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Selenoprotein Gene Nomenclature

Vadim N. Gladyshev[1,2,#], Elias S. Arnér[3], Marla J. Berry[4], Regina Brigelius-Flohé[5], Elspeth A. Bruford[6], Raymond F. Burk[7], Bradley A. Carlson[8], Sergi Castellano[9], Laurent Chavatte[10], Marcus Conrad[11], Paul R. Copeland[12], Alan M. Diamond[13], Donna M. Driscoll[14], Ana Ferreiro[15,16,17,18], Leopold Flohé[19,20], Fiona R. Green[21], Roderic Guigó[22,23], Diane E. Handy[24], Dolph L. Hatfield[8], John Hesketh[25,26,27], Peter R. Hoffmann[4], Arne Holmgren[3], Robert J. Hondal[28], Michael T. Howard[29], Kaixun Huang[30], Hwa-Young Kim[31], Ick Young Kim[32], Josef Köhrle[33], Alain Krol[34], Gregory V. Kryukov[35], Byeong Jae Lee[36], Byung Cheon Lee[32], Xin Gen Lei[37], Qiong Liu[38], Alain Lescure[34,39], Alexei V. Lobanov[1], Joseph Loscalzo[40], Matilde Maiorino[20], Marco Mariotti[1], K. Sandeep Prabhu[41], Margaret P. Rayman[42], Sharon Rozovsky[43], Gustavo Salinas[44], Lutz Schomburg[33], Ulrich Schweizer[45], Miljan Simonović [46], Roger A. Sunde[47], Petra A. Tsuji[48], Susan Tweedie[6,49], Fulvio Ursini[20], Yan Zhang[38]

[1] Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA
[2] Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA
[3] Division of Biochemistry, Department of Medical Biochemistry and Biophysics (MBB), Karolinska Institutet, SE-171 77, Stockholm, SWEDEN
[4] Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, 96813, USA
[5] German Institute of Human Nutrition Potsdam-Rehbruecke, 14558, Nuthetal, GERMANY
[6] HUGO Gene Nomenclature Committee (HGNC), European Bioinformatics Institute-European Molecular Biology Laboratory (EMBL-EBI), Hinxton, CB10 1SD, UK
[7] Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, 37232, USA
[8] Molecular Biology of Selenium Section, Mouse Cancer Genetics Program, Center for Cancer Research, National Institutes of Health, Bethesda, MD, 20892, USA
[9] Department of Evolutionary Genetics, Max Planck Institute for Evolutionary Anthropology, 04103, Leipzig, GERMANY
[10] Centre International de Recherche en Infectiologie, CIRI, INSERM U1111, and CNRS/ENS UMR5308, 69007, Lyon, FRANCE
[11] Helmholtz Zentrum München, Institute of Developmental Genetics, 85764, Neuherberg, GERMANY
[12] Department of Biochemistry and Molecular Biology, Rutgers-Robert Wood Johnson Medical School, Piscataway, NJ, 08854, USA
[13] Department of Pathology, University of Illinois at Chicago, Chicago, IL, 60607, USA
[14] Department of Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio, 44195, USA
[15] Pathophysiology of striated muscles laboratory, Unit of Functional and Adaptive Biology (BFA), University Paris Diderot, Sorbonne Paris Cité, BFA, UMR CNRS 8251, 75250, Paris, FRANCE
[16] Inserm U787, Myology group, Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, 75013, Paris, FRANCE
[17] UPMC, UMR787, 75013, Paris, FRANCE
[18] AP-HP, Centre de Référence Maladies Neuromusculaires Paris-Est, Groupe Hospitalier Pitié-Salpêtrière, 75013, Paris, FRANCE
[19] Universidad de la República, Facultad de Medicina, Departamento de Bioquímica, 11800, Montevideo, URUGUAY
[20] Department of Molecular Medicine, University of Padova, I-35121, Padova, ITALY
[21] Department of Biochemistry and Physiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7XH, UK

