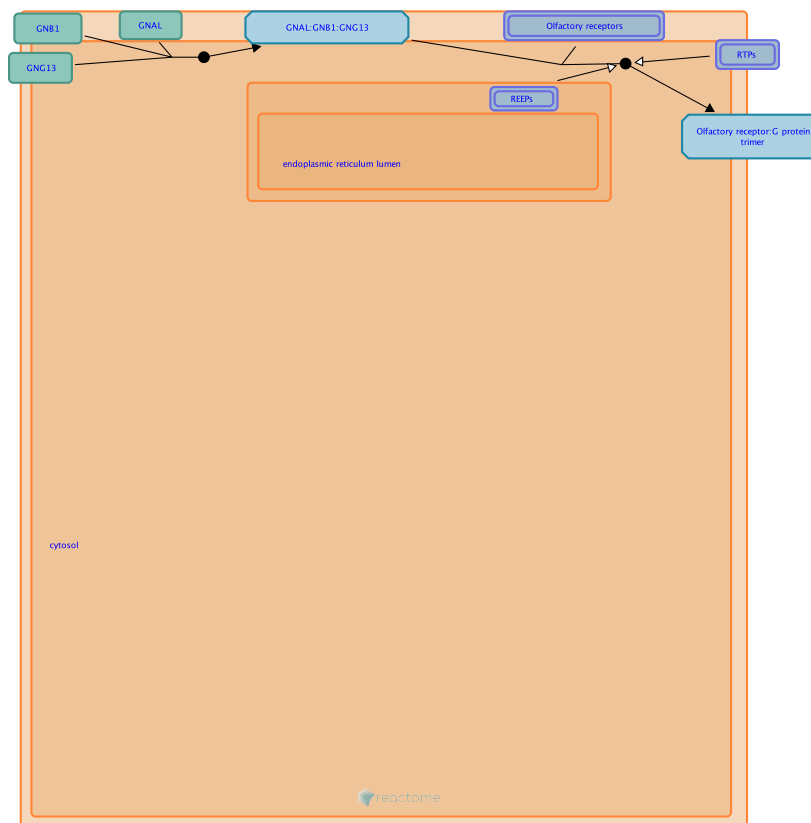


Olfactory Signaling Pathway



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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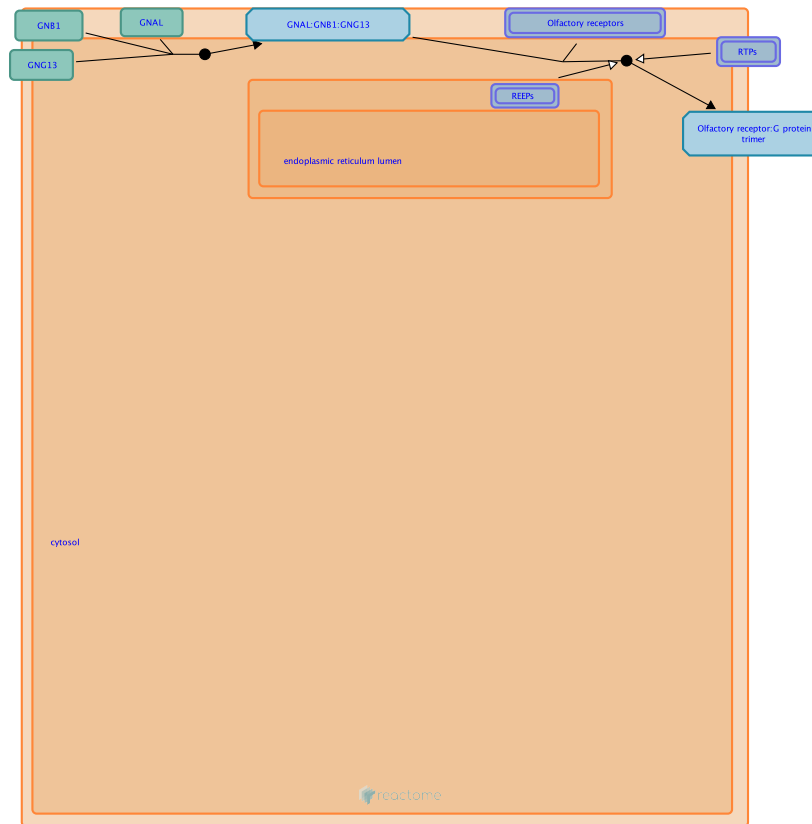
Reactome database release: 77

This document contains 1 pathway and 2 reactions ([see Table of Contents](#))

Olfactory Signaling Pathway ↗

Stable identifier: R-HSA-381753

Compartments: plasma membrane



Mammalian Olfactory Receptor (OR) genes were discovered in rats by Linda Buck and Richard Axel, who predicted that odorants would be detected by a large family of G protein-coupled receptors (GPCRs) that are selectively expressed in the olfactory epithelium. This prediction was based on previous biochemical evidence that cAMP levels increased in olfactory neurons upon odor stimulation. These predictions proved to be true, and Buck and Axel received a Nobel Prize for this and subsequent work (reviewed in Keller & Vosshall 2008).

