



# Contrasting Patterns of Gene Duplication, Relocation, and Selection Among Human Taste Genes

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**ABSTRACT:** In humans, taste genes are responsible for perceiving at least 5 different taste qualities. Human taste genes' evolutionary mechanisms need to be explored. We compiled a list of 69 human taste-related genes and divided them into 7 functional groups. We carried out comparative genomic and evolutionary analyses for these taste genes based on 8 vertebrate species. We found that relative to other groups of human taste genes, human TAS2R genes have a higher proportion of tandem duplicates, suggesting that tandem duplications have contributed significantly to the expansion of the human TAS2R gene family. Human TAS2R genes tend to have fewer collinear genes in outgroup species and evolve faster, suggesting that human TAS2R genes have experienced more gene relocations. Moreover, human TAS2R genes tend to be under more relaxed purifying selection than other genes. Our study sheds new insights into diverse and contrasting evolutionary patterns among human taste genes.

**KEYWORDS:** Taste gene, evolution, comparative genomics, gene duplication mode, collinearity, gene relocation, tandem duplication

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## Introduction

Taste genes code for proteins that facilitate the sensation of different tastes. The most frequently studied taste genes are sweet, umami, and bitter.<sup>1–5</sup> However, the underlying biological processes for salty and sour taste remain poorly understood.<sup>6–8</sup> The human taste system also detects noncanonical “tastes” such as water, fat, and complex carbohydrates, but the research on their reception mechanisms is in an early stage.<sup>2</sup>

The human TAS1R gene family with 3 members TAS1R1, TAS1R2, and TAS1R3 conducts conserved taste sensation functions in vertebrates. TAS1R1 + TAS1R3 heterodimer receptor functions as an umami receptor, while the TAS1R2 + TAS1R3 heterodimer receptor functions as the sweet receptor.<sup>9,10</sup> The human TAS2R gene family, with around 25 functional members, functions as bitter taste receptors.<sup>11,12</sup> In addition, 11 human TAS2R pseudogenes have been identified.<sup>13</sup> The epithelial sodium channel (ENaC) mediates the sensation of the salty taste.<sup>6,14</sup> The ENaC has 4 subunits,  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ , encoded by the non-voltage-gated sodium channel 1 genes SCNN1A, SCNN1B, SCNN1G, and SCNN1D. The transient receptor potential (TRP) cation channel is a large gene family with diverse sensation roles, including taste sensation.<sup>15</sup> The subfamily V (TRPV1–6) is a promising candidate for transduction of amiloride-insensitive cation-nonspecific salty taste.<sup>16,17</sup> The classical subfamily (TRPC) can sense membrane lipids.<sup>18</sup> TRPM5, a cation channel, has an essential role in the transduction of bitter, sweet, and umami tastes.<sup>19</sup> The acid-sensing ion channel genes (ASIC1–5) and PKD genes are receptors for acid

(sour) taste.<sup>8,20</sup> The free fatty acid receptors (FFAR1–4) are G protein-coupled receptors activated by free fatty acids (FFAs), which play essential roles as essential nutritional components.<sup>21</sup>

Evolution of taste genes may play an essential role in species adaptations to their specific chemical environments and feeding ecology.<sup>2</sup> Previous evolutionary studies on taste genes were mostly related to TAS1R and TAS2R gene families. TAS2R genes tend to be shorter, which are around 1 kb.<sup>1</sup> TAS1R genes are relatively conserved in evolution, while TAS2R genes are more variable and diverge tremendously among species.<sup>22,23</sup> TAS2R genes frequently experienced lineage-specific expansions and losses.<sup>13,24,25</sup> TAS2R pseudogenes are differently distributed among species, with some of them (eg, TAS2R38) being polymorphic among human populations.<sup>13,26</sup> Copy number variations play an important role in TAS2R genes, especially within the TAS2R43–45s genomic regions.<sup>27,28</sup> Moreover, potential positive selection on several TAS1R and TAS2R genes<sup>23,29–32</sup> and balancing selection on TAS2R genes<sup>32,33</sup> were reported.

It is still unknown what mechanisms have led to the distinct evolutionary patterns of TAS2R genes. Both single gene and whole-genome duplications (WGD) have recurred in vertebrate evolution.<sup>34,35</sup> Genes created by different modes often experienced different evolutionary tempos and gene loss rates.<sup>36,37</sup> Moreover, gene relocations frequently occur during evolution, which is often associated with increased evolutionary rates.<sup>38,39</sup> Genetic polymorphisms and genomic structures may interact to shape taste perception.<sup>27,28</sup> The aim of this



study is to better understand human taste genes' evolutionary mechanisms and humans' taste perceptions and eating behaviors via comparative genomic analysis of taste genes.

