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Complex evolutionary history of the vertebrate sweet/umami taste receptor genes

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Adaptive evolution plays a role in the functional divergence and specialization of taste receptors and the sense of taste is thought to be closely related to feeding ecology. To examine whether feeding ecology has shaped the evolution of taste receptor genes in vertebrates, we here focus on *Tas1r* gene family that encodes umami (Tas1r1 and Tas1r3 heterodimer) and sweet (Tas1r2 and Tas1r3 heterodimer) taste receptors. By searching currently available genome sequences in 48 vertebrates that contain 38 mammals, 1 reptile, 3 birds, 1 frog, and 5 fishes, we found all three members of *Tas1r*s are intact in most species, suggesting umami and sweet tastes are maintained in most vertebrates. Interestingly, the absence and pseudogenization of *Tas1r*s were also discovered in a number of species with diverse feeding preferences and distinct phylogenetic positions, indicating widespread losses of umami and/or sweet tastes in these animals, irrespective of their diet. Together with previous findings showing losses of tastes in other vertebrates, we failed to identify common dietary factors that could result in the taste losses. Our results report here suggest the evolution of *Tas1r*s is more complex than we previously appreciated and highlight the caveat of analyzing sequences predicted from draft genome sequences. Future work for a better understanding of taste receptor function would help uncover what ecological factors have driven the evolution history of *Tas1r*s in vertebrates.

sweet, umami, taste receptor, vertebrate, pseudogene, *Tas1r*, diet

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The evolution of animal chemosensory receptors has been investigated extensively, because chemosensation (olfaction and taste) is needed to find food, mates, offspring, predators, and is thus essential for the survival of individuals [1–3].

It is generally thought that natural selection drives the functional divergence and specialization of taste receptor genes to provide dietary information from food, and the taste perception is thus believed to be closely related to feeding ecology in animals. The evolution of taste receptor genes has been of great interest among molecular evolutionists since the genetic basis of taste perception was characterized in mice in the last decade [4–7]. Five basic taste modalities in vertebrates were discovered: sweet, umami, bitter, sour and salty, each taste is able to sense chemical compounds via specific taste receptor cells, which function through either ion channels (sour and salty) or G protein-coupled receptors (GPCRs) (sweet, umami, and bitter) [7]. Of them, sweet, umami, and bitter tastes are of particular interest, because their respective receptor genes are well characterized, and defective taste receptor genes were demonstrated to impair the taste function viatransgenic rescue experiments and behavioral studies [7–9], suggesting absence or inactivation of the receptor genes must cause inability of taste. Despite that there is no convincing evidence showing any vertebrates lack bitter taste receptor genes (*Tas2r*s), the losses of sweet and umami taste receptor genes (*Tas1r*s) have attracted extensive attention recently [8–14].

*Tas1r*s or *Tas1r* family consist of three members (*Tas1r1*, *Tas1r2*, *Tas1r3*) in most vertebrates [8]. Functional experiments have discovered that *Tas1r1* and *Tas1r3* combine to

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form a heterodimer of the umami taste receptor, whereas *Tas1r2* and *Tas1r3* form another heterodimer and function as the sweet taste receptor [15,16]. Sweet and umami tastes enable animals to recognize diets with nutritious carbohydrates and proteins respectively, and thus are pivotal for the survival of animals. Interestingly, genetic data showing absence/presence of intact *Tas1r*s are concordant with behavioral findings showing indifference/preference of certain diets. For example, cats are indifferent to sugar due to inactivation of *Tas1r2*, a subunit of sweet taste receptor [9]. This concordance has stimulated the inference of taste sensitivities from gene fragments and genome sequences [8–14,17]. However, this concordance between genetic and behavioral evidence has been challenged recently [12,14,18]. For example, pseudogenization of *Tas1r1* in the giant panda may be due to its dietary switch from meat to bamboo, whereas herbivorous horse and cow still possess an intact *Tas1r1* [12]. To probe the generality of the consistency between *Tas1r* functionality and feeding ecology, and to gain a comprehensive picture of *Tas1r*s evolution in vertebrates, more sampling across vertebrates are required to address these questions. By searching 48 currently available vertebrate genome sequences, we here show that there is no common dietary reason that is responsible for the losses of *Tas1r*s in a number of vertebrates, the evolution of the *Tas1r*s is more complex than we previously thought.