[22] Centre for Genomic Regulation (CRG), 08003, Barcelona, SPAIN
[23] Universitat Pompeu Fabra (UPF), 08002, Barcelona, SPAIN
[24] Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
[25] Institute for Cell and Molecular Biosciences, Newcastle University, NE1 7RU, Newcastle-upon-Tyne, UK
[26] Human Nutrition Research Centre, Newcastle University, NE1 7RU, Newcastle-upon-Tyne, UK
[27] The Medical School, Newcastle University, Newcastle-upon-Tyne, NE2 4HH, UK
[28] Department of Biochemistry, University of Vermont, Burlington, VT, 05405, USA
[29] Department of Human Genetics, University of Utah, Salt Lake City, Utah, 84112, USA
[30] Hubei Key Laboratory of Bioinorganic Chemistry & Materia Medica, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan, 430074, P. R. CHINA
[31] Department of Biochemistry and Molecular Biology, Yeungnam University College of Medicine, Daegu, 42415, SOUTH KOREA
[32] College of Life Sciences and Biotechnology, Korea University, Seoul, 02841, SOUTH KOREA
[33] Institute for Experimental Endocrinology, Charité -Universitaetsmedizin Berlin, D-13353, Berlin, GERMANY
[34] Architecture et Réactivité de l'ARN, Université de Strasbourg, Centre National de la Recherche Scientifique, Institut de Biologie Moléculaire et Cellulaire, 67084, Strasbourg, FRANCE
[35] KSQ Therapeutics, Cambridge, MA, 02139, USA
[36] School of Biological Sciences, Seoul National University, Seoul, 151-742, SOUTH KOREA
[37] Department of Animal Science, Cornell University, Ithaca, NY, 14853, USA
[38] Shenzhen Key Laboratory of Marine Biotechnology and Ecology, College of Life Science, Shenzhen University, Shenzhen, 518060, Guangdong Province, P. R. CHINA
[39] Centre National de la Recherche Scientifique, 75794, Paris, FRANCE
[40] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA
[41] Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, PA, 16802, USA
[42] Department of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7XH, UK
[43] Department of Chemistry and Biochemistry, University of Delaware, Newark, DE, 19716, USA
[44] Cátedra de Inmunología, Facultad de Química, Instituto de Higiene, CP11600, Montevideo, URUGUAY
[45] Rheinische Friedrich-Wilhelms Universität Bonn, Institut für Biochemie und Molekularbiologie, 53115, Bonn, GERMANY
[46] Department of Biochemistry and Molecular Genetics, University of Illinois at Chicago, Chicago, IL 60607, USA
[47] Department of Nutritional Sciences, University of Wisconsin, Madison, WI, 53706, USA
[48] Department of Biological Sciences, Towson University, Towson, MD, 21252, USA
[49] Department of Genetics, University of Cambridge, Cambridgeshire, CB10 1SD, UK

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[#] To whom correspondence should be addressed: vgladyshev@rics.bwh.harvard.edu

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ABSTRACT

The human genome contains 25 genes coding for selenocysteine-containing proteins (selenoproteins). These proteins are involved in a variety of functions, most notably redox homeostasis. Selenoprotein enzymes with known functions are designated according to these functions: TXNRD1, TXNRD2, and TXNRD3 (thioredoxin reductases), GPX1, GPX2, GPX3, GPX4 and GPX6 (glutathione peroxidases), DIO1, DIO2, and DIO3 (iodothyronine deiodinases), MSRB1 (methionine-*R*-sulfoxide reductase 1) and SEPHS2 (selenophosphate synthetase 2). Selenoproteins without known functions have traditionally been denoted by SEL or SEP symbols. However, these symbols are sometimes ambiguous and conflict with the approved nomenclature for several other genes. Therefore, there is a need to implement a rational and coherent nomenclature system for selenoprotein-encoding genes. Our solution is to use the root symbol SELENO followed by a letter. This nomenclature applies to SELENOF (selenoprotein F, the 15 kDa selenoprotein, SEP15), SELENOH (selenoprotein H, SELH, C11orf31), SELENOI (selenoprotein I, SELI, EPT1), SELENOK (selenoprotein K, SELK), SELENOM (selenoprotein M, SELM), SELENON (selenoprotein N, SEPN1, SELN), SELENOO (selenoprotein O, SELO), SELENOP (selenoprotein P, SeP, SEPP1, SELP), SELENOS (selenoprotein S, SELS, SEPS1, VIMP), SELENOT (selenoprotein T, SELT), SELENOV (selenoprotein V, SELV) and SELENOW (selenoprotein W, SELW, SEPW1). This system, approved by the HUGO Gene Nomenclature Committee, also resolves conflicting, missing and ambiguous designations for selenoprotein genes and is applicable to selenoproteins across vertebrates.