## Results

### *Functional groups of human taste genes*

We compiled a list of human taste genes, including 7 functional groups (Table 1). The first group is TAS1R genes, which have 3 members TAS1R1, TAS1R2, and TAS1R3. The second group is TAS2R genes, which are responsible for sensing bitter taste. We collected 24 TAS2R genes, including TAS2R1, TAS2R3, TAS2R4, TAS2R5, TAS2R7, TAS2R8, TAS2R9, TAS2R10, TAS2R13, TAS2R14, TAS2R16, TAS2R19, TAS2R20, TAS2R30, TAS2R31, TAS2R38, TAS2R39, TAS2R40, TAS2R41, TAS2R42, TAS2R43, TAS2R46, TAS2R50, and TAS2R60. The third group of sodium channels epithelia genes are responsible for salt taste perception, including SCNN1A, SCNN1B, SCNN1D, and SCNN1G. The fourth group acid-sensing ion channel genes are candidates for sour taste perception, including ASIC1, ASIC2, ASIC3, ASIC4, and ASIC5. The fifth group is calcium-sensing receptors, which have 2 members, CaSR and GPRC6A. The sixth group is free fatty acid receptors for sensing fatty acid taste, including FFAR1, FFAR2, FFAR3, and FFAR4. The last group is transient receptor potential channels suggested to have essential roles in the sensation of sweet, bitter, and umami tastes. This group includes TRPA1, TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, TRPC7, MCOLN1, MCOLN2, MCOLN3, TRPM1, TRPM2, TRPM3, TRPM4, TRPM5, TRPM6, TRPM7, TRPM8, PKD2, PKD2L1, PKD2L2, TRPV1, TRPV2, TRPV3, TRPV4, TRPV5, and TRPV6. Some genes we involved in the analysis might be just putative taste genes. However, generating an aggressive list of human taste genes will render a comprehensive comparison among different taste genes while not negatively affecting comparative genomic and evolutionary analyses. Detailed information regarding the human taste genes, including various comparative genomics and evolutionary metrics, is included in Supplemental Table S1.

### *Tandem duplications contribute to the expansions of TAS2R genes*

We classified human taste genes into different gene duplication modes, including singletons, whole genome/segmental (ie, collinear genes in collinear blocks), tandem (consecutive repeat), proximal (in the nearby chromosomal region but not adjacent), or dispersed (other modes than segmental, tandem, and proximal) duplications on their copy number and genomic distribution.<sup>38</sup> Among the 24 TAS2R genes, 14 have experienced tandem duplications, while among the 45 other genes, 9 have experienced tandem duplications. The comparison of proportions of tandem duplicates (58.3% vs 20.0%) is significant ( $P=3.19 \times 10^{-3}$ ,  $\chi^2$ ). This observation suggests that tandem duplications are a significant gene duplication mode

**Table 1.** Functional groups of taste genes.

FUNCTIONAL GROUP	GENE SYMBOL	CHROMOSOMAL POSITION
Taste 1 receptors	TAS1R1	chr1:6555307-6579755
	TAS1R2	chr1:18839599-18859682
	TAS1R3	chr1:1331280-1335314
Taste 2 receptors	TAS2R1	chr5:9629446-9712378
	TAS2R3	chr7:141764097-141765197
	TAS2R4	chr7:141776674-141781691
	TAS2R5	chr7:141790217-141791366
	TAS2R7	chr12:10801532-10802627
	TAS2R8	chr12:10806051-10806980
	TAS2R9	chr12:10809094-10810168
	TAS2R10	chr12:10825317-10826358
	TAS2R13	chr12:10907926-10909562
	TAS2R14	chr12:10937410-10939263
	TAS2R16	chr7:122994704-122995700
	TAS2R19	chr12:11021619-11022620
	TAS2R20	chr12:10995962-10997875
	TAS2R30	chr12:11133285-11134244
	TAS2R31	chr12:11030387-11031407
	TAS2R38	chr7:141972631-141973773
	TAS2R39	chr7:143183419-143184435
	TAS2R40	chr7:143222037-143223079
	TAS2R41	chr7:143477873-143478796
	TAS2R42	chr12:11185993-11186937
	TAS2R43	chr12:11091287-11092313
	TAS2R46	chr12:11061365-11062294
	TAS2R50	chr12:10985913-10986912
	TAS2R60	chr7:143443453-143444409
Sodium channels epithelia	SCNN1A	chr12:6347684-6377359
	SCNN1B	chr16:23302302-23381294
	SCNN1D	chr1:1280415-1292029
	SCNN1G	chr16:23182745-23216883
Acid-sensing ion channels	ASIC1	chr12:50057548-50083611
	ASIC2	chr17:33013087-34157294
	ASIC3	chr7:151048292-151052753
	ASIC4	chr2:219514330-219538772
	ASIC5	chr4:155829729-155866277