1 Materials and methods

We used published vertebrate *Tas1r* genes as query sequences and performed TblastN to search for *Tas1r1*, *Tas1r2*, and *Tas1r3* in 48 currently available vertebrate genome sequences in Enseml genome database (http://www.ensembl.org) (Table 1). To identify the 6 exons in each *Tas1r* gene, we downloaded the specific genomic scaffold containing *Tas1r*s, and conducted Blast 2 between each exon and the scaffold. Blast hit sequences were extended to both 5′ and 3′ directions along the genome scaffolds to attempt to identify the entire coding regions. All 6 exons were assembled and compared with published *Tas1r*s from closely related species using ClustalX 1.81 [19], indels (insertions/deletions) were recorded from the alignments. Newly identified *Tas1r*s were classified as 3 categories: intact, partial, and defective (Table 1). First, sequences containing no frame-shift mutations were examined by the TMHMM method [20] to check the presence of the protein transmembrane domains, the gene would be considered as intact if all seven transmembrane domains were predicted. Second, sequences contain no frame-shift mutations but possess unfinished sequencing regions (i.e. multiple "N" in the genome location) were considered as putatively intact or partial if the gene fragments are longer than 40% of the complete coding sequences. Third, sequences contain frame-shift mutations that cause multiple premature stop codons were classified as defective. Additionally, when we found no or too short blast hits (shorter than 300 base pairs), we would consider *Tas1r*s may be absent from the genomes if we could still identify the two neighbouring genes adjacent to each *Tas1r*.

2 Results and discussion

We searched currently available genome sequences of 48 vertebrate species across 5 Classes 25 Orders of vertebrates, containing 38 species of mammals, 1 species of reptiles, 3 species of birds, 1 species of amphibians, and 5 species of fishes (Table 1, Figure 1). After aligning our newly acquired *Tas1r* sequences with the orthologues from their closely related species, we examined the intactness of the new sequences and predicted their functionality, results are shown in Tables 1, 2, and Figure S1. We identified 36*Tas1r1*, 35*Tas1r2*, and 36*Tas1r3* sequences that appear to be intact or partial (putatively intact due to incomplete genome sequencing), indicative of functional genes. We confirmed previous findings, and showed that all three *Tas1r*s are pseudogenized in dolphin [17]; *Tas1r2* is absent from chicken, clawed frog, horse, pig [11,15]; *Tas1r2* is defective in cat [9]; *Tas1r1* is pseudogenized in panda and bats [11,14]; all three *Tas1r*s in the frog and *Tas1r1* and *Tas1r3* in the zebrafish are absent from the genomes [8]. Interestingly, despite that we found the two neighboring genes next to *Tas1r*s in the draft genomes, we failed to identify *Tas1r2* in horse, marmoset, armadillo, turkey, and zebra finch, and *Tas1r3* is absent from horse, rabbit, tree shrew, tarsier, and sloth, these absences suggest widespread losses of involved taste function. Additionally, indel mutations were detected in a number of species, including *Tas1r1* genes of mouse lemur, tarsier, kangaroo rat, tree shrew, pig, hyrax, tenrec, platypus, and wallaby, and *Tas1r2* genes of pika, tarsier, hyrax, and elephant, and *Tas1r3* genes of alpaca, marmoset, hyrax, and wallaby as well (Table 2, Figure S1). These indel mutations are random because of relaxation of selective constraint, they could occur at each exon, but most indels were discovered in exon 3 and exon 6, because both exons represent the longest coding regions of *Tas1r*s. For example, exons 3 and 6 make up 73.9% of the complete coding sequence of human *Tas1r1*, while the remaining 4 exons are composed of the rest 26.1%. Indels that are not multiple of 3 nucleotides result in altered open reading frame (ORF) and premature stop codons, both of which are hallmarks of pseudogenes. Among the indels, we failed to determine shared ORF-disrupting mutations, suggestive of independent defects. We observed ORF-disrupting mutations and premature stop codons that lead to loss of at least one functional domain of these receptors in the above species, and we thus predict that these genes are defective or nonfunctional (Table 2, Figure S1).

