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SCIENTIFIC COMMUNICATION

A Unified Nomenclature and Amino Acid Numbering for Human PTEN

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The tumor suppressor PTEN is a major brake for cell transformation, mainly due to its phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P_3] phosphatase activity that directly counteracts the oncogenicity of phosphoinositide 3-kinase (PI3K). PTEN mutations are frequent in tumors and in the germ line of patients with tumor predisposition or with neurological or cognitive disorders, which makes the PTEN gene and protein a major focus of interest in current biomedical research. After almost two decades of intense investigation on the 403-residue-long PTEN protein, a previously uncharacterized form of PTEN has been discovered that contains 173 amino-terminal extra amino acids, as a result of an alternate translation initiation site. To facilitate research in the field and to avoid ambiguities in the naming and identification of PTEN amino acids from publications and databases, we propose here a unifying nomenclature and amino acid numbering for this longer form of PTEN.

Since the discovery in 1997 of a major tumor suppressor gene encoding a protein with tyrosine phosphatase activity—which was named PTEN (phosphatase and tensin homolog on chromosome ten), MMAC1, or TEP1 (*1*–*3*)—an outburst of publications have documented the relevance of PTEN (currently used protein name; official gene name *PTEN*) on tumor biology and human disease (*4*). The human *PTEN* gene is located at chromosome 10q23, a locus frequently deleted in human cancers. In addition, *PTEN* is a common target of point mutations in tumors, including mutations at noncoding and nontranslated regions, as well as frameshift, missense, and nonsense mutations at coding regions. Patients with PHTS (PTEN hamartoma tumor syndrome), as well as a fraction of patients with ASD (autism spectrum disorders), carry germline *PTEN* mutations. In the case of PHTS patients, this confers high risk for several types of cancer, including (but not restricted to) breast and thyroid cancer (*5*–*7*). *PTEN* mutations at coding regions distribute all along the gene, and mutations are common in exons encoding the protein tyrosine phosphatase (PTP) catalytic domain, especially exon 5 (*8*). Although a large number of *PTEN* mutations found in tumors or in PHTS patients confer total loss of function to the protein, many mutations lead to partial loss of function or have a weak effect on PTEN phosphatase activity. Moreover, most of the germline *PTEN* mutations from ASD patients do not abrogate PTEN catalysis (*9*). This makes important not only identifying the *PTEN* mutation affecting the patient but also characterization of the functional properties of the corresponding mutated PTEN protein.

PTEN is one of relatively few genes in the human genome that encodes two proteins by noncanonical alternative initiation of translation (Fig. 1A). The shorter and more abundant PTEN protein contains 403 amino acids that distribute in two major domains: a catalytic PTP domain and a membrane-binding C2 domain (*10*). The recently identified and less abundant longer PTEN protein (named as PTEN-Long or PTENα, and here as PTEN-L) contains 173 additional amino-terminal intrinsically disordered amino acids, as a result of the usage of an alternative CUG translation initiation site upstream to the canonical AUG sequence used to produce the shorter 403-amino-acid form (*11*–*13*).

Different groups have proposed that PTEN-L can be secreted to enter other cells (*11*) and that it may form heterodimers with PTEN and regulate mitochondrial function (*12*). Adding to the functional complexity, PTEN also homodimerizes, which may be particularly important in tumors or patients coexpressing wild-type and mutated PTEN alleles (*14*). Mutations encoding residues in the specific region of PTEN-L occur in tumors or are reported as polymorphisms (*15*–*19*), and this region may control PTEN subcellular localization and tumor suppressor activity. For example, this region includes the internalization signal for uptake of PTEN-L into acceptor cells, a postulated physiologic mechanism for tumor suppression, which potentially could be used as a novel therapeutic approach to reconstitute PTEN activity in PTEN-deficient tumors (*11*, *20*).

Abundant literature exists using the amino acid numbering from the short PTEN form, but this numbering does not fit with the amino acid numbering of PTEN-L. In addition, the numbering of the specific residues from PTEN-L (1 to 173) is already used to number different residues in PTEN, which could generate confusion. For instance, residues 1 to 22 from PTEN-L form part of a predicted secretion signal peptide, whereas residues 6 to 32 from PTEN contain an overlapping PI(4,5)P_2-binding motif, nuclear localization signal, and cytoplasmic localization signal (Fig. 1A) (*21*–*23*). Thus, we propose a unified numbering to designate amino acids in PTEN and PTEN-L, so as to avoid ambiguity in the identification of PTEN residues from mutated samples or in the precise naming of PTEN residues in experimental work (Fig. 1, B and C). Our proposal is as follows:

- PTEN-Long is named PTEN-L.
- The amino acid numbering of PTEN does not change.
- The amino acid numbering of PTEN-L is followed by -L, for example, Leu^1-L, Glu^2-L … in three-letter code or L1-L, E2-L … in single-letter code up to Val^{576}-L or V576-L. Residues Leu^1-L to Ser^{22}-L form part of a predicted secretion signal and would not be present in a mature secreted form of PTEN-L protein.
- The equivalence between residues from PTEN and PTEN-L is calculated

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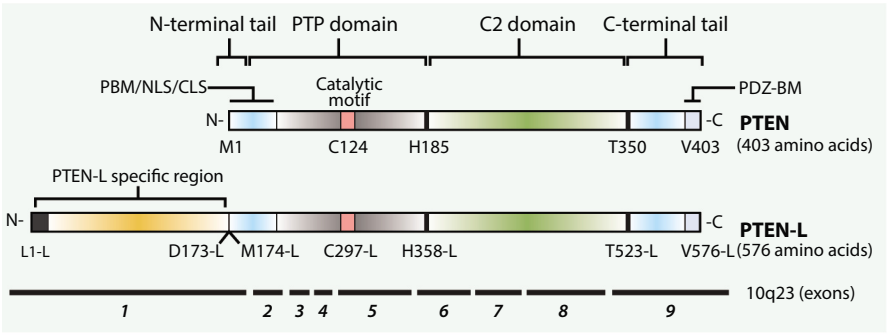
A