(Continued)

Table 1. (Continued)

FUNCTIONAL GROUP	GENE SYMBOL	CHROMOSOMAL POSITION
Calcium sensing receptors	CASR	chr3:122183668-122291629
	GPRC6A	chr6:116792085-116829083
Free fatty acid receptors	FFAR1	chr19:35351552-35353862
	FFAR2	chr19:35448301-35451767
	FFAR3	chr19:35358460-35360489
	FFAR4	chr10:93566682-93604480
Transient receptor potential channels	TRPA1	chr8:72021250-72075584
	TRPC1	chr3:142724034-142807888
	TRPC3	chr4:121874481-121952060
	TRPC4	chr13:37632063-37869772
	TRPC5	chrX:111774315-112082776
	TRPC6	chr11:101451564-101584007
	TRPC7	chr5:136212745-136365545
	MCOLN1	chr19:7522624-7534009
	MCOLN2	chr1:84925583-84997113
	MCOLN3	chr1:85018082-85048500
	TRPM1	chr15:31001061-31161273
	TRPM2	chr21:44350163-44443081
	TRPM3	chr9:70535944-71446835
	TRPM4	chr19:49157766-49211834
	TRPM5	chr11:2404515-2423045
	TRPM6	chr9:74722495-74887921
	TRPM7	chr15:50557158-50686797
	TRPM8	chr2:233917373-234019522
	PKD2	chr4:88007635-88077777
	PKD2L1	chr10:100288149-100330228
	PKD2L2	chr5:137889466-137942747
	TRPV1	chr17:3565444-3609411
	TRPV2	chr17:16415571-16437003
	TRPV3	chr17:3510502-3557812
	TRPV4	chr12:109783089-109833398
	TRPV5	chr7:142908101-142933746
TRPV6	chr7:142871208-142885745	

responsible for expanding human TAS2R genes. Moreover, there are 5 proximal duplicates (20.8%) among human TAS2R genes, while there are only 2 proximal duplicates (4.4%) among other genes. Although the contrast in proportions is obvious,

the comparison is not significant due to small numbers. Tandem duplications are believed to be caused by unequal crossing-over and are often associated with inversions.<sup>40</sup> This analysis suggests that human TAS2R genes tend to have experienced different duplication events among human taste genes.

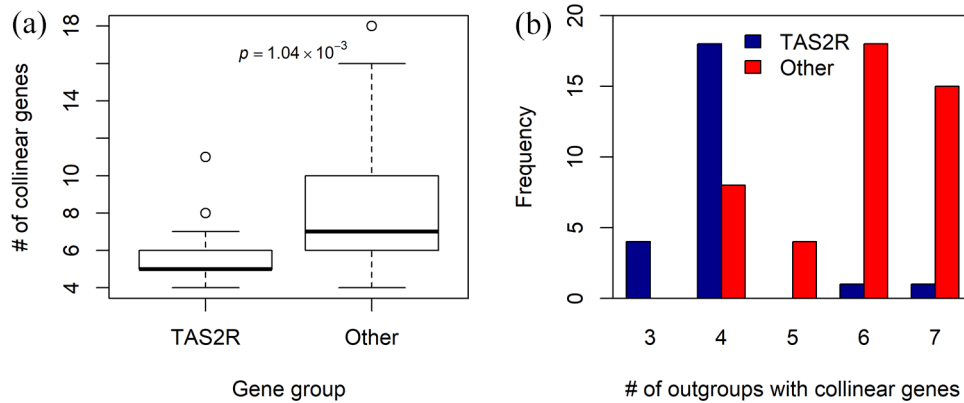
#### *Collinearity analysis of human taste genes*

Over the evolutionary course of eukaryotic genomes, genes may remain on corresponding chromosomes (synteny) and corresponding orders (collinearity).<sup>41</sup> Compared with outgroup genomes, we hypothesize that genes without collinear orthologs have undergone relocation, often associated with the reshuffling of chromosomal segments or transposon activities.<sup>40</sup> We generated collinear blocks among 8 vertebrate genomes. We computed the number of cross-species collinear genes for each human taste gene and the number of outgroup species with collinear genes. Comparisons of these 2 indicators between human TAS2R genes and other human taste genes (Figure 1) showed that human TAS2R genes tend to have less collinear genes in outgroup species ( $P=1.03 \times 10^{-3}$ , Wilcoxon test) and fewer outgroup species with collinear genes ( $P=6.93 \times 10^{-8}$ , Wilcoxon test). They are thus suggesting that human TAS2R genes have more frequently relocated during evolution.

