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Authors: Hervé Tostivint, Isabelle Lihmann, Hubert Vaudry

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New insight into the molecular evolution of the somatostatin family

Hervé Tostivint^{1,2}, Isabelle Lihmann^{1,2}, Hubert Vaudry^{1,2*}

¹*INSERM U413, Laboratory of Cellular and Molecular Neuroendocrinology;*

²*European Institute for Peptide Research (IFRMP 23), University of Rouen,
76821 Mont-Saint-Aignan, France*

* To whom correspondence should be addressed. Tel.: (33) 235-14-6624; Fax.: (33) 235-14-6946; E-mail: hubert.vaudry@univ-rouen.fr

Abstract

The present review describes the molecular evolution of the somatostatin family and its relationships with that of the urotensin II family. Most of the somatostatin sequences collected from different vertebrate species can be grouped as the products of at least four loci. The somatostatin 1 (SS1) gene is present in all vertebrate classes from agnathans to mammals. The SS1 gene has given rise to the somatostatin 2 (SS2) gene by a segment/chromosome duplication that is probably the result of a tetraploidization event according to the 2R hypothesis. The somatostatin-related peptide cortistatin, first identified in rodents and human, is the counterpart of SS2 in placental mammals. In fish, the existence of two additional somatostatin genes has been reported. The first gene, which encodes a peptide usually named somatostatin II (SSII), exists in almost all teleost species investigated so far and is thought to have arisen through local duplication of the SS1 gene. The second gene, which has been characterized in only a few teleost species, encodes a peptide also named SSII that exhibits a totally atypical structure. The origin of this gene is currently unknown. Nevertheless, because the two latter genes are clearly paralogous genes, we propose to rename them SS3 and SS4, respectively, in order to clarify the current confusing nomenclature. The urotensin II family consists of two genes, namely the urotensin II (UII) gene and the UII-related peptide (URP) gene. Both UII and URP exhibit limited structural identity to somatostatin so that UII was originally described as a “somatostatin-like peptide”. Recent comparative genomics studies have revealed that the SS1 and URP genes, on the one hand, and the SS2 and UII genes, on the other hand, are closely linked on the same chromosomes, thus confirming that the SS1/SS2 and the UII/URP genes belong to the same superfamily. According to these data, it appears that an ancestral somatostatin/urotensin II gene gave rise by local duplication to a somatostatin ancestor and a urotensin II ancestor, whereupon this pair was duplicated (presumably by a segment/chromosome duplication) to give rise to the SS1-UII pair and the SS2-URP pair.

Keywords: somatostatin, urotensin II, cortistatin, neuropeptides, molecular evolution, multigenic families, gene duplication, comparative genomics.

Abbreviations: CRH, corticotropin-releasing hormone; CST, cortistatin; GRH, growth hormone-releasing hormone; NPY, neuropeptide tyrosine; PACAP, pituitary adenylate cyclase-activating polypeptide; PAMNT, proadrenomedullin N-terminal peptides; PCST, procortistatin; PSS, prosomatostatin; SS, somatostatin; SST, somatostatin receptor; UII, urotensin II; URP, urotensin II-related peptide; UT: UII/URP receptor; VIP, vasoactive intestinal polypeptide.

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1. Introduction

In vertebrates, most neuropeptides are members of multigene families that have extended by successive gene duplications (Conlon and Larhammar, 2005). Owing to the characteristic tokens that these duplication events have left in the genome, comparative genomics has now become a very powerful approach to trace back the phylogenetic history of multigene families (Van de Peer, 2004; Durand and Hoberman, 2006). Two types of gene duplications are generally distinguished: local duplications that implicate individual genes, and segmental duplications that involve chromosomal segments or even the entire genome (Van de Peer, 2004). Vertebrates are known to have undergone several rounds of whole genome duplications that took place very early during their history (Dehal and Boore, 2005), and the occurrence of a third tetraploidization event in the ancestral fish lineage has been recently demonstrated (Jaillon et al., 2004).

Somatostatin has long been viewed as the sole representative of its family, at least in tetrapods. However, numerous studies have subsequently shown that many (possibly all) vertebrates, including amphibians, reptiles, birds and mammals, have a family of somatostatin genes (Conlon et al., 1997a; Lin et al., 2000a; Tostivint et al., 2004a). The aim of the present review is to briefly describe the diversity of somatostatin-related peptides, to revisit the evolutionary history of this multigene family at the light of recent data provided by comparative genomics, and to propose a new nomenclature taking into account these data.

2. Diversity of somatostatin-related peptides

The neuropeptide somatostatin is a cyclic tetradecapeptide (SS-14) that has been initially identified from ovine hypothalamic extracts on the basis of its ability to inhibit growth hormone release (Brazeau et al., 1973). Since the original discovery of this peptide (later called somatostatin 1; SS1) several other somatostatin-related peptides have been characterized in various vertebrate species. All somatostatin variants exhibit a relatively well conserved structure with only a few variations in sequence and size. They possess a cyclic

conformation ensured by the presence of two Cys residues, and their cyclic region encompasses the Phe-Trp-Lys motif that is essential for their biological activity (Veber et al., 1979). The somatostatin genes generally contain only one intron, located in the region encoding the cryptic domain, and the somatostatin peptides are all located at the C-terminal extremity of the precursors.

2.1. Somatostatin 1

Of all the structural variants of somatostatin, SS1 is the only one that is almost totally conserved and universally present in all vertebrate species (Fig. 1; Table 1). SS1 is widely distributed in the central nervous system where it affects locomotor, sensitive, autonomic and cognitive functions, as well as in various peripheral organs where it is involved in the control of the secretory activity and proliferation of a wide range of endocrine and exocrine cells (Olias et al., 2004). SS1 is synthesized as part of a larger precursor molecule, named prepro-SS1 (PSS1), which is also able to generate, notably in mammals, an N-terminally-extended form of 28 residues, called somatostatin-28 (SS-28; Fig. 1; Esch et al. 1980; Pradayrol et al., 1980). The two peptides SS1 and SS-28 are synthesized in variable amounts by distinct PSS1-producing cells as a result of differential precursor processing. Thus, SS1 is most abundant in the brain, stomach and pancreas, while SS-28 predominates in the intestine. In mammals, the actions of SS1 are mediated via five somatostatin receptor subtypes (SST₁₋₅) which all belong to the G protein-coupled receptor superfamily (Møller et al., 2003; Olias et al., 2004). SS1 binds to all five subtypes with comparable potency, but the affinity of SST₁₋₄ for SS1 is two to three times higher than for SS-28. In contrast, SST₅ appears to preferentially bind SS-28 than SS1 (Panetta et al., 1994; Patel et al., 1994). In fish, a total of four different SST subtypes have been characterized (SST₁₋₃, SST₅). In goldfish and trout, several isoforms of these receptor subtypes have been identified (Lin et al., 1999a, 2000b, 2002; Lin and Peter 2003; Slagter and Sheridan, 2004).

