

Genomics of Olfactory Receptors

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Abstract In many species, the sense of smell plays important roles in locating food, detecting predators, navigating, and communicating social information. The olfactory system has evolved complex repertoires of odor receptors (ORs) to fulfill these functions. Through computational data mining, OR repertoires of multiple species were identified, revealing a surprisingly large OR gene family in rodents and evolutionary fluctuation among different organisms. Characteristics of OR genes were explored through computational and experimental methods, showing a complicated gene structure and special genomic distribution. Utilizing high-throughput OR microarrays, expression profiles of the mouse and human OR repertoire were examined, their olfactory functions verified, and their zonal, ectopic and developmental expression determined. Variation in human smelling abilities results from different functional OR repertoires, variable expressional levels and polymorphisms in the copy number of the OR genes. These genomic approaches have both provided new data and generated new questions.

1 Introduction

The molecular era in olfaction began in 1991 with the landmark discovery of a large, multigene family of odor receptors in rat by Buck and Axel (Buck and Axel 1991). The first few olfactory receptors were cloned based on the assumption that olfactory receptors would comprise a diverse repertoire of G-protein coupled receptors (GPCRs) with seven-transmembrane topology, and they would be expressed exclusively in the olfactory epithelium. Later combined with the availability of numerous completely sequenced genomes, this pioneering discovery opened the way for the characterization of the OR gene family through exhaustive computational data mining.

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2 Data Mining of OR Repertoire

The coding region of OR gene sequences is encoded by a single exon with conserved amino acid motifs that distinguish them from other non OR seven-transmembrane proteins (Glusman et al. 2001). This feature facilitates genomic screening for putative OR genes in any species with known genome sequences. Different laboratories performed data mining for OR repertoires in multiple species using similar strategies (Glusman et al. 2001; Young et al. 2002; Young and Trask 2002; Zhang and Firestein 2002).

The general strategy comprises the following steps (see Fig. 1): First, known OR sequences which have been cloned and examined through classical molecular methods were compiled from gene databases, such as Genbank. Redundant sequences were removed to keep a representative group of known ORs. This group should be as diverse as possible to represent the width of the full repertoire. For example, 30 OR sequences from 30 different families will have better coverage than 30 sequences from a single family. Secondly, a well-assembled genome is searched with the representative sequences as query. The sequence quality of the genome would of course have an effect on the completeness of the OR sequences identified. For example, mistakenly assembled scaffolds will result in partial or pseudo genes if adjacent sites reside in OR genes. This

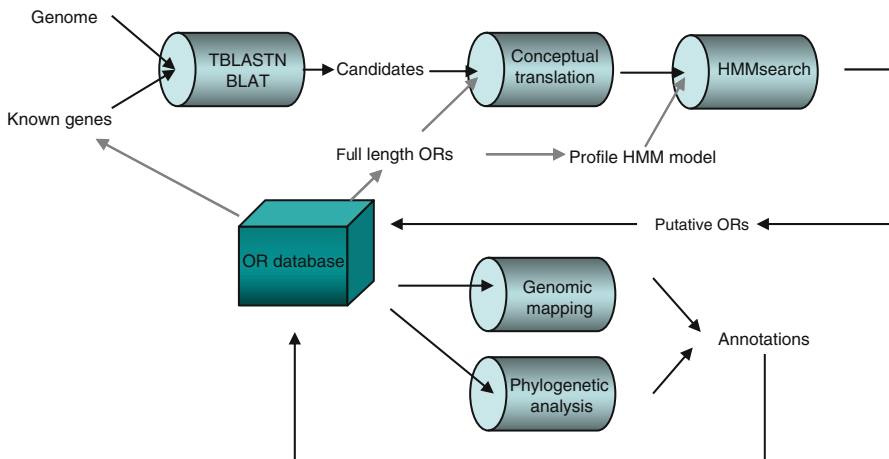


Fig. 1 *Reiterative Genomic Data Mining Pipeline Optimized for Large Gene Families.* To ensure the search is fast and exhaustive, a large number of BLAT searches or low stringent TBLASTN searches using representative genes was utilized in the first step. The output sequences from conceptual translation were matched to pHMM model which was built with the HMMER package and known ORs to achieve high specificity. Sequences with low p -values were selected as putative ORs. These low p -value OR candidates, combined with the original known ORs, were used as queries for the second-round search. The reiteration is stopped after no new sequences with p -values lower than the threshold are discovered

