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Minireview

New Nomenclature for Mammalian BSP Genes[1]

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ABSTRACT

BSP proteins and their homologs are a family of structurally related proteins characterized by the presence of tandem fibronectin type II domains. In the bovine species, BSP proteins were shown to be involved in sperm capacitation, a posttesticular maturation event necessary for sperm to acquire the ability to fertilize an oocyte. Recently, many new genes from this family have been discovered in numerous mammalian species. However, inconsistency in the nomenclature is creating much confusion. In light of the rapid growth of the BSP superfamily of proteins, we propose a new nomenclature in collaboration with the HUGO Gene Nomenclature Committee.

epididymis, male reproductive tract, seminal vesicles, sperm capacitation, sperm motility and transport

INTRODUCTION

Mammalian sperm undergo a series of maturation events before acquiring the ability to fertilize an oocyte. Over the past few decades, special attention has been paid to proteins present in seminal plasma and to their potential roles in sperm maturation events. In the bovine species, a family of closely related proteins (bovine seminal plasma, or BSP proteins) constituting approximately 60% of the total seminal plasma proteins was discovered and shown to be essential for bovine sperm capacitation, a maturation event taking place inside the female reproductive tract [1–3]. These proteins also have been shown to play a role in sperm binding to the bovine oviductal epithelium and formation of the oviductal sperm reservoir [4, 5]. Since the discovery of BSP proteins in bovine seminal plasma, homologs of these proteins have been identified in the seminal plasma of numerous other mammals, such as boar, stallion, goat, ram, and bison, indicating that these proteins would be ubiquitous in mammalian seminal plasma [6]. In addition, the characterized cDNA sequences of the bovine proteins [7] allowed for identification of homologous DNA sequences in the genomes of many other species, such as human, horse, mouse, rat, chimpanzee, dog, and rabbit [8]. The conservation of BSP-encoding genes across many mammalian species implies that these proteins constitute a family with an important role in reproduction.

Proteins of the BSP family are all of relatively low molecular mass (12–30 kDa) and can be glyscosylated or not [6]. These proteins were originally thought to be inhibins because they could inhibit the secretion of gonadotropins from cultured pituitary cells [1]. They share a common secondary structure composed of a variable N-terminal domain followed by two tandemly arranged fibronectin type II domains (~40 amino acids each) separated by a seven-amino acid linker, and a short, variable C-terminal domain (Fig. 1). In bovine, the type II domains confer many binding properties to BSP proteins, such as binding to glycosaminoglycans [9], choline phospholipids [10], high-density lipoproteins [11], gelatin [12], and sperm binding [13]. The bovine BSP proteins also bind to components of semen extenders (egg yolk low-density lipoproteins and milk caseins) used for semen preservation, and these interactions play a key role in protecting sperm during storage in liquid or frozen state [6, 14]. In boar, stallion, goat, ram, and bison, BSP proteins were isolated from the seminal plasma or seminal vesicle secretions because of the secretion of these proteins by seminal vesicles. However, important differences exist between these BSP family proteins and those found in mouse and human. First, the expression of mouse and human BSP homologs is detected in the epididymis rather than the seminal vesicles, which could suggest other functions [15]. In addition, the concentrations of BSP proteins or homologs found in the seminal plasma of bulls vary greatly compared with mice and humans [14]. Approximately 60% of the total seminal plasma proteins in bull are BSPs, compared with less than 0.01% in mice and humans [16].

Over the years, BSP family proteins and genes have been named by the groups that discovered them without much concern for a naming consensus and/or guidelines. For example, the bovine protein PDC-109 was first named according to its N- and C-terminal amino acids followed by the total number of amino acid residues [17]. PDC-109 is actually composed of two proteins, which differ only in their degree of glycosylation and which were later named BSP-A1 and BSP-A2, the "A" referring to their acidic nature [1]. BSP-A3, the third member of the bovine protein family, also was named in this way. However, BSP-30kDa was named according to its molecular mass [12, 18]. Reference to molecular mass also was employed when naming homologous proteins detected in goat [19], ram [20], stallion (HSP-12kDa) [21], and bison [22] seminal plasma. These names also indicate

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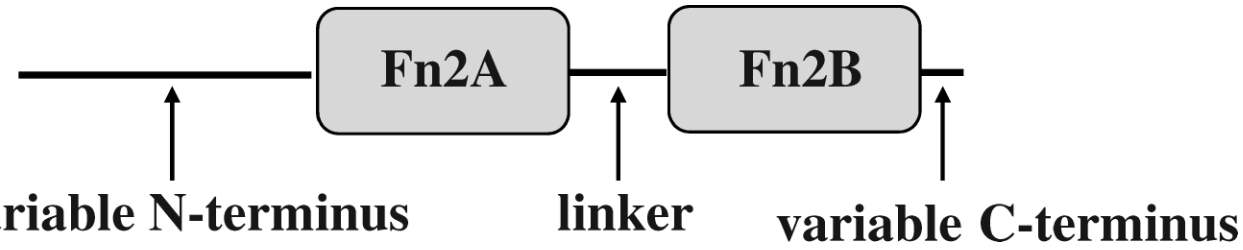