Because Tas1r1 is required for umami taste, Tas1r2 is essential for sweet taste, and Tas1r3 is needed for both of the tastes, absence or disruption of *Tas1r*s that encode these

Table 1 *Tas1r* functionality in vertebrates predicted from genome sequences[a)]

Class	Superorder	Order	Species	Genome coverage	Feeding preference	*Tas1r1*	*Tas1r2*	*Tas1r3*	Reference
Mammalia	Laurasiatheria	Cetartiodactyla	Dolphin	2.59×	Piscivorous	*Defective*	*Defective*	*Defective*	Jiang et al. 2012 [14]
			Cow	7×	Herbivorous	Intact	Intact	Intact	This study
			Pig	15.3×	Omnivorous	**Defective**	*Absent*	Intact	This study; Zhao et al. 2010 [9]
			Alpaca	2.51×	Herbivorous	Partial	Partial	**Defective**	This study
		Perissodactyla	Horse	6.79×	Herbivorous	Intact	*Absent*	**Absent**	This study
		Carnivora	Cat	1.87×	Carnivorous	Partial	*Defective*	Partial	Li et al. 2005 [6]; This study
			Dog	CanFam2.0	Carnivorous	Intact	Intact	Intact	Shi and Zhang [5]
			Panda	AilMel1	Herbivorous	*Defective*	Intact	Intact	Li et al. [7]; Zhao et al. [8]
		Chiroptera	Megabat	2.63×	Herbivorous	*Defective*	Intact	Intact	Zhao et al. [9]; Zhao et al. [11]
			Microbat	7×	Insectivorous	*Defective*	Intact	Intact	Zhao et al. [9]; Zhao et al. [11]
		Eulipotyphla	Hedgehog	1.86×	Omnivorous	Partial	Partial	Partial	This study
			Shrew	1.9×	Insectivorous	Partial	Partial	Partial	This study
	Euarchontoglires	Rodentia	Mouse	NCBIM37	Omnivorous	Intact	Intact	Intact	Shi and Zhang [5]
			Guinea pig	6.79×	Herbivorous	Partial	Partial	Partial	This study
			Squirrel	1.9×	Omnivorous	Intact	Partial	Intact	This study
			Kangaroo rat	1.85×	Herbivorous	**Defective**	Intact	Partial	This study
			Rat	RGSC 3.4	Omnivorous	Intact	Intact	Intact	Shi and Zhang [5]
		Lagomorpha	Rabbit	7×	Herbivorous	Intact	Intact	**Absent**	This study
			Pika	1.93×	Herbivorous	Partial	**Defective**	Partial	This study
		Scandentia	Tree shrew	2×	Omnivorous	**Defective**	Partial	**Absent**	This study
		Primates	Human	GRCh37	Omnivorous	Intact	Intact	Intact	Shi and Zhang [5]
			Bushbaby	1.5×	Omnivorous	Partial	Intact	Intact	This study
			Chimpanzee	6×	Omnivorous	Intact	Partial	Intact	This study
			Gibbon	5.6×	Herbivorous	Partial	Partial	Partial	This study
			Gorilla	35×	Herbivorous	Intact	Partial	Intact	This study
			Macaque	5.1×	Omnivorous	Intact	Intact	Partial	This study
			Marmoset	6×	Omnivorous	Intact	**Absent**	**Defective**	This study

(*To be continued on the next page*)

(*Continued*)