screening is a rough alignment between the known OR genes and the genome to identify the likely OR gene coordinates on the DNA. Thirdly, a conceptual translation is performed using a model of known ORs as the template and the DNA sequences obtained from the second step. This model is necessary in that it instructs the translation process by adding necessary frame-shifts within the coding region. Finally, we compare the similarity between the conceptually translated sequences and the model built with known ORs. Sequences that have high similarity with known ORs are selected and subject to additional filtering to avoid redundancy, followed by assigning them as “OR candidates”. These putative ORs share the conserved amino acid motifs that distinguish ORs from other non OR seven-transmembrane proteins. Receptors that also function in odor recognition but don’t share any sequence similarity with known ORs will not be identified in this searching. For example, the TAARs were missed in the data mining performed for ORs.

2.1 Olfactory Receptor Repertoire

The size of OR repertoire varies dramatically among different species, but the reasons for this are unknown. While many primates have a reduced repertoire of functional receptor genes, family size is not in general coordinated with the apparent dependence on olfaction in the species niche; for example dogs have many fewer than rats. Exhaustive data with updated genomes has revealed that humans have 851 olfactory receptors genes, but only 384 among them are functionally intact (Glusman et al. 2001; Aloni et al. 2006) (details in Table 1). Another primate, the chimpanzee, has a similar number of OR genes as humans. In rodents, the mouse has fewer OR genes than the rat, with a number of 1,375 versus 1,576 (Zhang et al. 2004a, 2007a). The olfactory subgenomes of other mammals were also explored as their genome sequences became available. For example, dog, being well-known for its excellent smelling capability has 971 ORs (July 2004 assembly of the boxer breed) (Olender et al. 2004). The chicken’s OR repertoire consists of 554 genes,

Table 1 A comprehensive collection of OR genes in complete mammalian genomes

Organism	Species name	Genome assembly	Number of OR genes	Number of Intact OR genes	Number of OR pseudogenes
Human	<i>Homo sapiens</i>	hg17	851	384	467
Chimp	<i>Pan troglodytes</i>	PCAP1O26	899	353	546
Dog	<i>Canis familiaris</i>	canFam1	971	713	258
Mouse	<i>Mus musculus</i>	mm5	1,375	1,194	181
Rat	<i>Rattus norvegicus</i>	rn3	1,576	1,284	292
Opossum	<i>Monodelphis domestica</i>	mon Dom1	1,516	899	617
Chicken	<i>Gallus gallus</i>	galGal2	554	78	476

while only 78 among them are intact (Aloni et al. 2006). Lower organisms, such as fishes and insects, have dozens of OR genes and they are more distantly related with each other than those of mammals. The Pufferfish has 44 ORs while the Zebrafish has 98 (Niimura and Nei 2005). Insects have similar sized OR gene families. For example, the fruit fly and mosquito have 62 and 79 ORs respectively (Hill et al. 2002; Robertson et al. 2003). Nematode worms have around 800 functional chemoreceptor genes, which are thought to have arisen independently compared to insects and vertebrates (Bargmann 1998).