2.2. Somatostatin 2 / cortistatin

Besides PSS1, numerous bony vertebrate species have been shown to express a second somatostatin precursor named SS2, also termed SSIII in non-mammalian species, and cortistatin (CST) in most mammals. Peptides derived from this second precursor exhibit a more variable structure than SS1 but all share a unique Pro residue at position 2 (Spier and de Lecea, 2000; Tostivint et al., 2004a) (Fig. 2; Table 2). In placental mammals, CST also possesses an additional Lys residue at its C-terminal extremity. Like SS1, CST and SS2 are flanked at their N-terminus by a dibasic cleavage site. Additional dibasic residues are present in the N-flanking region of the CST precursor (PCST) in some mammalian species including rat and human, suggesting that, in these species, N-terminally-extended forms of CST may also be produced. Consistent with this view, it has been shown that PCST is efficiently processed to both CST-14 and CST-29 in AtT-20 cells (Puebla et al., 1999). In contrast to the SS1 gene, the CST and SS2 genes are specifically expressed in the brain but not in the pancreas or gut (Fabre et al., 2004; Tostivint et al., 2004a). In the central nervous system, the distribution of CST or SS2 mRNA-containing cells is quite variable among the different taxa. Thus, in mammals, CST mRNA is almost exclusively present in the telencephalon, while in non-mammalian species, SS2 mRNA occurs in all subdivisions of the brain and in the spinal cord (Fabre et al., 2004; Tostivint et al., 2004a). As expected from their structural similarities, CST and SS2 can mimic several of the effects of SS1 (de Lecea et al., 1996; Jeandel et al., 1998). However, in rat, CST and SS1 have been found to induce differential responses, in particular on cortical electrical activity, locomotor behavior and paradoxical sleep (Fabre et al., 2004). Interestingly, structure-activity relationship studies have shown that the Pro moiety at position two and the C-terminal Lys residue are crucial for these distinctive effects (Criado et al., 1999). CST binds to all SST subtypes *in vitro* (Siehler et al., 1998) and interacts with the same binding sites as SS1 in the rodent brain (Spier et al., 2005). It has also been reported that the orphan receptor MrgX2 can selectively bind CST (Robas et al., 2003); however, whether CST is actually the natural ligand of this receptor is currently a matter of debate, since recent data indicate that MrgX2

is also able to bind with high affinity proadrenomedullin N-terminal peptides (PAMNT; Kamohara et al., 2005). Indeed, the active cores of CST and PAMNT exhibit some structural similarities *i.e.* they both contain two aromatic amino acids and a C-terminal basic residue that are all arranged in a similar manner (Nothacker et al., 2005).

2.3. Teleost somatostatin variants

Among vertebrates, teleost fish represent the group exhibiting the highest number of somatostatin variants. Thus, the occurrence of a third somatostatin precursors (PSSII) has been initially established in anglerfish (Hobart et al., 1980) and later on in other species of fish including trout (Moore et al., 1995, 1999) and goldfish (Lin et al., 1999b). Most peptides derived from PSSII, which are generally 25- to 28-amino acids in length, encompass a [Tyr⁷,Gly¹⁰]SS-14 sequence at their C-terminal extremity, although other amino acid substitutions have also been reported (Fig. 3; Table 3; Lin et al., 2000a). In some species such as catfish (Magazin et al., 1982; Andrews et al., 1984) and zebrafish (Devos et al., 2002), the third somatostatin variant which has been unsuitably also named SSII (see below) exhibits a very atypical structure (Fig. 4; Table 4). The SSII gene is expressed both in the central nervous system and in peripheral organs, especially in the gastrointestinal tract (Lin et al., 1999b; Moore et al., 1999). In the brain, SSII mRNA occurs almost exclusively in discrete hypothalamic nuclei (Canosa et al., 2004). The functional significance of SSII gene-derived peptides is still poorly understood. However, in some species, SSII and SS1 appear to exhibit distinct actions. For instance, in goldfish, it has been reported that SSII is a more potent inhibitor of basal GH release than SS1 or SS2 (Yunker et al., 2003). Likewise, in trout, SSII, but not SS1, reduces plasma insulin level (Eilerston and Sheridan, 1993). It is also interesting to note that, in trout, the two distinct isoforms of SST₁, *i.e.* SST_{1A} and SST_{1B}, exhibit higher affinity for PSS1- than for PSSII-derived peptides (Gong et al., 2004).

2.4. Other somatostatin variants

Two somatostatin variants have been characterized in the lampreys. One of them is SS1, and the other one is a 33- to 37-residue peptide which contains a [Ser¹²]SS-14 sequence at its C-terminal extremity (Fig. 5; Table 5; Andrews et al., 1988; Conlon et al., 1995a,b). In both *Lampetra fluviatilis* and *Petromyzon marinus*, SS1 predominates in the brain while the [Ser¹²]SS-14-containing variants are primarily found in the pancreas (Andrews et al., 1988; Sower et al., 1994; Conlon et al., 1995a). In *Geotria australis*, processing of the [Ser¹²]SS-14 precursor is tissue-specific: in the pancreas, [Ser¹²]SS-14 is the major molecular form while, in the intestine, the [Ser¹²]SS-14 precursor is processed almost exclusively to the 33-amino acid form (Conlon et al., 1995b; Wang et al., 1999a). Finally, a molecular variant of somatostatin containing the substitution Asn⁵ → Ser has been isolated from pancreas extracts of a holocephalan fish, the Pacific ratfish (Fig. 5; Table 5; Conlon, 1990). It is currently not known whether this species possesses other somatostatin-related peptides, particularly in the brain. Thus, the view that this [Ser⁵]SS-14 is a product of the SS1 gene cannot totally be ruled out.

3. Origin of the genes encoding somatostatin-related peptides

3.1. Somatostatin 1 gene

The occurrence of SS1 in all vertebrate classes indicates that the SS1 gene is a very ancient gene, that was likely already present more than 500 Myr ago in the ancestor of all extant vertebrates (Tostivint et al., 2004a). Although somatostatin-like immunoreactive material has been detected in numerous invertebrate species, and even in some plants and bacteria, so far, somatostatin-related peptides have been characterized only in vertebrates. It should be noticed, however, that several invertebrate species, such as *Ciona* and *Drosophila* possess somatostatin-like receptors. In *Ciona*, it has been established that two of these sequences (accession numbers: NP_001042 and NP_001044) are closely related to SST₃ and SST₅, respectively (Sekiguchi et al., 2007). In the same species, Deyts et al. (2006) have reported no less than 12 somatostatin-like receptor sequences. However, the natural ligands

for these receptors remain elusive. In *Drosophila*, two somatostatin-like receptors, referred to as Drostar-1 and -2, have been characterized (Popovici et al., 2001; Kreienkamp et al., 2002). A reverse pharmacological approach has shown that Drostar receptors bind to peptides of the allatostatin C family (Kreienkamp et al., 2002). Although allatostatin C peptides and somatostatin do not exhibit any appreciable sequence similarity (Fig. 6), it is interesting to note that peptides of these two families both possess a disulfide bond and derive from precursors exhibiting the same general organization, with the mature peptide located at the C-terminus (Kreienkamp et al., 2002). Moreover, allatostatin C peptides, as hypothalamic somatostatin, are produced by neurosecretory neurones and are involved in the control of growth (Bendena et al., 1999). Whether these two families of neuropeptides are evolutionarily related or whether their structural similarities are due to convergent evolution remains to be determined.

3.2. Somatostatin 2 / cortistatin gene

The SS2 and CST peptides share several important features: they both possess a Pro residue at position 2 and, in contrast to SS1, they are almost exclusively expressed in the brain but not in peripheral organs (Tostivint et al., 2004a). However, because their precursors exhibit very limited sequence similarity, apart from their C-terminus, the phylogenetic relationships between SS2 and CST have remained uncertain for a long time. This issue has been recently resolved when several homologous genes have been shown to occur in the vicinity of both the zebrafish SS2 and human CST genes (Fig. 7; Tostivint et al., 2004b), indicating that SS2 and CST actually derive from orthologous genes. In the opossum, the only marsupial species whose genome has been sequenced up to now, *in silico* analysis has revealed that the SS2 peptide does not possess a Lys moiety at its C-terminus (Fig. 1), suggesting that the acquisition of this residue is a recent event that happened late during evolution of the placental mammalian lineage.

In human, it has been shown that the SS2/CST gene maps to 1p36 close to several other genes that have relatives in the vicinity of the SS1 gene on 3q28. This observation strongly

suggests that 1p36 and 3q28 are two paralogous regions and thus arose by segmental duplication, potentially as part of a whole genome duplication event (Fig. 8; Tostivint et al., 2006). This duplication event may coincide with one of the two rounds of tetraploidization that, according to the 2R hypothesis, are thought to have occurred very early during vertebrate evolution, *i.e.* before the origin of gnathostomes (Dehal and Boore, 2005). To test this hypothesis, it would be interesting to look for the existence of an SS2 gene in elasmobranchs, and even in lampreys. Whether the lamprey [Ser¹²]SS-14 variant represents an SS2 gene product or results from gene duplication within the cyclostome lineage is currently unknown (Tostivint et al., 2004b).