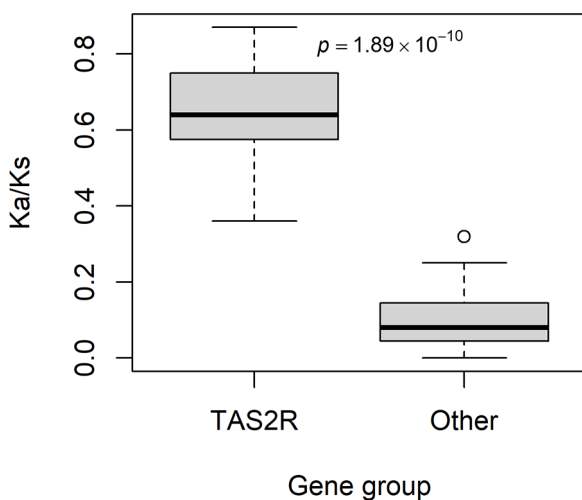
#### *Analysis of selection pressure on human taste genes*

Relative to TAS1R genes, TAS2R genes are more variable and diverge tremendously among species.<sup>22</sup> Here, we computed nonsynonymous ( $K_a$ ) and synonymous ( $K_s$ ) substitution rates for human-mouse orthologous pairs for the taste genes (see Methods). We used  $K_a/K_s$  to denote selection pressure. None of human taste genes displayed  $K_a/K_s > 1$  (Supplemental Table S1), indicating no signs of positive selection. We found that human TAS2R genes have significantly higher  $K_a/K_s$  than other genes (Figure 2,  $P=1.89 \times 10^{-10}$ , Wilcoxon test). TAS2R genes tend to be shorter than other taste genes ( $P=2.44 \times 10^{-10}$ , Wilcoxon test) and there was a significant correlation between gene lengths and  $K_a/K_s$  ( $r=-0.307$ ,  $P=.014$ ) in all taste genes. Thus, we computed gene length-adjusted  $K_a/K_s$  and compared it between TAS2R and other genes. A significant  $p$ -value ( $P=8.88 \times 10^{-8}$ , Wilcoxon test) was remained. This observation suggests that human TAS2R genes are under relaxed purifying selection, while other types of human taste genes tend to be under purifying selection.

We then computed Tajima's  $D$ <sup>42</sup> for each taste gene to detect departures from neutral selection, based on the African and European populations from the 1000 Genomes Project.<sup>43</sup> TAS2R genes did not show significantly higher Tajima's  $D$  than other genes ( $P=.701$  and  $.243$  for AFR and EUR respectively, Wilcoxon test). This analysis suggests that although individual TAS2R genes may have experienced balancing selection<sup>32,33</sup> or positive selection,<sup>30</sup> in general TAS2R genes do



**Figure 1.** Comparison of gene relocation between TAS2R and other genes in humans. Gene relocation is inversely related to the conservation of collinearity by comparison with multiple outgroup species: (a) comparison of the number of collinear genes and (b) comparison of the number of outgroup species with collinear genes.



**Figure 2.** Comparison of Ka/Ks between TAS2R and other genes in humans.

not show distinct deviation patterns from neural selection than other taste genes.

## Conclusions and Discussion

In this study, we carried out comparative genomic and evolutionary analyses for taste genes across 8 vertebrate species. Human TAS2R genes have a higher proportion of tandem duplicates and tend to have fewer collinear genes in outgroup species. Human TAS2R genes tend to evolve under relaxed purifying selection, while other genes tend to evolve under purifying selection. This study generates new insights into the diverse and contrasting evolutionary patterns of human taste genes.

Tandem duplications occur more frequently within TAS2R genes. Vertebrate genomes have experienced 2 rounds of WGDs during their early evolution.<sup>34</sup> More recent WGDs have also occurred in the teleost fish,<sup>44,45</sup> salmonid,<sup>46</sup> and *Xenopus laevis*<sup>47</sup> lineages, but not the human lineage. Tandem gene duplications, which may frequently

occur during evolution, provide a continuous and large amount of genetic materials for species' evolution and adaptation to specific environments and ecology.<sup>48</sup> Moreover, human-specific gene duplications such as BOLA2 have arisen exclusively in *Homo sapiens* and have been associated with human diseases.<sup>49</sup> TAS2R genes, under relaxed purifying selection, may quickly evolve new functions which may become fixed because coincidentally fitting to species' environment. Tandem duplicates have a higher evaporating (ie, gene death) rate.<sup>37</sup> However, many gene duplications offset the high evaporating rate while providing enough raw materials for selection to work.