The size of the OR repertoire is not the only feature to vary across species, the proportion of intact and pseudo genes are also significantly different. A startlingly high fraction of the human OR (around 55%) repertoire has degenerated to pseudogenes. Other primates, such as the chimpanzee, also have a similar percentage (Gilad et al. 2005). In contrast, the proportion is much lower in rodents. In the most current version of the rat genome, pseudogenes in the OR repertoire only constitute 18.5% of the total and in mouse they account for only 13.1% (Zhang et al. 2007a). This has resulted in the mouse effectively possessing over three times as many intact genes as humans. However, we do not know if this translates into a wider range of detectable odorants or a superior discriminatory ability in mouse over human. Intact human OR genes are found in most of mouse OR subfamilies through phylogenetic analysis (Zhang and Firestein 2002) suggesting that human receptors are well represented within the mouse repertoire. Unexpectedly the decline of the OR gene family in some primates has been found to coincide with the acquisition of trichromatic vision, suggesting that better visual capability may make olfaction partially redundant (Gilad et al. 2004).

Although it is often thought that a genomics is a relatively static inquiry, this is untrue and in fact this research is quite dynamic. Genome sequences are regularly updated and significant revisions occur. For example, mouse OR repertoire was reported to consist of 1,296 ORs and about 20% of them are pseudogenes by Zhang et al. in 2002 using the Celera first draft of mouse genome (Zhang and Firestein 2002). Through the same computational methods and thresholds, 1,375 mouse ORs were identified in mouse genome version mm5 (<http://hgdownload.cse.ucsc.edu/>), decreasing the fraction of pseudogenes to 13.1% and about 100 pseudogenes were corrected to be intact genes (Zhang et al. 2007a). As the assembly has been optimizing, we expected to see a few pseudogenes to be annotated as intact while the repertoire size are relatively similar. Results from different research groups also have small discrepancies because of using slightly variable filtering criteria or searching methods.

Additionally the curated database that includes functions likely for particular genes is occasionally discovered to be inaccurate. These errors can propagate through the database, as a gene incorrectly identified by its initial discoverer is used as a model in data mining, and all similar sequences are classified as having a similar function. If the initial identification is incorrect so will be the subsequent classifications.

Finally new bioinformatics tools are regularly introduced allowing new data to be derived from existing databases.

2.2 OR Gene Sequences

Mammalian ORs can be separated into two broad classes by phylogenetic analysis. Class I receptors resemble the family that was first found in fish and frog, but had been considered an evolutionary relic in mammals (Fig. 2). As identified in the human genome, at first, 102 Class I ORs constitute about one-tenth of the human OR repertoire (Glusman et al. 2001). In rodents, the mouse possesses 158 Class I ORs, and the rat has 153, also comprising about one-tenth of their repertoires respectively. In both human and rodents, the Class I ORs contain a lower fraction of pseudogenes than the Class II ORs. Class I ORs are also more conserved in terms of both genomic location and gene sequences. Class II ORs are dispersed on numerous chromosomes, while Class I ORs are tightly clustered on one chromosomal segment. For example, all human Class I ORs are located in one super cluster, 11p15; and the mouse Class I ORs are located in a single cluster on chromosome 7. Comparative genomic analysis revealed that sequences of Class I ORs are even more conserved between mouse and rat than those of Class II ORs (Zhang et al. 2007a).

Gene expression data showed that Class I ORs are restricted to the dorsal zone of the mouse olfactory epithelium (Zhang et al. 2004b). These unique features lead us to suspect that Class I ORs may have some special and important functions, driving positive evolutionary pressure on mammals to maintain a high level of conservation.