3.3 Teleost-specific somatostatin genes

As mentioned above, most peptides derived from PSSII contain the [Tyr⁷,Gly¹⁰]SS-14 sequence at their C-terminal extremity. In *Fugu*, as in *Tetraodon*, the SSII gene is in close proximity to the SS1 gene, suggesting that the two genes arose by a local duplication (Tostivint et al., 2004b). This local duplication likely occurred relatively early during teleost evolution since the SSII gene is also present in eel (Conlon et al., 1988a) which is viewed as a very basal euteleost species. It should be noted that this duplication event is totally distinct from the fish-specific genome duplication event also called 3R (see below).

In contrast to most other teleost SSII, catfish and zebrafish SSII exhibit a very unusual structure (Magazin et al., 1982; Andrews et al., 1984; Devos et al., 2002). The evolutionary relationship between the common SSII and this peculiar isoform has long remained unclear. The fact that, in zebrafish, atypical SSII and SS1 genes are localized on two distinct chromosomes strongly suggested that the SSII gene and the atypical SSII gene had distinct evolutionary histories and were thus paralogous genes (Tostivint et al., 2004a). We show here for the first time that the zebrafish genome contains a gene encoding for a [Tyr⁷, Gly¹⁰]SS14 variant (Fig. 3), in addition to the atypical SSII gene (Fig. 4). The fact that this gene maps very closely to the SS1 gene (Fig. 9), like in pufferfish, indicates that it is orthologous to the common SSII gene. The occurrence in a same species of both the

common SSII gene and the atypical SSII gene provides strong evidence that these two genes are paralogous. The atypical SSII gene may result from the 3R event that occurred relatively early in the ray-finned fish lineage. Alternatively, it may have appeared much later during teleost evolution. The fact that all the species possessing this gene – namely catfish, zebrafish and the fruit-eating fish, pacu (Ferraz de Lima et al., 1999) – belong to the group of ostariophysi would support the latter hypothesis.

In some species, such as the trout and goldfish (Uesaka et al., 1995; Lin et al., 1999b; Moore et al., 1999; Fig. 3), the occurrence of two copies of the typical SSII gene has been demonstrated. In the fugu, we have also detected two copies of the SS1 gene, that we propose to name SS1a and SS1b (Fig. 1). It is likely that all these copies result from the tetraploidization event that has occurred in the ray-finned fish lineage (Amores et al., 1998; Hoegg et al., 2004). Alternatively, in particular in trout, the two SSII gene copies may result from the additional tetraploidization event that has affected the salmonid fish genome about 25 Myr ago (Allendorf et al., 1983; Moghadam et al., 2005).

3.4. Other somatostatin genes

The occurrence of somatostatin-like immunoreactivity, that does not derive from the CST gene, has been reported in the proximal midgut of somatostatin-deficient mice, strongly suggesting the existence of a novel somatostatin-related gene in mammals (Ramirez et al., 2002). In support of this hypothesis, a novel peptide, termed thrittene, whose sequence corresponds to S-28₍₁₋₁₃₎ but does not derive from PSS1 or PCST, has also been characterized in the rat and monkey intestinal tract (Ensinck et al., 2002). Further studies will be necessary to identify the mysterious gene encoding this novel somatostatin-related peptide.

4. Evolutionary relationships between somatostatin- and urotensin II-related

Urotensin II (UII) has been first isolated from the caudal neurosecretory system of teleost fish on the basis of its smooth muscle contracting activity (Pearson et al., 1980). It has been

subsequently shown that UII exists in all vertebrate classes from agnathans to mammals, including human (Conlon et al., 1992; 1997a; Coulouarn et al., 1998, 1999). The primary structure of UII has been relatively well conserved during vertebrate evolution, notably in its C-terminal region (Conlon et al., 1997a; Coulouarn et al., 1998, 1999). The occurrence of a second UII isoform, named UII-related peptide (URP), has recently been reported in tetrapods and teleosts (Sugo et al., 2003; Tostivint et al., 2006). A single receptor for UII and URP, called UT, has been identified so far (Ames et al., 1999; Mori et al., 1999; Nothacker et al., 1999; Liu et al., 1999). Pharmacological studies have shown that UII and/or URP may be implicated in the control of a broad range of biological processes including cardiovascular activities, homeostasis, metabolic functions and behaviors (Douglas et al., 2004; Lihrmann et al., 2006; Do Rego et al., 2008). However, to date, the physiological roles of UII and URP have not been clearly identified.

It has been initially recognized that UII and SS1 exhibit limited structural similarities including a disulfide bridge and a common motif, Phe-Trp-Lys, which is essential for their biological activity (Fig. 10; Veber et al., 1979; Flohr et al., 2002; Labarrère et al., 2003; Chatenet et al., 2004), so that UII has been first described as a somatostatin-like peptide (Pearson et al., 1980). In addition, it has been found that the organization of the precursors of UII, SS1 and related peptides are globally similar (Shen et al., 1982; Ohsako et al., 1986; Tostivint et al., 1996; Coulouarn et al., 1998, 1999). Nevertheless, characterization of the cDNA encoding the UII precursor has shown that prepro-UII and prepro-SS1 do not exhibit appreciable sequence identity (Ohsako et al., 1986; Coulouarn et al., 1998, 1999) and hence, it was concluded that the UII and SS1 precursors were probably not derived from a common ancestral gene.

It has been recently shown however that, in several species, including human, rodent, chicken and zebrafish, the UII gene is closely linked to the SS2/CST gene, while the gene encoding the novel UII-related peptide, URP, is located in the same chromosomal region as the SS1 gene. From these data, it has been proposed that the genes encoding UII- and somatostatin-related peptides may have arisen from a common ancestral gene which

underwent two rounds of gene duplication (Tostivint et al., 2006). The local duplication must have occurred early during vertebrate evolution since both somatostatin and UII peptides are present in lampreys, while the segment/chromosome duplication may correspond to one of the whole genome duplications that have affected early vertebrates (Tostivint et al., 2006). The existence of both CST/SS2 and URP genes in fish (Tostivint et al., 2004b; 2006) supports this scenario.

As far as the receptors are concerned, SSTs and UT display relatively high sequence similarity (Marchese et al., 1995; Tal et al., 1995). A common evolutionary origin for SSTs and UT is also strongly supported by the chromosomal localization of their genes. Indeed, the SST₃ and UT genes are physically linked at the same locus, suggesting that the genes encoding the two receptors arose by local duplication (Tostivint et al., 2006).

Taken together, these observations provide strong evidence for a co-evolutionary process of the somatostatin/UII family of peptides and their cognate receptors SSTs/UT, consistent with the notion that related G protein-coupled receptors, such as NPY receptors (Cerdá-Reverter and Larhammar, 2000), VIP/PACAP receptors (Sherwood et al., 2000; Vaudry et al., 2000) and opiate receptors (Dores et al., 2002), are also usually activated by paralogous peptides.

5. Proposal for a novel nomenclature of somatostatin gene family

As mentioned above, only two somatostatin variants are known in mammals, namely SS1 and SS2. Because we are well aware that the designations somatostatin and cortistatin are widely accepted by all researchers working on mammalian somatostatin-related peptides, we think that it would not be judicious to change this nomenclature. We thus propose to maintain the terms somatostatin and cortistatin to designate mammalian SS1 and SS2, respectively. However, the current nomenclature used to designate somatostatin-related peptides in other vertebrate classes, particularly in fish, is really confusing. In particular, distinct peptides, such as the common and atypical SSII isoforms of teleosts, that derive from paralogous genes, have received the same designation (Su et al., 1988; Lin et

al., 1999). Reciprocally, some peptides, that are clearly encoded by orthologous genes, are named differently. This is the case for SS2, which in teleosts is also designated as somatostatin III (Lin et al., 1999; Nelson and Sheridan, 2005) or somatostatin 3 (Devos et al., 2002). We therefore suggest to reconsider this nomenclature, which was primarily based on the chronology of the characterization of all these variants, at the light of the evolutionary relationship between somatostatin peptides. Taking into account these considerations, we propose to apply the following rules: *i)* all peptides that derive from orthologous genes should receive, as far as possible, the same name; *ii)* each somatostatin-related peptide should be named SS followed by an arabian number; and *iii)* the numerical order of these numbers should reflect the phylogenetic history of the genes. Hence, we suggest to apply the following nomenclature, at least for comparative studies, involving non-mammalian species:

- SS1 should designate the common isoform (somatostatin-14), that occurs in all vertebrates.
- SS2 should designate variants containing a Pro residue at position 2, that occur in osteichthyans.
- SS3 should designate variants containing both Tyr⁷ and Gly¹⁰ residues, that occur in teleost fish.
- SS4 should designate variants containing Tyr, Ser, Arg and Ala residues at positions 6, 10, 11 and 13, respectively, that only occur in species of the group of ostariophysii.
- For all these peptides, as well as for UII-related peptides, the greek letters α and β should be used to designate variants occurring in some teleost species that likely arose from the fish-specific tetraploidization event 3R.