B

Protein	Catalytic activity		
	Phosphatase inactive	Lipid phosphatase inactive	Protein phosphatase inactive
PTEN	C124S	G129E	Y138L
PTEN-L	C297S-L	G302E-L	Y311L-L

C

Mutation	Nucleotide	Tumor type
A99T-L	-225G → A	HNSCC
H122Y-L	-156C → T	HNSCC
S129I-L*	-134G → T	HNSCC
T140I-L	-101C → T	Melanoma
R170G-L	-12A → G	LBCL
L171F-L	-9C → T	GBM
L171V-L*	-9C → G	–

D

Type of dimer	Dimer nomenclature	Examples
PTEN homodimer	PTEN:PTEN	PTEN:PTEN PTEN:PTEN C124S
PTEN-L homodimer	PTEN-L:PTEN-L	PTEN-L:PTEN-L PTEN-L:PTEN-L C297S-L
PTEN:PTEN-L heterodimer	PTEN:PTEN-L	PTEN:PTEN-L PTEN C124S:PTEN-L PTEN:PTEN-L C297S-L

Fig. 1. A nomenclature for PTEN-L amino acid numbering. (**A**) Schematic of human PTEN and PTEN-L and the proposed numbering of amino acids. The domains common to PTEN and PTEN-L are indicated at the top, and the amino acids flanking the domains are indicated below each protein depiction. C124 (PTEN) or C297-L (PTEN-L) corresponds to the catalytic Cys. The N- and C-terminal tails from PTEN, and the PTEN-L–specific region (residues L1-L to D173-L) are intrinsically disordered regions. The black box at the N terminus of PTEN-L corresponds to a predicted secretion signal (predicted cleavage site at amino acid S22-L). PBM, PI(4,5)P_2-binding motif; NLS, nuclear localization sequence; CLS, cytoplasmic localization sequence; PDZ-BM, PDZ-binding motif. Numbers at the bottom correspond to exon numbering. (**B**) Examples of nomenclature for commonly used PTEN mutations totally or partially defective for phosphatase activity (*25*–*27*). (**C**) Examples of nomenclature for identified PTEN mutations targeting PTEN-L–specific amino acids. Loss of function has been experimentally observed for mutations A99T-L, H122Y-L, and R170G-L [(*11*); note that in reference (*11*) the amino acid numbering is one unit less]. *Reported as polymorphisms (*15*, *17*). HNSCC, head and neck squamous cell carcinoma; LBCL, large B cell lymphoma; GBM, glioblastoma multiforme. **(D)** Examples of nomenclature for PTEN dimers. Examples are provided of different combinations of PTEN and PTEN-L wild-type and mutated homodimers and heterodimers. PTEN:PTEN homodimers (*14*) and PTEN:PTEN-L heterodimers (*12*) have been demonstrated experimentally. The possibility also exists of dimers containing two mutated proteins (with the same mutation or different mutations).

by adding 173 to—or subtracting it from —the corresponding numbering. For instance, Cys^{124} (C124) from PTEN is equivalent to Cys^{297}-L (C297-L) from PTEN-L.

• Amino acid changes, either through site-directed mutagenesis or through naturally occurring mutations, are indicated as the residue and number without any extension for PTEN (for example, C124S), and with the -L extension for PTEN-L (for example, C297S-L) when the name of the protein is not immediately preceding the mutation name. Mutations commonly used in experimental work to abrogate the catalytic activity of PTEN are shown in Fig. 1B.

• Nucleotide numbering to desig-nate mutations at the PTEN-L–specific residues follows the Human Genome Variation Society (HGVS) recommendations (*24*). For instance, nucleotides –3 to –1 would encode Asp^{173}-L; –6 to –4 would encode Pro^{172}-L; up to –519 to –517, which would encode Leu^{1}-L (Fig. 1C). Note that CUG –519 to –517 nucleotides in the HGVS-recommended numbering for human *PTEN* gene correspond to CUG 513 to 515 nucleotides in the human *PTEN* cDNA entry (NM_000314).

• Homodimers and heterodimers of PTEN proteins are designated with the appropriate extension as needed (Fig. 1D).

• Newly identified PTEN proteins with starting amino acids distinct from Met^{1} from PTEN or Leu^{1}-L from PTEN-L could be named alphabetically as PTEN-M, PTEN-N, and so on, or by using another appropriate capital letter, and the nomenclature for amino acids and amino acid changes would follow the rules as above for PTEN-L.

• The same rules apply to other mammalian PTEN-L protein orthologs, especially those from animal models usually handled in biomedical research.

The possibility of numbering PTEN-L–specific residues with negative numbers starting at and going upstream from the canonical AUG initiation codon of PTEN (as recommended by the HGVS for mutations that introduce in proteins new translation initiation sites) is not practical in the case of PTEN-L, because this form is produced from a natural, not mutation-created, upstream alternative translation initiation codon (CUG) that generates a natural longer protein. The mutations affecting the PTEN-L–specific residues do not introduce new translation initiation sites, but rather change residues in PTEN-L.

We think that this unified nomenclature will facilitate to both researchers and clinicians the unambiguous identification of amino acids from PTEN and PTEN-L and aid in the description of any new forms that may be identified in the future.

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