INTRODUCTION

Selenium is an essential trace element in humans, which is present in proteins in the form of the 21st proteinogenic amino acid, selenocysteine (Sec). Sec is co-translationally inserted into a polypeptide chain in response to in-frame UGA codons directed by the Sec insertion sequence element, a stem-loop structure in the 3'-UTRs of selenoprotein mRNAs. The human genome contains 25 selenoprotein genes (1), and selenoproteins are essential for embryo development and human health (2, 3). Among the selenoproteins, 13 have known functions; at least 12 of them serve as oxidoreductases, wherein Sec is the catalytic redox-active residue. The redox theme is also common for selenoproteins in other organisms (4).

The remaining 12 selenoproteins either have no known function, or their functions are only partially established. One of the selenoproteins, selenoprotein P (5), requires special mention as it has more than one Sec. It is a major plasma selenoprotein that delivers selenium primarily from the liver to other organs (6,7), and is involved in selenium transport and metabolism within organs. However, this protein also has an N-terminal Sec-containing thioredoxin domain similar to that found in most selenoproteins with known functions, which points to a potential redox function. Several other selenoproteins, including selenoproteins H, M, T, V, W and Sep15, also possess thioredoxin-like domains, suggesting redox-related functions (8).

Selenoproteins are not all homologous, but are characterized by their incorporation of Sec. Historically they have been given designations by the groups that discovered them, *e.g.*, owing to its presence in plasma the respective selenoprotein was named Selenoprotein P (9,10), or because of its size another protein was called the 15 kDa selenoprotein or Sep15 (11). However, some selenoproteins were identified independently by two or more groups, which created confusion and discrepancies in the field. For example, the same protein was named Selenoprotein R by one group (12), but discovered concurrently and designated by another group as Selenoprotein X (13). This protein was then functionally characterized (14) and renamed MsrB1 (for methionine-*R*-sulfoxide reductase 1) (15), but all three designations persist in the literature and/or databases. Another problematic example is the nomenclature used for thioredoxin reductases. The names for the first thioredoxin reductase, which had been known decades before its selenoprotein nature was discovered (16), are generally internally consistent, although they differ in the abbreviations used, *e.g.*, TR1 and TrxR1 (17). The second and third thioredoxin reductases

discovered, however, were named inconsistently by the authors, wherein the mitochondrial thioredoxin reductase was designated as TrxR2 (18) and TR3 (19), and the testis-specific thioredoxin-glutathione reductase has been alternatively labeled as TR2 (19), TrxR3 or TGR.

Designations are also confusing for several other selenoproteins. For example, Selenoprotein S was named SelS (1), but a later paper introduced the designation VIMP (20). Similarly, Selenoprotein H was named SelH (1), but also C11orf31, and Selenoprotein I was named SelI (1), but also called EPT1 (21). To avoid confusion, and at the instigation of the HUGO Gene Nomenclature Committee (HGNC), we describe a new standardized designation system for human (and other vertebrate) selenoproteins.

RESULTS AND DISCUSSION

Resolving the nomenclature of selenoprotein genes Human gene designations are approved by the HUGO Gene Nomenclature Committee (HGNC), and genes in other mammals follow the same designations. Selenoproteins have traditionally been published using SEL or SEP symbols followed by a letter or a number. Unfortunately, for naming the genes encoding these proteins, the SEL root was not an option as it was already approved for the selectin gene family; for example, *SELP* is the approved gene symbol for selectin P (P-selectin) and not Selenoprotein P. Some selenoprotein genes had been approved using the root SEP (i.e., *SEPN1*, *SEPP1*, *SEPW1*) but this could not be utilized for all selenoproteins as Selenoprotein T gene would then be *SEPT* or *SEPT1*, and *SEPT#* is already used for the septin genes. HGNC does not use the same root for unrelated groups of genes (*e.g.*, SEL for selectins and selenoproteins) and does not endorse the use of multiple root symbols for genes sharing a common name (*e.g.*, SEP and SEL for selenoprotein). With a view to solving these issues, HGNC approached selenoprotein researchers to propose a new unifying root symbol for all selenoprotein genes.

