

## A plea for standardized nomenclature of snake venom toxins

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### Toxicon

DOI:  
[10.1016/j.toxicon.2014.08.070](https://doi.org/10.1016/j.toxicon.2014.08.070)

Published: 27/08/2014

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

*Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):*  
Hargreaves, A. D., & Mulley, J. F. (2014). A plea for standardized nomenclature of snake venom toxins. *Toxicon*, 90, 351-353. <https://doi.org/10.1016/j.toxicon.2014.08.070>

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1 Title page

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3 Letter to the Editor

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5 **A plea for standardized nomenclature of snake venom toxins**

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27 "...they have all one language; and this they begin to do: and now nothing will be restrained  
28 from them, which they have imagined to do. Go to, let us go down, and there confound their  
29 language, that they may not understand one another's speech."

30 Genesis, Chapter 11, verses 6-7

31

32 In the book of Genesis a spiteful God replaces a single, unifying language with a diversity of  
33 different ones, removing at a stroke mankind's ability to work together towards a common goal.  
34 We believe that the Tower of Babel myth has clear relevance to the snake venom literature,  
35 particularly to the nomenclature of snake venom toxins.

36 An established nomenclatural system for human genes, administered by the Human Genome  
37 Organisation (HUGO) Gene Nomenclature Committee (HGNC), has existed since 1979 (Shows  
38 et al., 1979) and similar systems also exist for mice (administered by the International  
39 Committee on Standardized Genetic Nomenclature for Mice) and zebrafish (administered by the  
40 Zebrafish Nomenclature Committee (ZNC)), as well as various other animal models. As a result,  
41 orthology, paralogy and the evolutionary relationships of these genes are clear for all to see. A  
42 nomenclatural committee was established by the International Society on Toxinology (IST) in  
43 1992 after several exchanges in the 'Letters to the Editor' section of *Toxicon* in the early 1990's  
44 (Aird, 1990, Kaiser, 1990, Kumar et al., 1990), and more recently there have been suggestions  
45 for rational nomenclatural systems in spiders (King et al., 2008), scorpions (Tytgat et al., 1999),  
46 sea anemones (Oliveira et al., 2012) and centipedes (Undheim et al., 2014). However, despite  
47 over 20 years of asking, a nomenclatural system for reptile toxins has still not been established.  
48 The lack of widely-accepted, unifying standards for the nomenclature of snake venom toxins  
49 has resulted in huge diversity and disparity in the literature. In most cases the names assigned  
50 provide no insight into the evolutionary origins or relationships of the toxins, complicating  
51 comparative studies of venom composition, function or evolution both within and between  
52 species. For example, the similar sounding *ophanin* (accession AY181984, (Yamazaki et al.,

53 2003)), *opharin* (accession AY299475, Direct submission) and *ohanin* (accession DQ103590,  
54 (Pung et al., 2005)) from the king cobra (*Ophiophagus hannah*) are members of two different  
55 gene families – *ophanin* and *opharin* are cysteine-rich secretory proteins (CRISPs) and *ohanin*  
56 is a vespryn-like gene. Conversely, the differently sounding *pseutarin C* from *Pseudonaja textilis*  
57 (accession AY260939, (Rao et al., 2004)) and *trocarin D* from *Tropidechis carinatus* (accession  
58 DQ017707, (Reza et al., 2007)) are both *coagulation factor X* genes and *barietin* from *Bitis*  
59 *arietans* (accession FJ554635, (Yamazaki et al., 2009)), *apiscin* from *Agkistrodon piscivorus*  
60 (accession FJ554636, (Yamazaki et al., 2009)) and *cratrin* from *Crotalus atrox* (accession  
61 FJ554637, (Yamazaki et al., 2009)) are all *vascular endothelial growth factor F (vegf-f)* genes.  
62 The snake venom literature is replete with further examples, all of which obscure the  
63 relationships and functions of the toxins themselves – who would imagine that “cobra venom  
64 factor” which has been known since the late 19<sup>th</sup> century (Vogel, 1991) is part of the  
65 complement system from its name alone? Indeed, we have recently shown (Hargreaves et al.,  
66 2014a) that the *complement c3* gene has in fact been duplicated in cobras, giving rise to *cobra*  
67 *venom factor*, which should more accurately be called *complement c3b* to reflect its true  
68 evolutionary history.

69 We have previously suggested (Hargreaves et al., 2014b) that the “evolutionary characterization  
70 code” proposed by the Anolis Gene Nomenclature Committee (AGNC) for lizards of that genus  
71 (Kusumi et al., 2011) should be applied to snake venom toxins, and we reiterate that suggestion  
72 here. Full details of this classification code can be found in the relevant reference (Kusumi et  
73 al., 2011), but we provide a brief summary of some of the most relevant points below:

- 74 • Gene symbols should be written completely in lower case and in italics, for example  
75 *“gene2”*.
- 76 • Punctuation (dashes, periods, slashes) should not be used unless they are part of a  
77 human or mouse gene symbol.

- 78 • Whenever orthology can be assigned, this should be present in the gene name, for  
79 example if the human gene symbol is “*GENE2*” then the reptile gene symbol would be  
80 “*gene2*”.
- 81 • If an orthologous gene cannot be identified in any currently sequenced genome, a novel  
82 name may be selected by the investigators.
- 83 • Gene symbols should not start with letters to indicate genus/species.
- 84 • Gene duplicates should be assigned the suffix “a” or “b” to indicate them as being  
85 paralogs, e.g. *gene2a* and *gene2b*.

86 In addition, we would suggest that where toxins are known only from peptide or protein  
87 sequences, without accompanying characterized gene sequences, they should be named on  
88 the basis of similarity to existing toxins using the suffix “-like” or be acknowledged as  
89 uncharacterized toxins. We should not shy away from acknowledging our ignorance, nor from  
90 presenting challenges to future researchers. That being said, it seems likely that the availability  
91 of genomic and transcriptomic data from an ever-growing range of species (see next section)  
92 will go at least some way to facilitating the identification of toxins in proteomic studies.

93 With the recent publication of the whole genome sequences of two species of snake (the  
94 Burmese python *Python molurus bivittatus* and the king cobra, *Ophiophagus hannah* (Castoe et  
95 al., 2013, Vonk et al., 2013)), ongoing projects for several more (Castoe et al., 2011) and  
96 increasing amounts of transcriptomic data becoming available for a wide variety of species it is  
97 now more important than ever that these data are made as easily accessible, understandable  
98 and useable as possible. Whilst we appreciate the historical nature of the names of many snake  
99 venom toxins and do not argue that their sometimes rich history should be neglected, we must  
100 also consider the needs of the present and the future. The field of snake venom research should  
101 not distance itself from the rest of biology via the continued use of non-standardized  
102 nomenclature. If we want to facilitate collaboration with those from other research fields it is

103 important that we all speak the same language – only then can we work together to better  
104 understand the origins and evolution of snake venom; its composition and function and its  
105 possible utility in the development of novel therapeutics.

106 We note that *Toxicon*, unlike many other journals, does not currently suggest or enforce a  
107 standard nomenclature of genes reported in its papers. We therefore respectfully suggest that  
108 the Editors of this journal are well-placed to lead the way in the acquisition and development of  
109 a standardized nomenclatural system for snake venom toxins (and, indeed, for the toxins of  
110 other venomous animals). After all, what is the point of being an Editor if you can't play God  
111 once in a while?

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