Class	Superorder	Order	Species	Genome coverage	Feeding preference	*Tas1r1*	*Tas1r2*	*Tas1r3*	Reference
			Mouse lemur	1.93×	Insectivorous	Partial	Partial	**Defective**	This study
			Orangutan	6×	Herbivorous	Intact	Partial	Partial	This study
			Tarsier	1.82×	Insectivorous	**Defective**	**Defective**	**Absent**	This study
	Xenarthra	Pilosa	Sloth	2.05×	Herbivorous	Partial	Partial	**Absent**	This study
		Cingulata	Armadillo	2×	Omnivorous	Partial	**Absent**	Partial	This study
	Afrotheria	Afrosoricida	Tenrec	2×	Insectivorous	**Defective**	Partial	Partial	This study
		Hyracoidea	Hyrax	2.19×	Herbivorous	**Defective**	**Defective**	**Defective**	This study
		Proboscidea	Elephant	7×	Herbivorous	Intact	**Defective**	Partial	This study
	Marsupialia	Diprotodontia	Wallaby	2×	Herbivorous	Defeetive	Partial	**Defective**	This study
		Didelphimorphia	Opossum	7.33×	Omnivorous	Intact	Intact	Intact	Shi and Zhang [5]
	Prototheria	Monotremata	Platypus	6×	Carnivorous	**Defective**	Partial	Partial	This study
Reptilia		Squamata	Anole lizard	6.3×	Omnivorous	Intact	Intact	Intact	This study
Aves		Galliformes	Chicken	7.1×	Herbivorous, insectivorous	Intact	*Absent*	Intact	Shi and Zhang [5]
			Turkey	Turkey_2.01	Omnivorous	Partial	**Absent**	Partial	This study
		Passeriformes	Zebra finch	6×	Herbivorous, insectivorous	Partial	**Absent**	Partial	This study
Amphibians		Anura	Clawed frog	7.65×	Insectivorous	*Absent*	*Absent*	*Absent*	Shi and Zhang [5]
Fish		Tetraodontiformes	Fugu	FUGU 5.0	Herbivorous, zooplanktivorous	Intact	Intact	Intact	Shi and Zhang [5]
			Pufferfish	TETRAODON 7	Herbivorous, zooplanktivorous	Intact	Intact	Intact	Shi and Zhang [5]
		Beloniformes	Medaka	6.7×	Herbivorous, zooplanktivorous	Partial	Intact	Intact	This study
		Perciformes	Stickleback	11×	Herbivorous, zooplanktivorous	Partial	Intact	Intact	This study
		Cypriniformes	Zebrafish	Zv9	Herbivorous, zooplanktivorous	*Absent*	Intact	*Absent*	Shi and Zhang [5]

a) "Intact" means putatively functional *Tas1r*s, "Partial" indicates incompletely intact and putatively functional *Tas1r*s, "Defective" indicates pseudogenes due to frame-shift mutations and premature stop codons, "Absent" means inability to identify *Tas1r*s from genome sequences. Gene losses such as absent or defective *Tas1r*s were highlighted in either bold (this study) or italics (previous study). High coverage genomes without detailed coverage information were provided the released versions of the genome assemblies.