Proposal for a new nomenclature We propose that all selenoproteins (except those that have been functionally characterized, *e.g.*, with enzymatic activity) use the root symbol SELENO followed by a letter. This gene nomenclature is designed to highlight selenium, the key functional site in these proteins, and to provide a new and unambiguous root for these genes. The new nomenclature applies to 12 human selenoprotein genes as detailed in Table 1. Selenoproteins with known functions will continue to use the same designations (Table 2). Once functions are established for other selenoproteins, they may be renamed, as required. The proposed designations apply to the selenoprotein genes; although the same designations may be used for many of the encoded proteins, traditional names of selenoproteins, e.g. Selenoprotein P, may also be used.

Selenoprotein gene designation in other species The new HGNC nomenclature will automatically be used to designate orthologous selenoprotein genes in other vertebrates and extended to accommodate selenoprotein genes with no orthologs in human (22) (Table 3). Where vertebrate gene duplications have occurred, the additional paralogs will be named in line with the human genes, but with suffixes on the symbols, *e.g.*, zebrafish selenot1a, selenot1b and selenot2. Selenoproteins are widespread in all three domains of life. Despite the fact that land plants, yeast, and some other species have lost selenoprotein biosynthesis pathways, a unifying nomenclature beyond vertebrates might be desirable. We suggest using the human nomenclature described in this paper for orthologs of vertebrate selenoprotein genes. This nomenclature may also be extended to accommodate additional selenoprotein genes as they are discovered. While we use human designations in this paper, we note that, according to HGNC guidelines, most vertebrates use all uppercase letters for genes and proteins (italics for genes), rodents use title case for genes (uppercase for proteins), Xenopus and zebrafish use lower case for genes and title case for proteins, and Anolis use lowercase for genes and uppercase for proteins.

Designations of proteins that do not contain selenocysteine There exists another class of selenium-containing proteins, those which contain a bound atom of selenium but do not

contain a UGA-encoded Sec, for which there is also ambiguous nomenclature. For example, the Selenium Binding Protein 1 (SBP1), also referred to as SELENBP1 or hSP56, is one such protein (23). The naming of such proteins will not be included in the new nomenclature as they lack Sec. Similarly, the machinery for Sec biosynthesis and insertion will not be renamed.

Implementation The new selenoprotein gene nomenclature has been approved by the HGNC, can be found on their website (http://www.genenames.org/cgi-bin/genefamilies/set/890), and will be found in all major genomic resources in due course. We recommend that future publications primarily use the new SELENO designations, but supplement them (as secondary designations/synonyms) with the names previously used by the community. Once the new nomenclature is consistently used, the old designations will no longer be needed. We hope that other researchers in the field will join us in implementing this new nomenclature.

Conflict of Interest: The authors declare that they have no conflicts of interest with the contents of this article.

Author Contributions: The manuscript was drafted by VNG in consultation with other authors. All authors contributed to revisions and discussion.

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FOOTNOTES

The abbreviations used are: Sec, selenocysteine; TXNRD, thioredoxin reductases; GPX, glutathione peroxidase; DIO, iodothyronine deiodinase; MSRB, methionine-*R*-sulfoxide reductase; SEPHS2, selenophosphate synthetase 2; SELENOF, 15 kDa selenoprotein; SELENOH, selenoprotein H; SELENOI, selenoprotein I; SELENOK, selenoprotein K; SELENOM, selenoprotein M; SELENON, selenoprotein N; SELENOO, selenoprotein O; SELENOP, selenoprotein P; SELENOS, selenoprotein S; SELENOT, selenoprotein T; SELENOV, selenoprotein V; SELENOW, selenoprotein W; SBP1, Selenium Binding Protein 1; HGNC, HUGO Gene Nomenclature Committee.