FIG. 1. General structure of BSP proteins. Fn2A, first Fn2 domain; Fn2B, second Fn2 domain.

the species and biological fluid from which each protein was detected and/or isolated; for example, in the name BiSV-16kDa, "Bi" stands for bison, whereas "SV" designates seminal vesicle fluid. Stallion seminal plasma also contains two other homologs of the BSP proteins that are named horse seminal plasma proteins 1 and 2 (HSP-1 and HSP-2), where the numbers simply indicate the order in which they were discovered [23, 24]. For the above-mentioned species, the genes encoding the BSP homologs have yet to be characterized. In the case of the porcine homolog, pB1, the name simply represents porcine seminal plasma protein 1 [25]. Another porcine seminal plasma protein, DQH, named after the first three amino acids at the amino terminus, appears to be a homolog of pB1 [26]. The cDNA encoding the porcine homolog DQH has been cloned [27].

Fibronectin type II domains, also called Fn2 domains, are really the signature of BSP proteins (Fig. 1). Recently, an extensive bioinformatics analysis of all proteins containing Fn2 domains in fully or partially sequenced genomes of several mammalian species was conducted, identifying many new potential homologs of BSP proteins [8]. In mouse and human, these genes were named according to their homology to the bovine BSPs (*hBSPH1* for human BSP homolog 1; and *mBSPH1*, *mBSPH2*, and *mBSPH3* representing mouse BSP homologs 1, 2, and 3, respectively). The complete cDNA sequences of these genes have been cloned and their mRNA expression patterns investigated, which indicated that the *mBSPH3* gene was not actively expressed [15]. Similar naming approaches were used for the homologous DNA sequences identified in rat and chimpanzee [8]. The complete list of BSP homologs discovered to date is catalogued in Table 1.

The heterogeneous naming style used to designate genes of the BSP family is beginning to create confusion, especially with the expansion of this emerging superfamily. It is becoming necessary to create a standardized manner for naming these genes. In this paper, we propose a unified approach to naming BSP family members, which includes reviewing and renaming. Table 1 groups all the BSP genes discovered thus far, along with their proposed new names, in accordance with the HUGO Gene Nomenclature Committee (http://www.genenames.org). In addition, there may be many more homologs belonging to this family that have yet to be discovered. Upon their identification, we propose that these genes be named according to the following nomenclature guidelines.

GUIDELINES

First, the signification of the name BSP, which presently stands for bovine seminal plasma, will be changed to binder of sperm. This avoids mentioning the species in the gene name and no longer alludes to the protein source. Although sperm binding has not been demonstrated for all BSP family proteins, we propose that the symbol BSP be conserved for historical

TABLE 1. Proposed nomenclature for the BSP gene family.

GenBank or Ensembl accession numbers	Species	Existing gene symbol	Proposed gene symbol	Proposed gene name	Aliases	Reference
NP_001001145	*Bos taurus*	*PDC-109*[a]	*BSP1*	Binder of sperm 1	PDC109[a], SVSP109[b], BSP-A1/A2	[17]
NP_777265	*Bos taurus*	*SVS8*[c]	*BSP3*	Binder of sperm 3	BSP-A3	[28]
ENSBTAG00000023432*	*Bos taurus*	*BSPH4*	*BSP4*	Binder of sperm 4		[8]
NP_777267	*Bos taurus*	*BSPH1*[d]	*BSP5*	Binder of sperm 5	BSP-30kDa	[7, 29]
ENSBTAG00000004042*	*Bos taurus*	*BSPH5*	*BSPH1*	Binder of sperm homolog 1		[8]
ENSBTAG00000040054*	*Bos taurus*	*BSPH6*	*BSPH2*	Binder of sperm homolog 2		[8]
NA†	*Canis familiaris*	*CDK105*	*BSP1*	Binder of sperm 1		–
NP_001075402	*Equus cabalus*	*SP1*[e]	*BSP1*	Binder of sperm 1	SP-1[e], HSP1[e]	–
NP_001075347	*Equus cabalus*	*SP2*[f]	*BSP2*	Binder of sperm 2	SP-2[f], HSP2[f]	–
NP_001121798	*Homo sapiens*	*hBSPH1*	*BSPH1*	Binder of sperm homolog 1		[8]
ENSPTRG00000011220*	*Pan troglodytes*	*pBSPH1*	*BSPH1*	Binder of sperm homolog 1		[8]
NP_001028590	*Mus musculus*	*mBSPH1*	*Bsph1*	Binder of sperm homolog 1		[8]
XP_001079751	*Rattus norvegicus*	*rBSPH1*	*Bsph1*	Binder of sperm homolog 1		[8]
NP_001074411	*Mus musculus*	*mBSPH2*	*Bsph2a*	Binder of sperm homolog 2a		[8]
NA†	*Mus musculus*	*mBSPH3*	*Bsph2b*	Binder of sperm homolog 2b		[8]
NA†	*Rattus norvegicus*	*rBSPH2*	*Bsph2*	Binder of sperm homolog 2		[8]
NP_001075516	*Oryctolagus cuniculus*	*EP52C1*[g]	*BSP1*	Binder of sperm 1	EP52-C1[g]	–
NP_998997	*Sus scrofa*	*pB1*[h]	*BSP1*	Binder of sperm 1		[27]