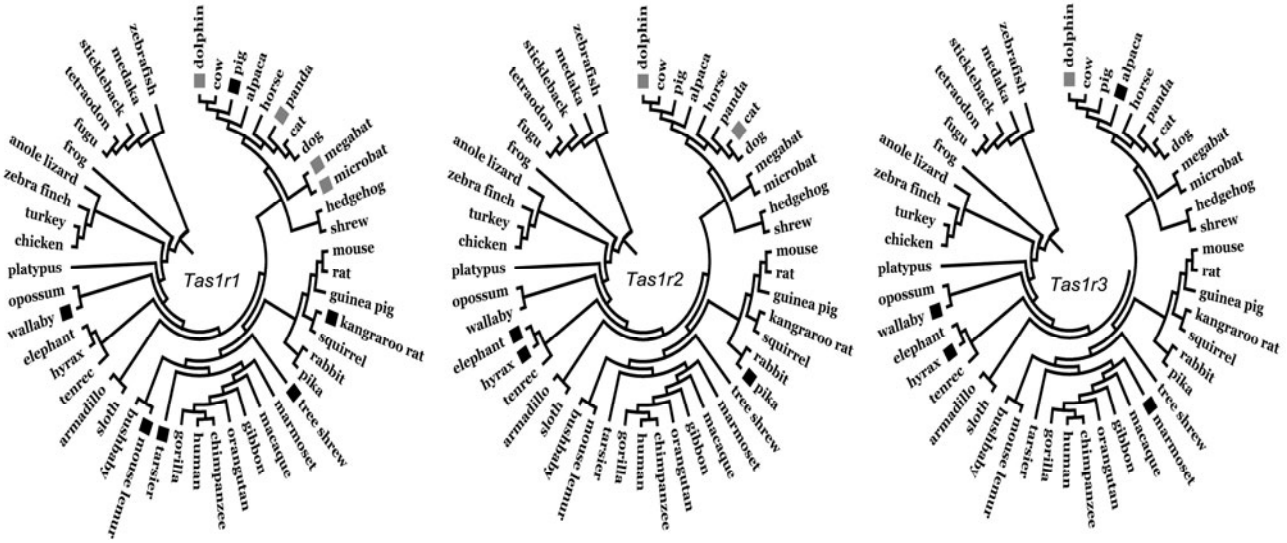

Figure 1 Species tree showing *Tas1r1*, *Tas1r2* and *Tas1r3* functionality. Pseudogenes or gene losses were indicated by black (this study) and gray (previous studies) squares.

receptors must result in loss or greatly reduction of sweet and umami tastes. On the basis of our new observations (Table 1), we infer that both sweet and umami tastes are lost in pig, horse, rabbit, tree shrew, marmoset, mouse lemur, tarsier, hyrax, while pika, armadillo, elephant, turkey, and zebra finch have only lost sweet reception, kangaroo rat, tenrec, platypus lack umami detection (Figure 1). Combining with published findings that argued losses of tastes in other vertebrates, we failed to discover a common dietary factor that is responsible for the loss of a specific taste, it seems that loss of tastes could occur in any species, regardless of feeding preferences. For example, umami taste is absent from the piscivorous (dolphin), omnivorous (pig), herbivorous (kangaroo rat) animals (Table 1, Figure 1). Hence, we cannot explain why sweet and/or umami tastes are dispensable in these vertebrates based solely on diets. However, pseudogenization of *Tas1r1* in the giant panda indeed coincides with its dietary switch from meat to bamboo, suggesting *Tas1r1* plays a role in the feeding ecology of the bamboo-eating species [11]. Moreover, extreme narrowness of diets has rendered vampire bats' tastes useless, and resulted in pseudogenization of all three *Tas1r*s in these exclusive blood feeders [12]. Together, the evolution of taste receptor genes is sometimes explained by feeding ecology, is sometimes inconsistent to our hypothesis proposed from dietary differences [12,18]. The complexity of the potential ecological factors impacting *Tas1r*s evolution suggests that our current understanding of the physical functions of *Tas1r*s is still far from complete. Interestingly, it was discovered that the sweet taste receptors play a role in the gut and the bitter taste receptors could help breathe easier in the lungs, suggesting such reasons instead of diet might explain the evolution of taste receptor genes in vertebrates. It would be helpful to understand the functions of these genes or tastes in detail using mice with some taste receptor genes being knocked out in future.