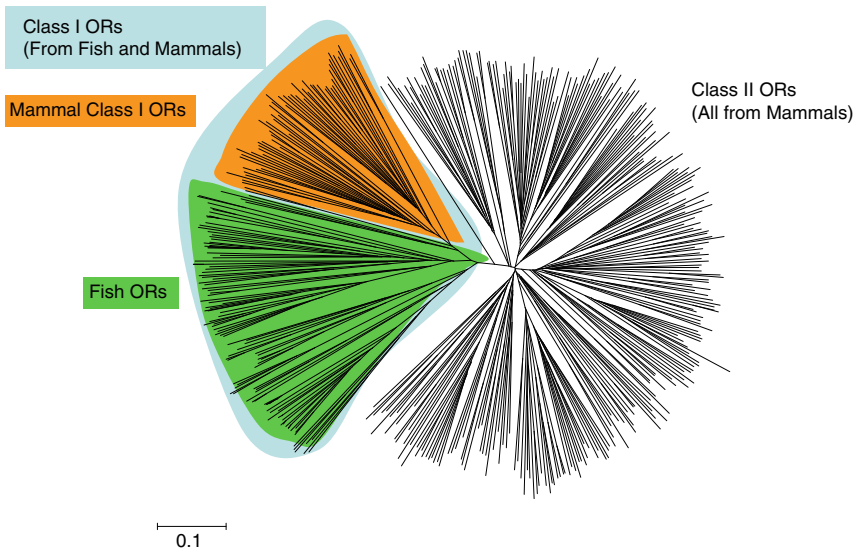


Fig. 2 *Classification of Fish and Mammalian ORs.* OR genes can be separated into two classes based on their sequences. Mammals have both Class I and Class II ORs, whereas all fish ORs belong to Class I. Insect ORs are quite different from each other and also different from fish and mammal ORs. All Class I ORs are shaded in blue. Class I ORs from mammals are shaded in orange and fish ORs are shaded in green

OR gene structures are complicated by their multiple splicing alternatives. Although the coding regions are encoded by a single exon about 1 kb long, the entire gene has multiple exons up and downstream of the coding region (Sosinsky et al. 2000). It is the coding regions of OR sequences that have been identified through computational exploration, leaving the upstream exons and downstream UTRs of most ORs yet to be identified. Through cDNA library screening, Young et al. disclosed that many OR genes have several transcriptional isoforms showing alternative splicing of their 5' untranslated exons or utilizing more than one polyadenylation site (Young et al. 2003). The mechanisms of transcriptional control of OR genes are yet to be discovered. Whether OR transcriptional isoforms have functional significance is also not determined.

OR proteins are composed of highly conserved and variable residues fulfilling corresponding functions. First of all, each OR has seven transmembrane helices (TM1–TM7) interconnected by extracellular (EC) and intracellular (IC) loops. Additionally there is an extracellular N-terminal chain and an intracellular C-terminal chain (Buck and Axel 1991; Pilpel and Lancet 1999). In analogy to other Class A GPCRs, ligand-binding activities are thought to take place in a pocket formed by the TM helices. The helix bundles appear to form two pockets. One is formed by TM1, TM2, TM3, and TM7 and a second one is formed by TM3 through TM7 (Liu et al. 2003). Secondly, OR proteins are characterized by conserved amino acid motifs that distinguish them from other seven-transmembrane proteins. ORs share some highly conserved motifs with other non OR GPCRs, however, they do have specific motifs that only occur in ORs. These OR signature sequences are likely to participate in critical OR-specific functional activities. For example, motif “KALSTCASHLLVV” positioned partly in IC3, is expected to bind with Golf upon activation. Furthermore, different positions of OR proteins have variable degrees of conservation. Computational analysis showed that TM4, TM5, the central region of TM3, and the last segments of the N- and C-terminals are highly variable. Since ORs can bind with a variety of ligands, those globally variable residues with high specificity are considered likely to participate in ligand-binding (Liu et al. 2003).

2.3 Genomic Organization and Gene Regulation

OR genes appear haphazardly spread over dozens of loci in the genome, as singletons or in tight clusters. In mouse and rat, the isolated genes occur quite rarely, occupying only 1.5% of the OR repertoire. These isolated genes have higher fraction of pseudogenes than genes in clusters. In the mouse genome version mm5 (<http://hgdownload.cse.ucsc.edu/>), OR genes are distributed in 43 clusters, with an intergenic distance within the clusters of 19–45 kb. These clusters are distributed on almost all chromosomes except chromosome 18 and the Y chromosome. The largest clusters are localized on chromosome 2 and 7, which harbor 344 and 267 ORs respectively. The second large mouse cluster, which consists entirely of all the

Class I ORs, is one of the densest clusters with an average distance of 19.1 kb between neighboring genes (Zhang et al. 2007a).

