with encouragement by the Mouse Genomic Nomenclature Committee (MGNC) and consultation with the Human Genome Organization Genomic Nomenclature Committee (HGNC). The nomenclature recommendations were agreed upon without dissent (Table 1).

Nomenclature based upon variations of the most obvious terms, PAT, LSD, etc., suffer from alternative and prior usage. For example, LSD also designates Lysine Specific Demethylase; these LSD complexes regulate histone methylation and dynamic aspects of chromatin structure and transcriptional control (25). We, thus, selected *PERILIPIN* as the founding root term based on its precision and elegance, with the gene symbols *Plin* and *PLIN*, for the murine and human genomes, respectively. The MGNC and HGNC have approved this nomenclature.

Following the *Plin/PLIN* gene symbol, each family member is numbered sequentially in the order *PLIN1* for *PERILIPIN*, *PLIN2* for *ADFP*, *PLIN3* for *TIP47*, *PLIN4* for *S3-12*, and *PLIN5* for *LSDP5*. Both new and old terminologies (e.g., *PLIN2/ADFP*) may be of use in the short-term, but we strongly discourage continuous reference to additional alternatives, such as adipophilin, *PP17*, *PAT1*, *OXPAT*, *MLDP*, and *LSD*.

As standard for human and rodent nomenclature, human gene symbols are fully capitalized, whereas for mouse, only the first letter is upper case. For both systems, gene symbols are italicized, whereas full-length gene names are nonitalics, lower case. Protein symbols are nonitalics, upper case for both human and mouse.

## SPLICE VARIANTS

The murine *Plin1* gene organization is the most fully characterized of the *Plin* gene family (1). There are four splice variant transcripts. As well, closely situated alternative 5′-transcriptional start sites have been described. The mRNA splice variants are predicted to encode four distinct proteins, previously termed perilipin A, B, C, and D; three of these proteins have been confirmed (5, 6). Lower case letters will now denote alternative protein forms PLIN1a, PLIN1b, PLIN1c, and PLIN1d, with *Plin1a*, *Plin1b*, *Plin1c*, and *Plin1d* as their respective mRNAs. Alternative 5′-starts would be noted as the mRNA variants *Plin1a_v1, Plin1a_v2,* etc. Similar nomenclature will follow for the other members.

## EVOLUTIONARY RELATIONSHIPS AMONG *PLIN* GENE FAMILY MEMBERS

Sequence similarity argues strongly for orthologs of PLIN1, PLIN2 (ADFP), and PLIN3 (TIP47) in Osteichthyes and Amphibia. Multiple PLIN family members are present in Insecta, and one is found in *Dictyostelium* (1, 19). These nonvertebrate proteins clearly associate with lipid storage droplets, even when expressed in mammalian cells (19), but their current nomenclatures derive from an LSD protein root (e.g., LSD or LSDP). Nonetheless, the common exon/intron gene organizations among the murine *Plin1*, murine *Plin2/Adfp*, and *Drosophila LSDP-1* genes

TABLE 1. A unified nomenclature for the mammalian perilipin-related, PAT-family of intracellular, lipid storage droplet proteins

| | | | Human | | Mouse | |
|---|---|---|---|---|---|---|
| Approved Human Symbol | Approved Name | Previous Aliases | Entrez GeneID | Chr. Location | Entrez GeneID | Chr. Location |
| *PLIN1* | perilipin 1 | perilipin, PERI, PLIN | 5346 | 15q26 | 103968 | 7 D3 |
| *PLIN2* | perilipin 2 | ADRP, ADFP, adipophilin | 123 | 9p22.1 | 11520 | 4 38.9 cM |
| *PLIN3* | perilipin 3 | TIP47, PP17, M6PRBP1 | 10226 | 19p13.3 | 66905 | 17 D |
| *PLIN4* | perilipin 4 | S3-12 | 729359 | 19p13.3 | 57435 | 17 D |
| *PLIN5* | perilipin 5 | PAT1, LSDP5, OXPAT, MLDP | 440503 | 19p13.3 | 66968 | 17 D |

indicate an ancient evolutionary origin for the entire *PLIN* gene family (1). In addition, the insect proteins exhibit lipolytic regulation of LSDs that are comparable to that of mammalian PLIN family members (26–28).

The *PLIN*-based nomenclature is sufficiently flexible and unifying to allow inclusion of all members of this evolutionarily diverse gene family and we encourage all genome annotating organizations to consider the use of *PLIN* in their current and future nomenclatures. Hence, the single *Dictyostelium PLIN* member *LSD1/DdlSD* (*DDB_G0279791*) would now be cross-referenced as *Plin*. As with other orthologous genes, particularly in distantly related species, identical nomenclature (e.g., *PLIN1*) would not imply a common function.

## OTHER LIPID STORAGE DROPLET BINDING PROTEINS

The defining characteristics of PLIN proteins include a conserved PAT-domain (1) and an 11-mer repeating helical organization (29). Although, the extreme N-terminal ~100 amino acids are the most conserved in PLIN1, 2, 3, and 5 proteins, similarity extends through ~250 amino acids. PLIN4/S3-12 is somewhat distinct, with a highly expanded (>75n) 11-mer repeat region. Although structurally similar 11-mer motifs (29) are found in other lipid-associated proteins (e.g., apolipoproteins and α-synuclein), their sequences are unrelated to the PLIN family and are not classified as PAT domains. Although the lipid droplet-binding protein CIDEC/FSP27 (and related family members) shares some limited sequence similarity to PLIN1, it has an unrelated genomic organization (30, 31). Additional lipid storage droplet proteins, such as the plant oleosins, hepatitis C virus core protein, caveolins, and METTL7A/B, which possess other domains for lipid interaction (32–35), are also not members of the PLIN family. Thus, the PLIN nomenclature should not be applied to proteins within a functional category defined by constitutive or transient localization to lipid droplets, but reserved for proteins with an evolutionary relationship that yields conservation of the primary amino acid sequence. We also recognize that PLIN-family member functions may not be solely restricted to their lipid-binding character.

## CONCLUSION

In summary, we recommend adoption of PLIN nomenclature for lipid droplet binding proteins within the *PERILIPIN* gene family. This nomenclature will reduce confusion over the multiplicity of names for the individual members of the family.

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