6. Concluding remarks

The data presented here support the existence of at least four distinct somatostatin genes in vertebrates as illustrated in figure 11: *i)* the somatostatin 1 (SS1) gene which clearly represents the ancestral gene of the family, *ii)* the somatostatin 2/cortistatin (SS2/CST) gene which occurs in all osteichthyans and arose from the SS1 gene by segment/chromosome

duplication, *iii*) the somatostatin 3 (SS3) gene, previously termed SSII gene, which exists only in teleosts and results from a local duplication of the SS1 gene, and *iv*) the somatostatin 4 (SS4) gene, previously termed atypical SSII gene, which is restricted to the group of ostariophysi and whose origin is currently unknown. In teleost species, some of these genes can be found in two copies that may result from the fish-specific genome duplication (Fig. 11). The data also suggest that somatostatin- and urotensin II-related peptides most likely derive from a same ancestral gene, as the result of a local duplication that arose very early during vertebrate evolution. Finally, they show that SS2 and URP genes arose simultaneously by a segment/chromosome duplication that can be interpreted within the 2R framework (Fig. 11).

Gene duplication is thought to have played an important role in the appearance of novel gene functions, since newly created genes are under relaxed selected pressure and are thus free to diverge and evolve novel functions or subfunctionalize and acquire distinct expression patterns (Lynch and Force, 2000; Lynch, 2002; Cusack and Wolfe, 2007). The physiological roles of SS1 have been thoroughly investigated and it has been shown that the actions of SS1 on various organs are associated with a wide range of regulations on growth, development, metabolic and immune responses (Olias et al., 2004). Other somatostatin isoforms, such as CST in mammals (Fabre et al., 2004) and, to a lesser extent, SSII in teleost fish (Nelson and Sheridan, 2005) have been shown to exert some markedly different effects as compared to SS1, consistent with their distinct tissue distribution. However, their physiological significance is currently largely unknown. Further studies will be necessary to better understand the functional implications of the structural diversity of somatostatin-related peptides.

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Legends to figures

Fig. 1. Alignment of the amino acid sequences of prepro-somatostatin 1-derived peptides. Conserved residues are in bold characters.

Fig. 2. Alignment of the amino acid sequences of prepro-somatostatin 2- / prepro-cortistatin-derived peptides. Conserved residues are in bold characters. The Pro² residue that is characteristic of SS2 is boxed.

Fig. 3. Alignment of the amino acid sequences of prepro-somatostatin 3- (previously designated prepro-somatostatin II-) derived peptides. Conserved residues are in bold characters. Characteristic residues of SS3 are boxed.

Fig. 4. Alignment of the amino acid sequences of prepro-somatostatin 4- (previously designated atypical prepro-somatostatin II-) derived peptides. Conserved residues are in bold characters. Characteristic residues of SS4 are boxed.

Fig. 5. Alignment of the amino acid sequences of other somatostatin-related peptides. Conserved residues are in bold characters. Characteristic residues of these variants are boxed.

Fig. 6. Comparison of the amino acid sequences and predicted secondary structures of somatostatin 1 (SS1) and *Drosophila* allatostatin C (AIIIC).

Fig. 7. Map showing chromosomal positions of the somatostatin 2 (SS2) gene in zebrafish and the cortistatin (CST) gene in human. A conserved synteny on zebrafish linkage group 23 (LG23) and human 1p36 can be observed. All distances, expressed in Mb, were retrieved from Ensembl. The chromosome locations of the zebrafish genes were taken from the 7th

assembly (version Zv7) of the zebrafish genome, released on July 13, 2007. CTNNBIP1, catenin beta-interacting protein 1; HKR3, *Homo sapiens* GLI-Kruppel family member 3; MASP, mannose-binding lectin-associated serine protease; PGD, phosphogluconate dehydrogenase; TARDBP, TAR DNA binding protein; SDR1, short-chain dehydrogenase/reductase 1.

Fig. 8. Map showing chromosomal positions of the genes encoding somatostatin 1 (SS1), cortistatin (CST), urotensin II (UII) and urotensin II-related peptide (URP) in human. A conserved synteny on 1p36 and 3q28 can be observed. All distances, expressed in Mb, are taken from Ensembl. CLCN, chloride channel; MASP, mannose-binding lectin-associated serine protease; TP73, tumor protein 73; TP73L, tumor protein 73-like; UII, urotensin II; URP, urotensin II-related peptide.

Fig. 9. Map showing chromosomal positions of the genes encoding somatostatin 1 (SS1), somatostatin 3 (SS3; previously designated SSII) and somatostatin 4 (SS4; previously designated atypical SSII) in zebrafish. All distances, expressed in Mb, were taken from the Ensembl database, version Zv7.

Fig. 10. Comparison of the amino acid sequences and predicted secondary structures of somatostatin 1 (SS1), goby urotensin II (UII) and mammalian urotensin II-related peptide (URP).

Fig. 11. Proposed gene duplication scheme for the SS/UII superfamily. The crossed-through genes were probably lost after duplication events. SS, somatostatin; CST, cortistatin; UII, urotensin II; URP, urotensin II-related peptide. α and β isoforms designate variant genes that occur in some teleost species which probably arose from the fish-specific tetraploidization event. So far, only one copy of the URP gene has been identified, suggesting that the second

copy has been lost during teleost evolution. The origin of the SS4 gene (previously designated atypical SSII gene) is currently unknown.

