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# Olfactory receptor gene repertoires in mammals

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**Abstract**

In mammals, olfaction is mediated by two distinct organs that are located in the nasal cavity: the main olfactory epithelium (MOE) that binds volatile odorants is responsible for the conscious perception of odors, and the vomeronasal organ (VNO) that binds pheromones is responsible for various behavioral and neuroendocrine responses between individuals of a same species. Odorants and pheromones bind to seven transmembrane domain G-protein-coupled receptors that permit signal transduction. These receptors are encoded by large multigene families that evolved in mammal species in function of specific olfactory needs.


*Keywords:* Olfaction; Receptors; Gene repertoire; Odorants; Pheromones; Evolution; Mammals

## 1. Introduction

Chemodetection is achieved in mammals by olfaction (detection of odorants and pheromones) and taste (gustatory perception) (Fig. 1). These three functions enable an animal to detect chemicals in the external environment and to identify chemical cues from conspecifics. In the present review, we will focus on the evolution of the olfactory receptor gene repertoires devoted to olfaction (sniffing of chemical compounds permitting the detection of odorants and pheromones).

The sense of smell is an ancient sensory system that is present in most species (worms, insects, fish, birds and mammals). Although in humans, olfaction is viewed rather as an esthetic sense, it is essential for survival in other species such as mouse for locating food, mates or predators.

Surprisingly, until 1991, olfaction was poorly characterized at the gene level. In 1991, Buck and Axel discovered the olfactory receptor (OR) gene family in rat [1]. This founder paper opened the door for deciphering the mechanisms of olfaction. For this major discovery, Linda Buck and Richard Axel won the Nobel Prize in Physiology or Medicine in October 2004. Fifteen years after this initial discovery, OR genes have been found in most species, and since this date, the public release of the complete sequence of numerous species (>12 in mammals) has allowed different teams to characterize the complete OR gene repertoires of these species and to trace their evolutionary story. Similarly, pheromone receptors (VR) were described more recently as two differents receptor families (V1R and V2R) in mouse [2–4]. Searches for VR in different species, particularly the V1R family, have also permitted to follow the evolution of pheromone detection. These past 10 years, a number of data about odorant and pheromone receptor genes have been accumulated and various reviews have been written on the principles of odor/pheromone detection. Here, we will focus on the recent data concerning the evolution of these gene repertoires in mammals with a comparison of odor and pheromone detection.

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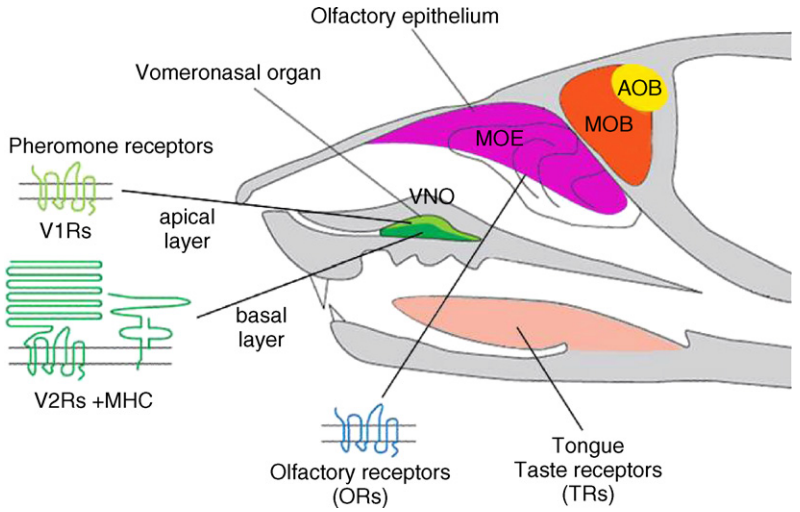


Fig. 1. Chemosensory organs of the mouse. Pheromone and olfactory receptors are unrelated heptahelical G-protein-coupled receptors. Olfactory receptors are expressed in the sensory neurons of the main olfactory epithelium (MOE). Pheromone receptors V1R are expressed in sensory neurons of the apical layer of the vomeronasal organ (VNO), whereas V2R that are coexpressed with MHC-1b-like molecules are expressed in neurons of the basal layer. Axons of sensory neurons of the VNO project to the accessory olfactory bulb (AOB), whereas those of the MOE project to the main olfactory bulb (MOB). Adapted from [30].

## 2. Odor detection

### 2.1. Background

Odor detection is achieved in every species by the binding of odorants by olfactory receptors (OR). This interaction induces a transduction pathway that ultimately transmits a signal to the central nervous system that results in a sensation of smell. In vertebrates, OR are mainly expressed on the cilia of the dendrites of olfactory sensory neurons that emerge in the nasal olfactory epithelium and for some of them in mature male germ cells. ORs are heptahelical G-protein-coupled receptors (GPCR) that share a significant homology in vertebrates, particularly in conserved domains. However, although OR are invariably GPCR, they do not share any significant homology when comparing those of worms (*C. elegans*), insects and vertebrates.

Some years ago, we demonstrated for the first time that the OR gene repertoire in humans was largely distributed in the genome and that the number of functional genes was very low (∼30%), providing a possible explanation for the reduced sense of smell of humans compared with that of other species such as dog or mouse [5]. Later the release of the complete sequence of the human genome permitted to precise these results [6]. Briefly, the human genome contains ∼1000 OR genes dispersed in >50 chromosomal locations and organized mostly in clusters. About 65% of them have incurred deleterious mutations during evolution through a pseudogenization process, leading to only ∼300–350 potentially functional OR genes. ORs are distributed in two main classes: class I that corresponds to fish-like receptors that bind water-soluble odorants, and class II that contains mammal-like receptors dedicated to binding volatile odorants. Actually, sequence analysis of the human genome revealed that the complete OR gene repertoire originated from a class I OR cluster located on chromosome 11. This cluster duplicated first in another location of chromosome 11 to generate a class II cluster that was in turn duplicated on chromosome 1. From this latter location the repertoire expanded by multiple duplications throughout the genome to generate the present OR repertoire [6].

Starting from the observations that humans have a reduced functional OR repertoire, we then asked the question whether this pseudogenization was specific of the hominization process. To answer this question we sampled the genomes of various primate species [7]. In summary, we found that there is an acceleration in the pseudogenization process from New World monkeys (NWM, low pseudogene content as in mouse) to Old World monkeys (OWM, ∼30% pseudogenes) and apes (∼45% pseudogenes) with humans having the highest pseudogene content (∼65%). It was therefore tempting to speculate that during evolution, primates lost a part of their olfactory ability because, on the contrary to mouse, they do not rely anymore on olfaction for survival.