The size of the repertoire and the peculiar genomic organization pose a formidable challenge to OR gene regulation. Under the “one neuron, one receptor” hypothesis, a single olfactory sensory neuron (OSN) expresses only one OR of the repertoire (Mombaerts 2004). OR genes are expressed in a monoallelic fashion, with transcripts derived from either the paternal or maternal allele in different OSNs within an individual (Chess et al. 1994). The physical proximity between clustered genes reflects a likely evolutionary proximity, whereas their global regulatory networks must still be verified by further experimental evidence. The “H region”, a 2 kb DNA element upstream of the mouse MOR28 OR cluster and conserved between rodents and humans was identified bioinformatically by Sakano’s group as a possible regulatory element. Experimentally it has been shown that this region of DNA loops back and interacts with the downstream OR genes acting to promote gene choice. Negative feedback regulation has been proposed in this model to insure the one receptor-one olfactory neuron rule in mouse (Serizawa et al. 2003). While positioning the H element in different positions relative to other genes can alter expression levels. The H element can also interact with active OR gene promoters from different clusters, indicating the non cluster specific ‘avidity’ of H elements (Lomvardas et al. 2006). However, deletion of the H element does not effect the expression of homologous genes located in trans, nor other genes located on different chromosomes (Fuss et al. 2007). These data indicate that the H element functions as an enhancer, perhaps interacting with a single promoter of OR genes to promote OR gene choice.

2.4 Expression of OR Genes

OR repertoires were initially identified through computational methods solely based on sequence similarity with known ORs. Using a high-throughput custom microarray, Zhang et al. showed that a majority of OR genes are specifically enriched in the olfactory epithelium, substantiating their function in olfaction (Zhang et al. 2004b, 2008) (see Fig. 3). Certain OR genes are exclusively or predominantly expressed in non olfactory tissues, such as testis (Spehr et al. 2004), prostate (Yuan et al. 2001) and heart (Drutel et al. 1995). It may be that these were misidentified as ORs based on sequence similarity, but should be more properly considered as OR-like GPCRs of other functions. Since there are no ligands associated with these receptors they are effectively a group of new orphan GPCRs and therefore possible targets for therapeutic drugs. One of these receptors, hOR17-4, mediates directed chemotactic movement of human sperm in vitro (Spehr et al. 2003), and also functions in olfactory sensory neurons to detect the odor bougeonal (Spehr et al. 2004). Using the VNO or OE as the baseline for comparison, 30–100 OR genes were found to be enriched in each of several different tissues, including heart, liver, lung, and kidney (Zhang et al. 2004b). Ectopic expression of