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Figure 2

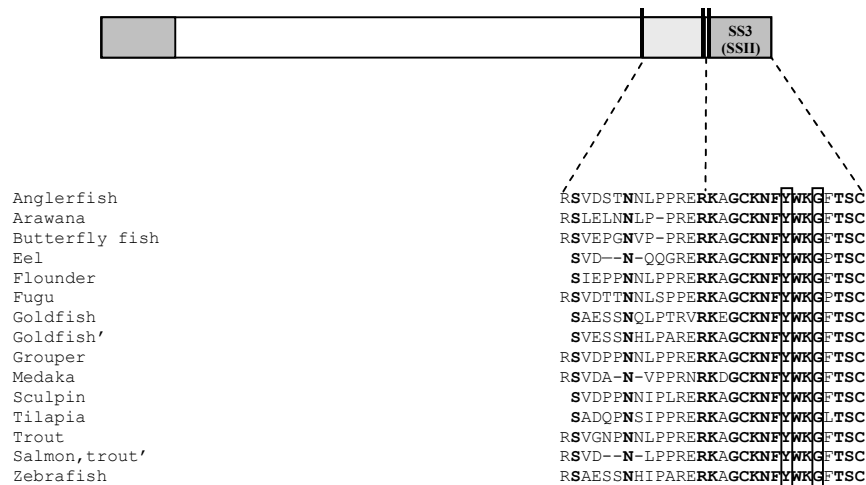


Figure 3

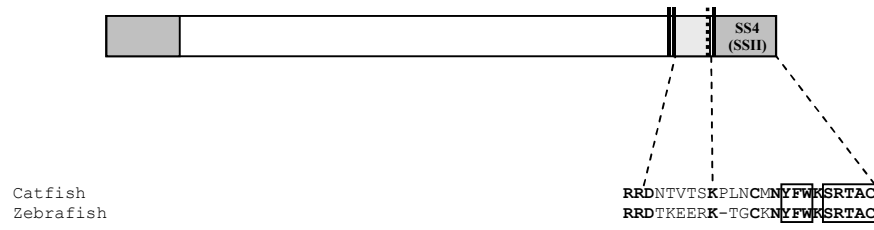


Figure 4

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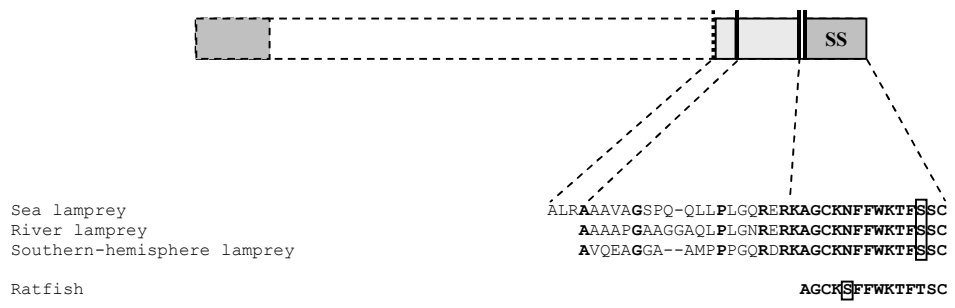


Figure 5

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Table 5.
Characterization of the sequences of other somatostatin-related peptides

Species	Source	References
River lamprey, <i>Lampetra fluviatilis</i>	P	Conlon et al., 1995a
Sea lamprey, <i>Petromyzon marinus</i>	P	Andrews et al., 1988
Southern-hemisphere lamprey, <i>Geotria australis</i>	P	Conlon et al., 1995b
Pacific ratfish, <i>Hydrolagus collieri</i>	P	Conlon, 1990

P, sequences were determined from peptides.