Table 1. Selenoprotein genes using the new SELENO root. New HGNC selenoprotein gene nomenclature is indicated in the column "symbol". Previous HGNC symbols (shown with *) will become synonyms, along with other previously used designations.

Symbol	Name	Synonyms	Refs
SELENOF	Selenoprotein F	selenoprotein 15, SEP15	24
SELENOH	Selenoprotein H	SELH, C11orf31*	1
SELENOI	Selenoprotein I	SELI, EPT1*	1,21
SELENOK	Selenoprotein K	SELK	1
SELENOM	Selenoprotein M	SELM, SEPM	25
SELENON	Selenoprotein N	SEPN1*, SELN	11
SELENOO	Selenoprotein O	SELO	1
SELENOP	Selenoprotein P	SEPP1*, SeP, SELP, SEPP	26
SELENOS	Selenoprotein S	SELS, SEPS1, VIMP*	1
SELENOT	Selenoprotein T	SELT	12
SELENOV	Selenoprotein V	SELV	1
SELENOW	Selenoprotein W	SELW, SEPW1*	27

Table 2. Selenoprotein genes named based on encoded enzymatic activity. Note that the nomenclature of these genes will not be changing to use the SELENO root.

Symbol	Name	Synonyms	Refs
TXNRD1	Thioredoxin reductase 1	TR1, TRXR1	16,28,29
TXNRD2	Thioredoxin reductase 2	TRXR2, TR3, mitochondrial Thioredoxin reductase	13,14
TXNRD3	Thioredoxin-glutathione reductase	TGR, TRXR3, TR2	14
GPX1	Glutathione peroxidase 1	Cytosolic glutathione Peroxidase, GSHPX1	30-35
GPX2	Glutathione peroxidase 2	GSHPX-GI	36
GPX3	Glutathione peroxidase 3	Plasma glutathione peroxidase	37
GPX4	Glutathione peroxidase 4	Phospholipid hydroperoxide glutathione peroxidase, PHGPX	38,39
GPX6	Glutathione peroxidase 6		1
DIO1	Iodothyronine deiodinase 1	D1	40, 41
DIO2	Iodothyronine deiodinase 2	D2	42
DIO3	Iodothyronine deiodinase 3	D3	43
MSRB1	Methionine-*R*-sulfoxide reductase 1	SELR, SELX, SEPX1	12-14
SEPHS2	Selenophosphate synthetase 2	SPS2	44

Table 3. Vertebrate selenoproteins absent in human and mouse. New HGNC selenoprotein gene nomenclature is indicated in the column "symbol".

Symbol	Name	Synonyms	Refs
SELENOJ	Selenoprotein J	SELJ	45
SELENOU	Selenoprotein U	SELU	46
SELENOL	Selenoprotein L	SELL	47
SELENOE	Fish selenoprotein 15	FEP15	48
SELENOP2	Selenoprotein P2	SEPP2, SELPb	49,50

Selenoprotein Gene Nomenclature

Vadim N. Gladyshev, Elias S. Arnér, Marla J. Berry, Regina Brigelius-Flohé, Elspeth A. Bruford, Raymond F. Burk, Bradley A. Carlson, Sergi Castellano, Laurent Chavatte, Marcus Conrad, Paul R. Copeland, Alan M. Diamond, Donna M. Driscoll, Ana Ferreiro, Leopold Flohé, Fiona R. Green, Roderic Guigó, Diane E. Handy, Dolph L. Hatfield, John Hesketh, Peter R. Hoffmann, Arne Holmgren, Robert J. Hondal, Michael T. Howard, Kaixun Huang, Hwa-Young Kim, Ick Young Kim, Josef Köhrle, Alain Krol, Gregory V. Kryukov, Byeong Jae Lee, Byung Cheon Lee, Xin Gen Lei, Qiong Liu, Alain Lescure, Alexei V. Lobanov, Joseph Loscalzo, Matilde Maiorino, Marco Mariotti, K. Sandeep Prabhu, Margaret P. Rayman, Sharon Rozovsky, Gustavo Salinas, Lutz Schomburg, Ulrich Schweizer, Miljan Simonovic, Roger A. Sunde, Petra A. Tsuji, Susan Tweedie, Fulvio Ursini and Yan Zhang

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