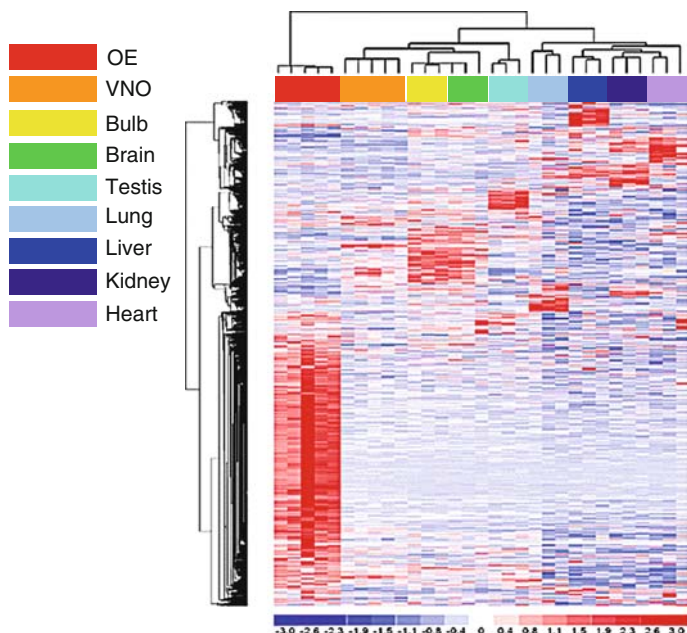


Fig. 3 *Expression profiles of OR genes across tissues.* These data show OE-specific and ectopic expression of OR genes. All tissues are from 2-month-old adult mice. Five sample replicates were collected for OE and VNO, and three sample replicates for other tissues. The gene expression values are standardized such that the mean is 0 and standard deviation is 1 for each gene. The color represents expression values as shown in the scale bar, with red corresponding to higher-than-mean expression values and blue corresponding to lower-than-mean values. The dendrogram on the left shows the clustering of genes, and the top dendrogram shows clustering of the samples based on the expression data. All genes showing expression in any tissue are chosen for the clustering analysis and are shown in the figure. 1,383 probe sets representing 1,095 OR genes are shown

olfactory receptor genes was also explored via EST and previously available microarray data in mouse and human (Feldmesser et al. 2006). Each different tissue was found to have a specific relatively small subset of OR genes. Human–mouse orthologous pairs did not show any correlation in the expressional level. The function or functions of these ectopically expressed ORs remain to be discovered.

In the olfactory epithelium, a given OR gene is expressed in a very small subset of OSNs within one of four parallel stripes or ‘zones’ that run rostral to caudal across the turbinates within the olfactory epithelium (OE). This spatial expression pattern has been determined by in situ investigation and microarray analysis (Sullivan et al. 1995; Qasba and Reed 1998; Zhang et al. 2004b). Notably, OR genes expressed in different zones often appear segregated on the chromosomes. Mouse class I ORs, which are located in one tight cluster on chromosome 7, are solely expressed in the most dorsal regions (zone 1) of the OE (Zhang et al. 2004b).

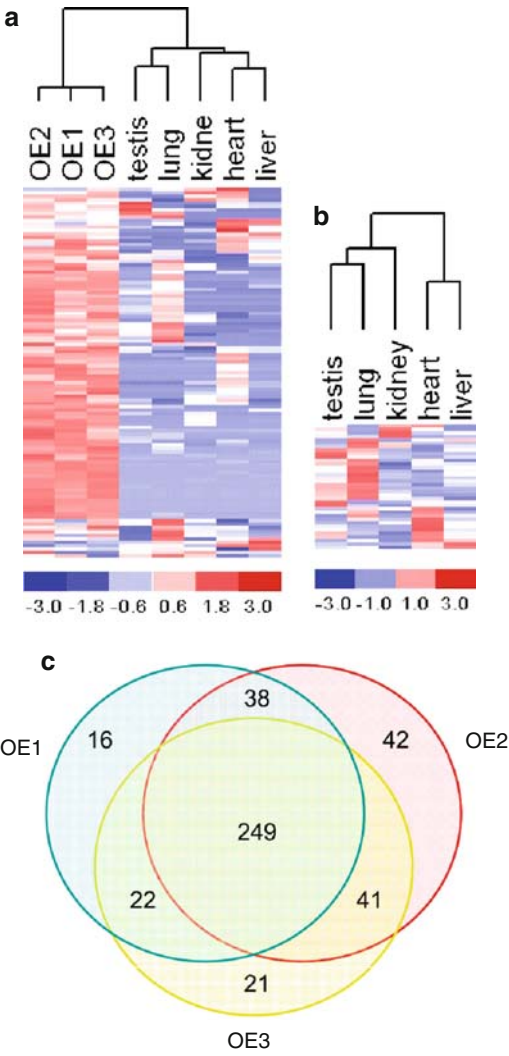
The biological importance of this compartmentalization remains unclear. Considering that zone 1 ORs cover more than one-third of the OR repertoire and the specific expression of class I ORs in zone 1, the separation between zone 1 and other zones might be especially significant.