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Figure 6

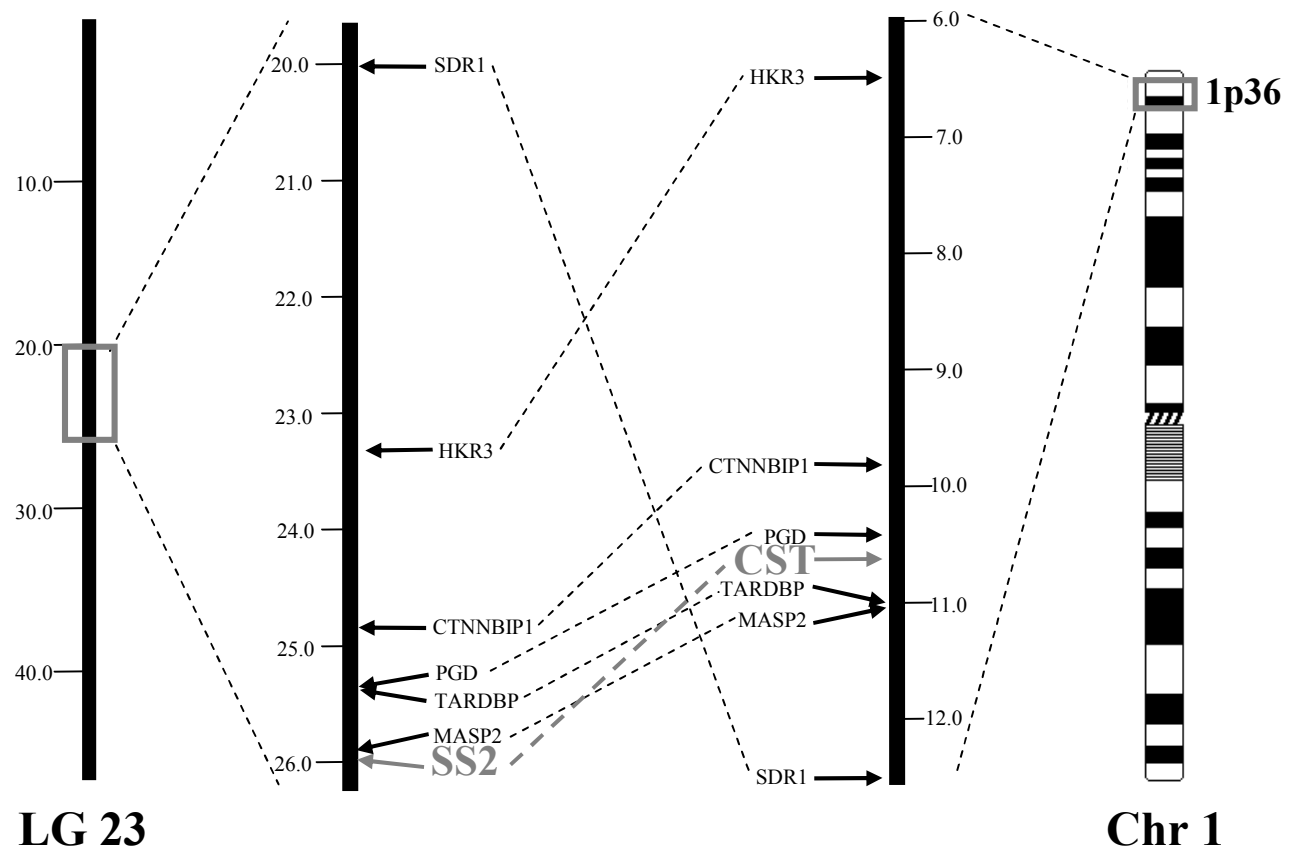


Figure 7

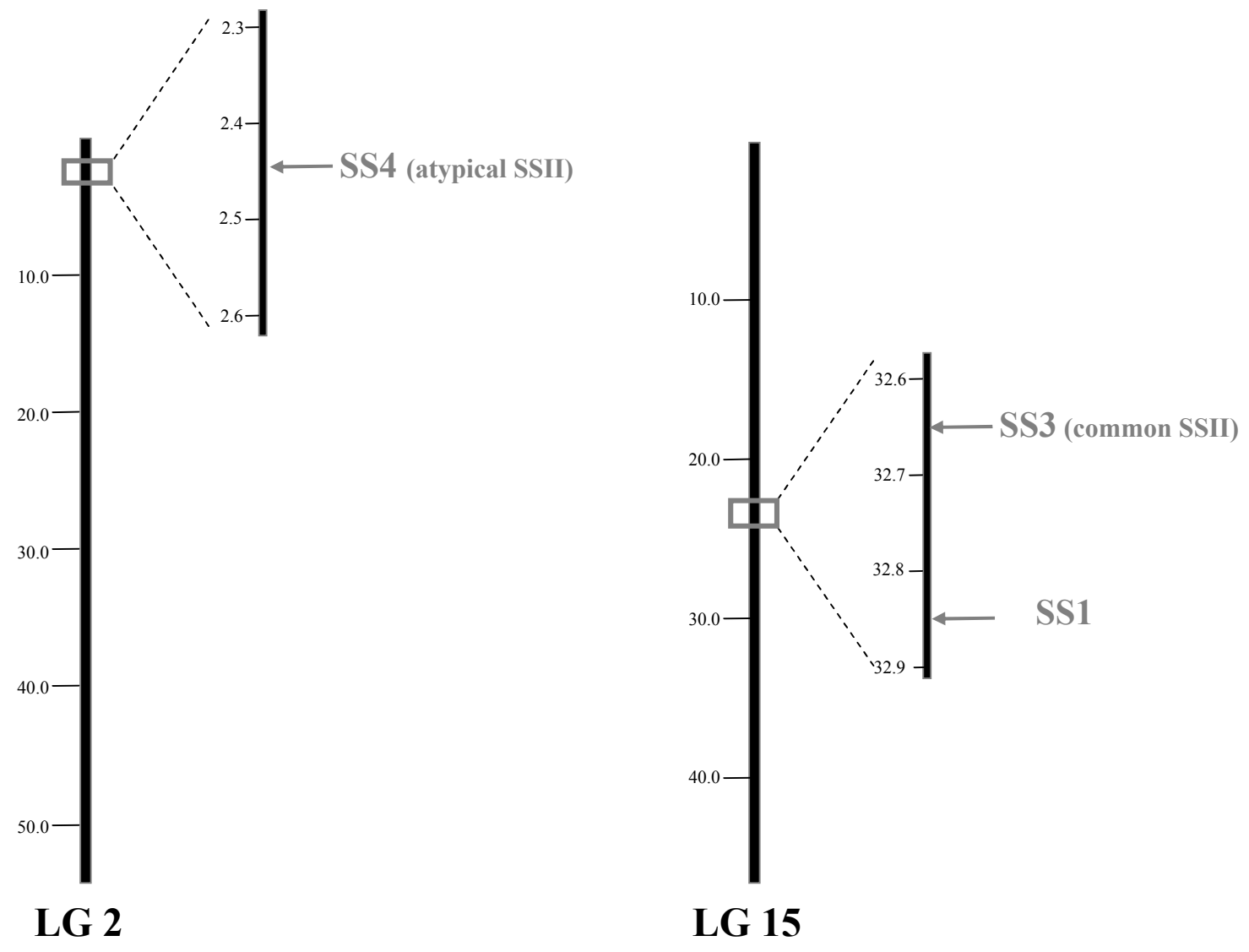


Figure 9

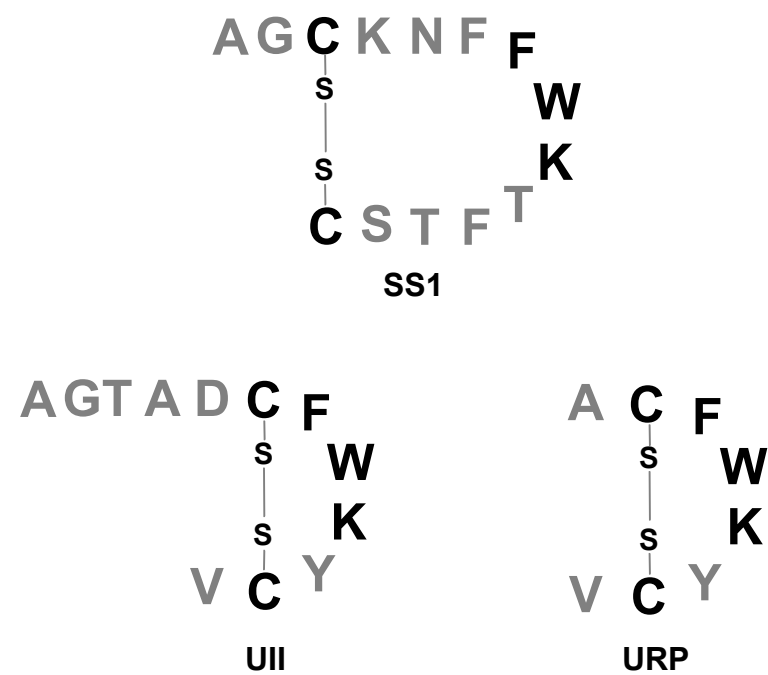


Figure 10

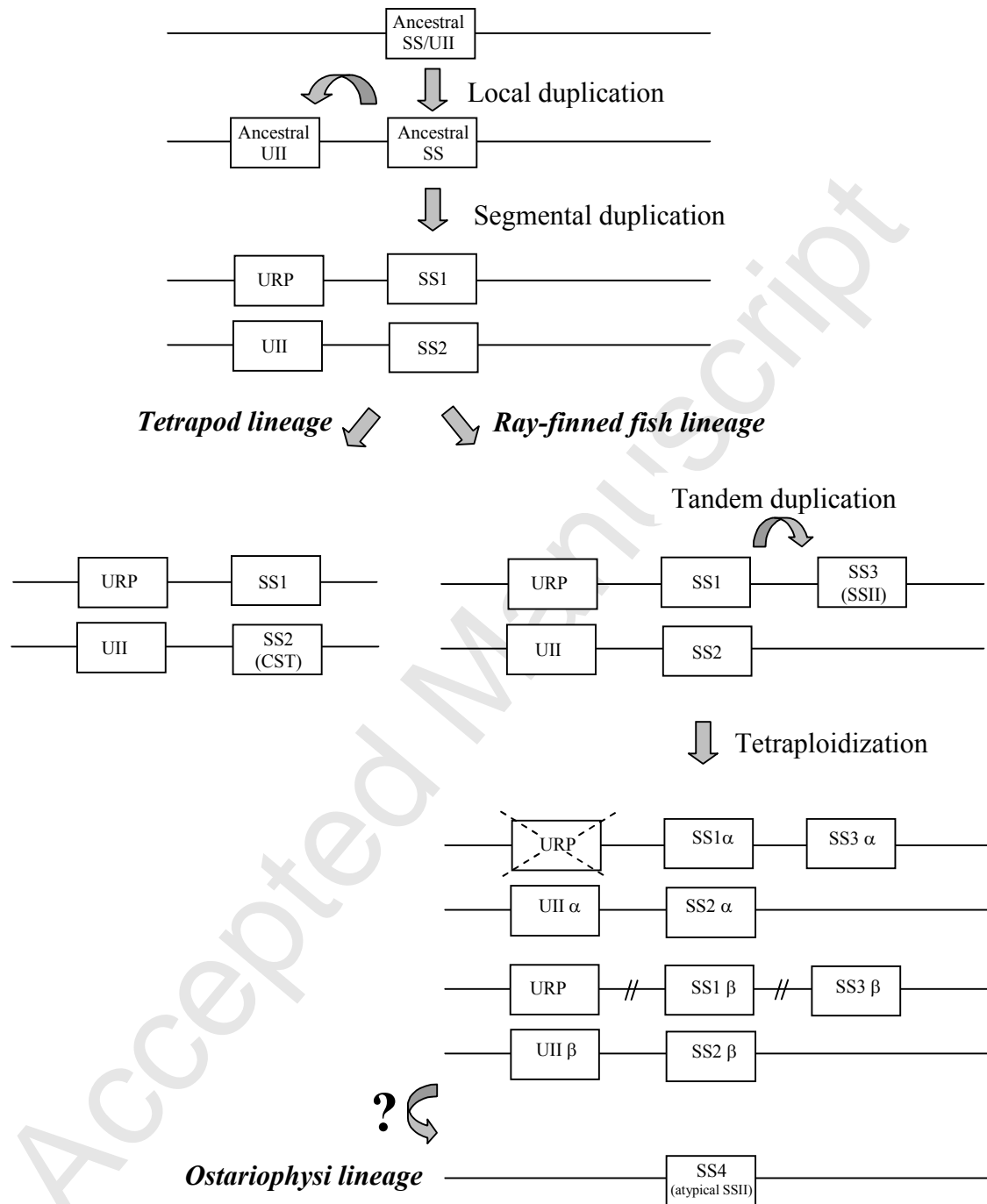


Figure 11

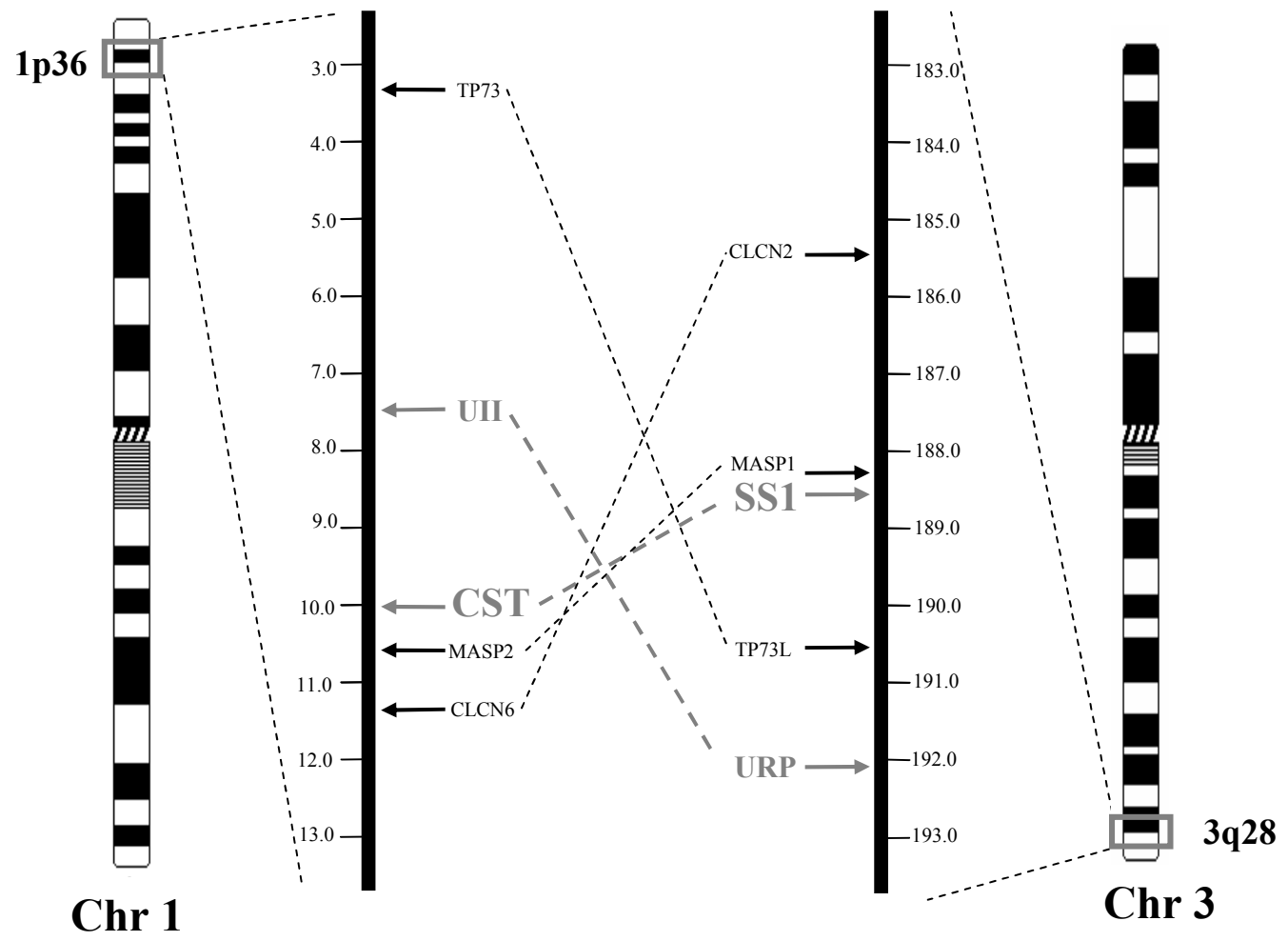


Figure 8

Table 4.
Characterization of the sequences of somatostatin 4 (previously designated atypical somatostatin II) in teleosts

Species	Source	References
Catfish, <i>Ictalurus punctatus</i>	P	Andrews et al., 1984
	C	Magazin et al., 1982
Pacu, <i>Piaractus mesopotamicus</i>	P	Ferraz de Lima et al., 1999
Zebrafish, <i>Danio rerio</i>	C	Argenton et al., 1999
	W (Chr.2)	(DS) ENSDARG00000014190

Sequences determined from: P, peptides; C, cDNA; W, whole genomes (chromosome localization).
DS, direct submission (Ensembl).

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Table 3.
 Characterization of the sequences of somatostatin 3 (previously designated somatostatin II) in teleosts

Species	Source	References
Anglerfish, <i>Lophius americanus</i>	C	Hobart et al., 1980
	P	Andrews et al., 1984
Freshwater butterflyfish, <i>Pantodon buchholzi</i>	C	(DS2) AF292651
Coho salmon, <i>Onchorhynchus kisutch</i>	P	Plisetskaya et al., 1986
Daddy Sculpin, <i>Cottus scorpius</i>	P	Conlon et al., 1987
Eel, <i>Anguilla anguilla</i>	P	Conlon et al., 1988a
Flounder, <i>Platichthys flesus</i>	P	Conlon et al., 1987
Fugu, <i>Takifugu rubripes</i>	W	(DS) SINFRUG00000161986
Goldfish, <i>Carassius auratus</i>	P	Uesaka et al., 1995
	C	Lin et al., 1999b
Medaka, <i>Oryzias latipes</i>	W	(DS) ENSORLG00000019158
Orange spotter grouper, <i>Epinephelus coioides</i>	C	Xing et al., 2005
Silver arawana, <i>Osteoglossum bicirrhosum</i>	C	(DS2) AF292650
Tilapia, <i>Oreochromis nilotica</i>	P	Nguyen et al., 1995
Trout, <i>Oncorhynchus mykiss</i>	C	Moore et al., 1995; 1999
Zebrafish, <i>Danio rerio</i>	W (Chr.15)	(DS) ENSDARG00000033161