Note that draft genome sequences are not sufficient to conclude whether a gene is intact or defective, numerous sequencing errors could occur in the publicly available genome database. For example, indels of the megabat *Tas1r1* inferred from its draft genome are quite different from those observed from the new sequencing result [14]. According to the known functions of *Tas1r*s, because *Tas1r3* is essential for both umami and sweet tastes, *Tas1r1* and *Tas1r2* would be useless if *Tas1r3* is lost, it is unlikely that *Tas1r1* and *Tas1r2* are intact while *Tas1r3* is absent from the rabbit genome (Table 1). Similarly, the functionality of *Tas1r*s in alpaca, horse, marmoset, mouse lemur should be checked by re-sequencing in future (Table 1). Meanwhile, the gene annotations in the genome database are sometimes incorrect. For example, the dolphin *Tas1r2* is annotated as an intact gene in Ensembl [12], it is indeed a pseudogene inferred from its draft genome [17]. While available genome assemblies provide an opportunity for sequence analysis, caution should be taken if we draw conclusions from the draft genome sequences. This said, in the case of *Tas1r*s evolution, the loss of *Tas1r1* in most, if not all, bats with diverse diets (blood, insects, or fruits) provided strong evidence that *Tas1r*s evolution is sometimes cannot be explained by diets [14]. Our results report here suggest the evolution of *Tas1r*s is more complex than we previously appreciated and highlight the caveat of analyzing sequences predicted from draft genome sequences. Future work on more accurate and complete functional characterizations of taste receptors would help uncover what ecological factors have shaped the evolution history of *Tas1r*s in vertebrates.

Table 2 Indels (insertions/deletions) and premature stop codons of defective *Tas1r* genes[a)]

Tas1r1	Exon 1		Exon 2		Exon 3		Exon 4		Exon 5		Exon 6		No. of premature stop codons
Species	Insertion	Deletion	Insertion	Deletion	Insertion	Deletion	Insertion	Deletion	Insertion	Deletion	Insertion	Deletion	
Mouse lemur	0	0	0	0	4 bp	4 bp	NA	NA	NA	NA	0	1 bp; 1 bp	1 at exon 6
Tarsier	NA	NA	0	0	0	1 bp	0	0	NA	NA	0	1 bp	6 at exon 3; 3 at exon 6
Kangaroo rat	0	0	NA	NA	0	0	0	0	0	0	0	1 bp	11 at exon 6
Tree shrew	NA	NA	1 bp	1 bp	0	0	0	0	0	1 bp	2 bp; 1 bp; 1 bp; 1 bp; 2 bp; 2 bp; 1 bp; 1 bp	0	2 at exon 3; 7 at exon 6
Pig	0	0	0	0	1 bp	1 bp; 1 bp; 1 bp	9 bp	0	0	0	0	0	2 at exon 3
Wallaby	6 bp	6 bp	0	0	0	3 bp; 6 bp	1 bp	0	0	0	0	0	2 at exon 4
Tas1r2													
Pika	0	0	0	0	0	6 bp; 12 bp	0	0	0	0	1 bp	0	3 at exon 6
Hyrax	NA	NA	NA	NA	0	0	0	0	0	0	1 bp	1 bp; 1 bp; 1 bp; 1 bp; 1 bp	6 at exon6
Elephant	0	0	0	0	0	1 bp; 1 bp; 1 bp	0	0	0	0	1 bp	1 bp; 1 bp	2 at exon3; 9 at exon6
Tas1r3													
Alpaca	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5 bp	1 bp; 1 bp; 1 bp; 1 bp; 4 bp	2 at exon 6
Marmoset	0	0	0	0	0	0	0	0	0	0	1 bp; 3 bp; 1 bp	1 bp; 4 bp	1 at exon 6
Hyrax	11 bp; 7 bp	0	0	0	0	1 bp	0	1 bp	0	0	4 bp	3 bp; 1 bp	3 at exon 4
Wallaby	NA	NA	1 bp	0	3 bp	0	0	0	0	0	1 bp; 1 bp; 4 bp	1 bp; 3 bp; 1 bp	4 at exon 2

a) NA indicates no available information because of incomplete genome sequencing.

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Supporting Information

Figure S1 Alignments of newly identified pseudogenes with human orthologous genes as references. Dashes indicate alignment gaps, question makers denote unavailable data, indels (deletions or insertions) were highlighted in red.

The supporting information is available online at csb.scichina.com and www.springerlink.com. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.