* These genes predicted from genomic sequences can be found in the Ensembl database (http://ensembl.org).
† NA, not available; these genes predicted from genomic sequences are not currently annotated in Genbank or Ensembl.
[a–h] Name associated with existing gene symbol. [a]protein with N-terminal aspartic acid and C-terminal cysteine, having 109 amino acids; [b]seminal vesicle secretory protein; [c]seminal vesicle secretion 8; [d]bovine seminal plasma protein-like1; [e]seminal plasma or horse seminal plasma protein 1 precursor; [f]seminal plasma or horse seminal plasma protein 2 precursor; [g]epididymal protein 52; [h]boar seminal plasma protein.

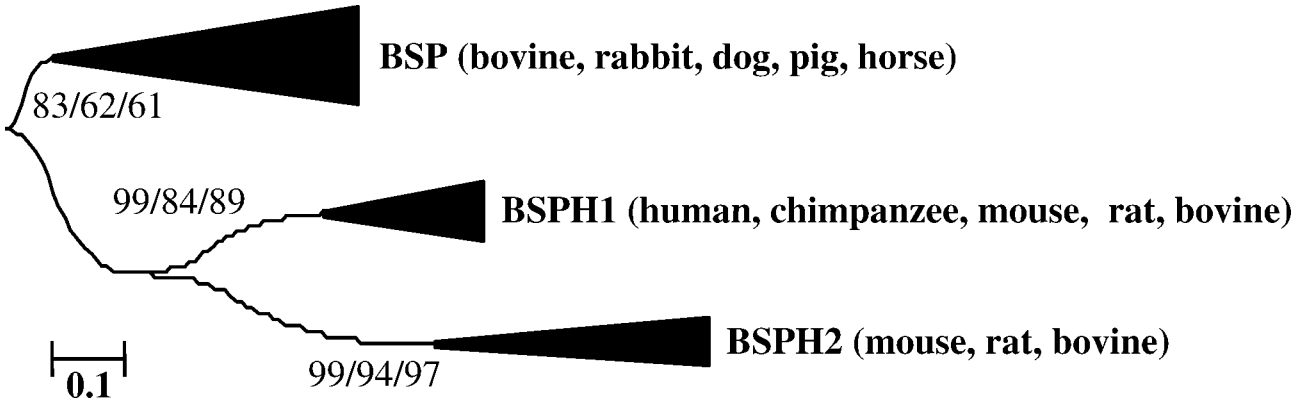

FIG. 2. The BSP clade is composed of three subfamilies. Neighbor-joining trees of the two Fn2 domains of BSP-related proteins, showing that BSP proteins and their relatives are separated into three subfamilies: BSP, BSPH1, and BSPH2. Bootstrap values from 1000 replicates for neighbor-joining (first number), 1000 replicates for maximum parsimony (second number), and 100 replicates for maximum likelihood (third number) are indicated at the nodes and were used to assess the robustness of the trees. Genetic distance is indicated as the number of substitutions per amino acid site (see details in Fan et al. [8]).

reasons. The proposed new gene symbols and names for existing BSP genes based on Figure 2 are enumerated in Table 1. In addition, the following guidelines are proposed for naming newly discovered BSP genes.

1. Only proteins containing two Fn2 domains, which are defined within the lineages as described previously [8], will be considered members of the BSP superfamily. The name BSP should not be attributed to proteins that are homologous to only one of the Fn2 domains or to proteins that contain more than two of these domains.

2. If and when new genes and gene families are discovered within this superfamily in mammalian species, we propose that they be given the names BSP, BSPH1, or BSPH2, depending on their phylogenetic relationships, or named BSPH3, BSPH4, etc. in the case of new gene families.

3. We propose that the symbol BSPL [no.] (BSP-like group [no.]) may be used to designate genes that fulfill these criteria and:

- are from organisms other than mammals
- are homologous to BSPs (i.e., homology to both Fn2 domains)
- do not fall within the established family.

In consensus with the proposed gene names, the proteins encoded by these genes would be designated in the same manner but without italics. Interestingly, in ungulates like ram (*Ovis aries*), bison (*Bison bonasus*), and goat (*Capra hircus*), three to four BSP-homologous proteins have been purified from either seminal plasma or seminal vesicle secretions [19, 20, 22]. However, the genes encoding these proteins have not yet been characterized. In addition, one BSP gene is predicted from genomic sequences in the chimpanzee (*Pan troglodytes*) as well as two in the rat (*Rattus norvegicus*) [8]. We hope that these naming guidelines will aid in eliminating the confusion existing with the current names attributed to BSP genes. In addition, these guidelines will allow a standardized way to name newly discovered genes of the BSP superfamily of proteins.

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