Sequences determined from: P, peptides; C, cDNA; W, whole genomes (chromosome localization).
 DS, direct submission (Ensembl).

Table 2.
Characterization of the sequences of somatostatin 2/cortistatin

Species	Source	References
Chimpanzee, <i>Pan troglodytes</i>	W (Chr.1)	(DS) ENSPTRG0000000130
Cow, <i>Bos taurus</i>	W(Chr.16)	(DS) ENSBTAG00000013531
Elephant, <i>Loxodonta africana</i>	W	(DS) ENSLAFG00000009597
Hedgehog, <i>Echinops telfairi</i>	W	(DS) ENSETEG0000000662
Human, <i>Homo sapiens</i>	C	Fukusumi et al., 1997; de Lecea et al., 1997
	W (Chr.1)	(DS) ENSG00000175279
Macaque, <i>Macaca mulatta</i>	W	(DS) ENSMMUG00000023030
Mouse, <i>Mus musculus</i>	C	De Lecea et al., 1997
	G	Calbet et al., 1999
	W (Chr.4)	(DS) ENSMUSG00000028971
Rabbit, <i>Oryctolagus cuniculus</i>	W	(DS) ENSOCUG00000017682
Rat, <i>Rattus norvegicus</i>	C	De Lecea et al., 1996
Opossum, <i>Monodelphis domestica</i>	W	(DS) ENSMODG00000002663
Platypus, <i>Ornithorhynchus anatinus</i>	W	(DS) ENSOANG00000002799
Chicken, <i>Gallus gallus</i>	C	Trabucchi et al., 2003
	W (Chr. 21)	(DS) ENSGALG00000003034
European green frog, <i>Rana ridibunda</i>	P	Vaudry et al., 1992
	C	Tostivint et al., 1996
African lungshish, <i>Protopterus annectens</i>	C	Trabucchi et al., 1999
Fugu, <i>Takifugu rubripes</i>	W	(DS) SINFRUG00000143244
Goldfish, <i>Carassius auratus</i>	C	Lin et al., 1999b
Medaka, <i>Oryzias latipes</i>	W	(DS) ENSORLG00000005136
Orange spotter grouper, <i>Epinephelus coioides</i>	C	Xing et al., 2005
Tetraodon, <i>Tetraodon nigroviridis</i>	W (Chr.9)	(DS) GSTENG00028263001
Zebrafish, <i>Danio rerio</i>	W (Chr.23)	(DS) ENSDARG00000031649
Russian sturgeon, <i>Acipenser gueldenstaedti</i>	P	Nishii et al., 1995
White sturgeon, <i>Acipenser transmontanus</i>	C	Trabucchi et al., 2002

Sequences determined from: P, peptides; C, cDNA; W, whole genomes (chromosome localization).
DS, direct submission (Ensembl).