The developmental course of wide scale OR gene expression has remained largely undocumented until custom MOR arrays were utilized. At embryonic day 13 (E13), OR gene expression in the epithelium does not show a significant difference with non OE tissues, mostly because there are few OR-positive cells, making microarray detection difficult. OR expression in a relatively larger number of cells is thought to occur by about day E15-16 (Sullivan et al. 1995). Nonetheless, a large number of OR genes appear to be detected only after birth. At around postnatal day 20 (P20), the number of detected OR genes reaches a peak and remains high. Some ORs are no longer expressed as mice age, for example, at age 18 months. Even more intriguingly, the expression level of ORs can be classified into different patterns. For example, some ORs reach a peak of expression between P10 and P20 and then reduce to a low level. Other ORs reach a peak at P10, then continue to express at this high level until sometime between 7 and 18 months. These patterns may correlate with their functions; for example, the first pattern may be related to nursing, the latter one to the reproductive cycle (Zhang et al. 2008). One caveat that should be noted is that all these levels refer to mRNA, not protein, which cannot currently be measured directly.

2.5 Population Variation of Human ORs

There is an enormous diversity in the repertoire of functional OR genes among different people. Roughly 60% of human odorant receptor genes have mutated into nonfunctional pseudogenes in a relatively recent genomic process; thus a substantial fraction of human odor receptors might be expected to segregate between an intact and a pseudogene form in different individuals. Menashe et al. genotyped 51 odor receptor loci in 189 individuals of several ethnic origins to screen for SNPs that distinguish the intact and pseudogenic forms (Menashe et al. 2003). Remarkably, of the 189 individuals, 178 functionally different genomes were found. Additional variation in the population may come from differences in gene expression. Experiments with custom microarrays specialized for detecting human odorant receptor genes have found that the expressed receptor repertoire of any pair of individuals differs by at least 14% (Zhang et al. 2007b) (see Fig. 4), suggesting that polymorphisms exist not only in coding regions but also in promoter and other regulatory regions. Additionally, the copy number variation of human olfactory receptor genes also contributes significantly to individual differences in olfactory abilities (Young et al. 2008).

Fig. 4 *Expression profile of human OR genes across tissues and variation in three human samples.* The log transformed detection *P* values for OR genes in all tissues were standardized to have a mean of 0 and a standard deviation of 1 and are color coded (red and blue shades indicate values above and below the mean, respectively). The dendrograms on top of each panel illustrate the clustering of tissue samples based on the profile of OR gene expression. (a) All 578 predicted OR genes are included in a comparison between olfactory epithelium (OE) and non olfactory tissues. (b) Shown are the data for only the 147 OR genes with significantly elevated expression in non olfactory tissues. (c) The number of predicted human OR genes whose expression was detected (at $P < 0.05$) in one or more of the three olfactory epithelium (OE) samples. As can be seen, there is a substantial difference in the expressed OR gene repertoire of each of the three OE samples



2.6 Summary and Perspective

With the cloning of the superfamily of odor receptors it became clear that one of the great challenges in olfaction would be handling the large numbers of receptor genes and potential ligands. Bioinformatics and microarray technologies are both well suited for managing large data sets with high throughput, their application here has advanced the understanding of the dynamics and organization of this largest of gene families in the nervous system, and has provided new insights into chemical sensing, sensory coding, gene regulation and nervous system development. It has also opened

up many new questions in evolution, individual variation, gene choice, and numerous questions about the entire gene locus beyond the coding region. Importantly, these analyses have brought the olfactory system to the attention of the wider community of neuroscientists and have demonstrated its value as a model system in which questions of general neurobiological significance can be profitably investigated.

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