Variations in the TAS1R genes were previously reported to be under positive selection.<sup>23,29</sup> Among TAS2R genes, TAS2R16 and TAS2R38 were previously reported to be under recent positive selection.<sup>30-32</sup> TAS2R38 might have also experienced balancing selection.<sup>26</sup> Variations within the TAS1R3 promoter were found to be associated with human taste sensitivity to sucrose and show signs of departure from neutral selection.<sup>50</sup> We did not find signatures of positive selection in human taste genes, which is consistent with a recent study.<sup>51</sup> Our finding that human TAS2R genes tend to be under relaxed purifying selection aligns with the neural evolution hypothesis.<sup>13,52</sup>

A limitation is that it remains unclear when the relaxation of purifying selection on TAS2R genes started. Although alignments of ancient human genomes such as Neanderthal, Denisovan, archaic sapiens were available, the sequencing depths did not allow us to accurately predict their taste genes.

## Methods

### Identification of taste genes in humans

We collected the best-characterized families of human taste genes for sweet and umami, bitter, salty, sour, ENaC-independent salt, noncanonical tastes, fat, and complex carbohydrates from HGNC at <https://www.genenames.org>.

### Gene sequences and homology search

Whole-genome protein sequences, CDS sequences in FASTA format, and gene positions for human, gorilla, macaque, mouse, chicken, lizard, frog, and zebrafish were retrieved Ensembl at <https://uswest.ensembl.org/info/data/ftp/index.html>.

We only selected the longest transcript was selected in the annotation for any genes that had more than 1 transcript. To search for homology between humans with 2 other primates and 5 non-primate genomes, we conducted an all-vs-all BLASTP for each above genome against human and human against each genome. Respectively, we used an e-value cut-off of  $1e-10$  and reported the best 5 non-self-hits in each target genome. We also performed BLASTP for the human genome against itself with the same setting but kept the best 6 self-hits.

We searched the Ensembl database for each human taste gene to identify human-mouse orthologous pairs and kept 1-1 ortholog. We treated Tas2r136 as the mouse ortholog for TAS2R19, TAS2R20, TAS2R30, and TAS2R50 because of its highest gene order conservation score. TAS2R5, TAS2R8, TAS2R9, TAS2R45, and SCNN1D had no mouse ortholog.

### Detection of syntenic blocks and collinear genes

To identify syntenic blocks and collinear genes between multiple species genomes, we concatenated all above inter-/intra-species m6 BLASTP outputs into a .blast concatenated all gene positions of different species into a .gff file. Then, we analyzed the homologous genes by scanning syntenic blocks using the software MCSanX<sup>53</sup> with all default parameters among 8 genomes (a match score of 50, gap penalty of -1, E-value of  $1e-5$ , maximum gap size between any 2 consecutive protein pairs of 25, and at least 5 consecutive proteins to define a syntenic region). We also generated self-syntenic blocks within the human genome using MCSanX with the same setting.

### Classification of duplicate gene origins

We uploaded the output of Human self-genome BLASTP to MCSanX. Then we used duplicate\_gene\_classifier from MCSanX to detect duplicate genes and classify them into different origins.

### Ka and Ks calculation

We computed Ka and Ks using the Yang and Nielsen method,<sup>54</sup> available in the yn00 module of the PAML package.<sup>55</sup>

### Neutral mutation test

We collected all taste receptor genes' variant calls of Europeans and Africans for Human (GRCh38.p13) with "Data Slicer" from 1000 Genomes Project at [https://uswest.ensembl.org/Homo\\_sapiens/Tools/DataSlicer](https://uswest.ensembl.org/Homo_sapiens/Tools/DataSlicer). Then Tajima's  $D^{42}$  was calculated at the population and gene levels using vcfTools v0.1.13.<sup>56</sup>

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### Author Contributions

Y.W. and P.V.J conceived the study. Y.W. and Y.S. made the programs. Y.W. and Y.S. performed the analyses. Y.W. and P.V.J wrote the manuscript.

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### Data Availability

The data underlying this article are available in the article and its Supplemental Material.

### Supplemental Material

Supplemental material for this article is available online.

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