Table 1.
Characterization of the sequences of somatostatin 1 in vertebrates

Species	Source	References
Armadillo, <i>Dasypus novemcinctus</i>	W	(DS1) ENSDNOG00000013697
Cat, <i>Felis catus</i>	W	(DS1) ENSFCAG00000006706
Chimpanzee, <i>Pan troglodytes</i>	W(Chr.3)	(DS1) ENSPTRG00000015727
Cow, <i>Bos taurus</i>	C	Su et al., 1988
	G	Furu et al., 1999
Dog <i>Canis familiaris</i>	W (Chr.1)	(DS1) ENSBTAG00000017312
	W (Chr.34)	(DS1) ENSCAF00000013891
Elephant, <i>Loxodonta africana</i>	W	(DS1) ENSLAF00000012303
Guinea pig, <i>Cavia porcellus</i>	P	Conlon, 1984
	W	(DS1) ENSCPOG00000009662
Hedgehog, <i>Echinops telfairi</i>	W	(DS1) ENSETEG00000014520
Hedgehog, <i>Erinaceus europaeus</i>	W	(DS1) ENSEEUG00000006120
Human, <i>Homo sapiens</i>	P	Conlon and McCarthy, 1984
	C	Shen et al., 1982
	G	Shen and Rutter, 1984
	W (Chr.3)	(DS1) ENSG00000157005
Macaque, <i>Macaca fascicularis</i>	C	Travis and Sutcliffe, 1988
	W (Chr.2)	(DS1) ENSMUG00000000850
Macaque, <i>Macaca mulatta</i>	C	(DS2) NM_009215
	G	Fuhrmann et al., 1990
Mouse, <i>Mus musculus</i>	W (Chr.16)	(DS1) ENSMUSG00000004366
	P	Schally et al., 1976
Pig, <i>Sus scrofa</i>	C	(DS2) NM_001009583
	W	(DS1) ENSOCUG00000007564
Rabbit, <i>Oryctolagus cuniculus</i>	P	Bohlen et al., 1981
Rat, <i>Rattus norvegicus</i>	C	Funckes et al., 1983; Goodmann et al., 1982
	G	Montminy et al., 1984; Tavianini et al., 1984
	W (Chr.11)	(DS1) ENSRNOG00000001837
	P	Brazeau et al., 1973
Sheep, <i>Ovis aries</i>	C	Bruneau and Tillet, 1998
	W	(DS1) ENSTBEG00000009329
Tree Shrew, <i>Tupaia belangeri</i>	W	(DS1) ENSMODG00000008503
Opossum, <i>Monodelphis domestica</i>	W	(DS1) ENSOANG00000000871
Platypus, <i>Ornithorhynchus anatinus</i>	W	(DS2) NM_205336; X60191
Chicken, <i>Gallus gallus</i>	C	(DS1) ENSGALG00000007361
	W (Chr. 9)	P
Pigeon, <i>Columba livia</i>	P	Wang and Conlon, 1993a
Alligator, <i>Alligator mississippiensis</i>	P	Conlon et al., 1997b
Python, <i>Python molurus</i>	P	Conlon and Hicks, 1990
Red-eared slider turtle, <i>Trachemys scripta</i>	P	Wang et al., 1999b
Tortoise, <i>Gopherus agassizii</i>	P	Cavanaugh et al., 1996
Amphiuma, <i>Amphiuma tridactylum</i>	P	Vaudry et al., 1992
European green frog, <i>Rana ridibunda</i>	C	Tostivint et al., 1996
	P	Takami et al., 1985
Leopard frog, <i>Rana pipens</i>	C	(DS1) AY316318 (a); AY319522 (b)
Toad, <i>Xenopus laevis</i>	W	(DS1) ENSXETG00000014247; ENSXETG00000019777
African lungfish, <i>Protopterus annectens</i>	C	Trabucchi et al., 1999
Anglerfish, <i>Lophius americanus</i>	P	Noe et al., 1979
	C	Hobart et al., 1980
Catfish, <i>Ictalurus punctatus</i>	C	Minth et al., 1982
Clown knifefish, <i>Chitala chitala</i>	C	(DS2) AF292653
Coho salmon, <i>Onchorhynchus kisutch</i>	P	Plisetskaya et al., 1986
Daddy sculpin, <i>Coitus scorpionis</i>	P	Conlon et al., 1987
Eel, <i>Anguilla anguilla</i>	P	Conlon et al., 1988a
European flounder, <i>Platichthys flesus</i>	P	Conlon et al., 1987
Goldfish, <i>Carassius auratus</i>	C	Lin et al., 1999b
Medaka, <i>Oryzias latipes</i>	W	(DS1) ENSORLG00000019152
Megalobrama, <i>Megalobrama pellegrini</i>	C	(DS2) AY247267
Orange spotter grouper <i>Epinephelus coioides</i>	C	Xing et al., 2005
Pacu, <i>Piaractus mesopotamicus</i>	P	Ferraz de Lima et al., 1999
Stickleback, <i>Gasterosteus aculeatus</i>	W	(DS1) ENSGACG00000004479
Stone flounder, <i>Kareius bicoloratus</i>	P	Andoh and Nagasawa, 1998
Tetraodon, <i>Tetraodon nigroviridis</i>	W	(DS1) GSTENG00021180001
Tilapia, <i>Oreochromis nilotica</i>	P	Nguyen et al., 1995
Trout, <i>Oncorhynchus mykiss</i>	C	Kittilson et al., 1999
Weakly electric fish, <i>Gnathonemus petersii</i>	C	(DS2) AF292652
White sucker, <i>Catostomus commersoni</i>	C	(DS2) AF292654
Zebrafish, <i>Danio rerio</i>	C	Devos et al., 2002
	W (Chr.15)	(DS1) ENSDARG00000004799
Bowfin, <i>Amia calva</i>	P	Wang et al., 1993b
American paddlefish, <i>Polyodon spathula</i>	P	Conlon, unpublished data
Pallid sturgeon, <i>Scaphirhynchus albus</i>	P	Kim et al., 2000
White sturgeon, <i>Acipenser transmontanus</i>	C	Trabucchi et al., 2002
Ray, <i>Torpedo marmorata</i>	P	Conlon et al., 1985
River lamprey, <i>Lampetra fluviatilis</i>	P	Conlon et al., 1995a
Sea lamprey, <i>Petromyzon marinus</i>	P	Sower et al., 1994
Southern-hemisphere lamprey, <i>Geotria australis</i>	P	Wang et al., 1999a
Hagfish, <i>Myxine glutinosa</i>	P	Conlon et al., 1988b

Sequences determined from: P, peptides; C, cDNA; G, genes; W, whole genomes (chromosome localization).
DS, direct submission (1: Ensembl; 2: GenBank).

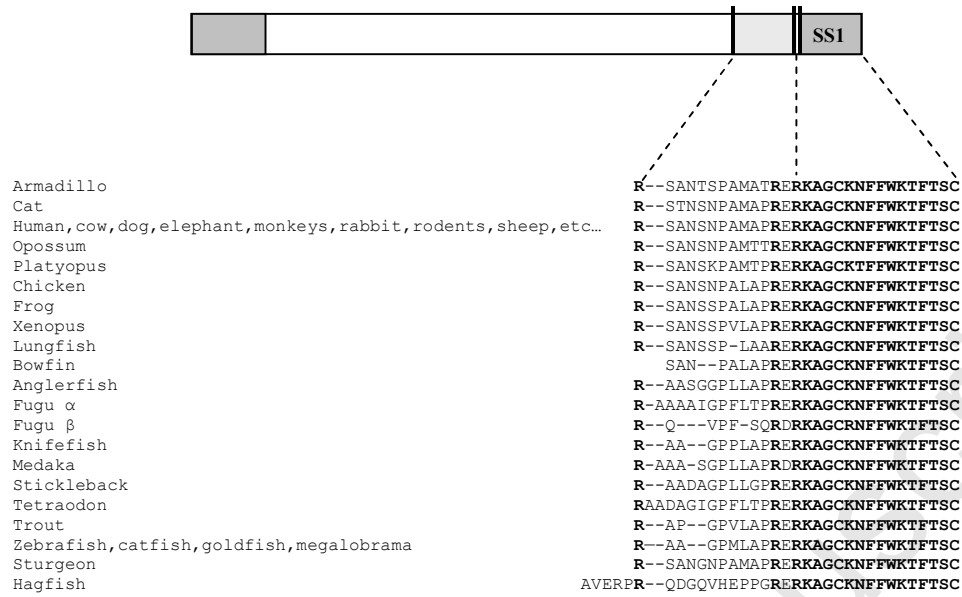


Figure 1