Subsequent work in mice and other vertebrates has confirmed that OR genes are comprised of a very large family of G Protein-Coupled Receptors (GPCRs) that are selectively-expressed in olfactory epithelium. Although some OR are also expressed selectively in one or a few other tissues, their expression in olfactory-epithelium generally indicates a functional role in mediating olfaction, where they couple binding by odorant ligands with intracellular olfactory signaling. (Note: the other subclasses of GPCR signaling pathways are described under "GPCR Signaling".)

The ligands for ORs are diverse, ranging from chemical compounds to peptides. Intracellular signaling by OR proteins in mice and other mammalian systems is known to be mediated via direct interactions of OR proteins with an olfactory specific heterotrimeric G Protein, that contains an olfactory-specific G alpha protein: G alpha S OLPH (also named "GNAL").

There are two models for GPCR-G Protein interactions: 1) ligand-GPCR binding first, then binding to G Proteins; 2) "Pre-coupling" of GPCRs and G Proteins before ligand binding (Oldham & Hamm 2008). Both models may be true for certain GPCRs in different contexts. Pre-coupling is likely to be functionally important, as pre-coupling of receptor and G Protein allows much more rapid kinetic response once ligand is bound, because the ligand-bound receptor is immediately able to transduce the signal, rather than hav-

ing to diffuse around within the plasma membrane until it encounters a G Protein to interact with (Oltham & Hamm 2008).

The pre-coupling model is used here to characterise the reaction of the human ORs with G Proteins in the absence of ligand, because the ligands in humans are almost completely undocumented experimentally.

In model genetic systems such as mice, many candidate OR genes have been shown experimentally to function in olfactory signaling (reviewed in (Keller & Vosshall 2008)). For the human OR genes, experimental analysis has been much more limited, although some specific OR genes, such as OR7D4 and OR11H7P have been confirmed to mediate olfactory response and signaling in humans for specific chemical odorants (Keller et al. 2007, Abbafy 2007). Mice and other rodents are believed to have about 1000 functional OR genes, as well as many additional pseudogenes. Based on sequence similarities, there are 960 human OR genes, but approximately half of these are pseudogenes (Keller 2008). In mice, essentially all olfactory signaling requires G-alpha-S (OLF); mouse G-OLF knockouts have been shown to lack olfactory responses (Belluscio 1998). Bona fide human OR genes identified by sequence similarity (not pseudogenes with function-blocking mutations) that are expressed in olfactory epithelium are expected to interact with G alpha S OLF containing G Protein trimers.

Of the 960 human OR genes and pseudogenes, there is experimental evidence that indicates over 430 are expressed in human olfactory epithelium, including 80 expressed OR pseudogenes (Zhang 2007).

When expressed in model cell systems mammalian odorant receptors (OR) are typically retained in the ER and degraded by the proteasome (McClintock et al. 1997). A study using *Caenorhabditis elegans* showed that the transport of ORs to the cilia of olfactory neurons required the expression and association of ORs with a transmembrane protein, ODR4 (Dwyer et al. 1998). Co-transfection of rat ORs with ODR4 enhanced the transport and expression of ORs at the cell-surface (Gimelbrant et al. 2001). These studies suggested that olfactory neurons might have a selective molecular machinery that promotes expression of ORs at the cells surface. Two human protein families have been identified as potential accessory proteins involved in the trafficking of ORs to the plasma membrane (Saito et al. 2004). Receptor transporting proteins 1 and 2 (RTP1, RTP2) both strongly induced expression of several ORs at the cell-surface. To a lesser extent, the receptor expression enhancing protein 1 (REEP1) also promoted cell-surface expression. These proteins are specifically expressed in olfactory neurons with no expression in testis, where a subset of ORs are expressed (Parmentier et al. 1992, Spehr et al. 2003). Other members of the RTP and REEP families have a widespread distribution. RTP3 and RTP4 have been shown to promote cell-surface expression of the bitter taste receptors, TAS2Rs (Behrens et al. 2006). REEP1 and REEP5 (also known as DP1) are involved in shaping the ER by linking microtubule fibers to the ER (Park et al. 2010, Voeltz et al. 2006). A recent study looking at the role of REEP in the trafficking of Alpha2A- and Alpha2C-adrenergic receptors showed that REEP1-2 and 6 enhance the cell-surface expression of Alpha2C, but not Alpha2A, by increasing the capacity of ER cargo, thereby allowing more receptors to reach the cell-surface (Bjork et al. 2013). Unlike RTP1, REEP1-2 and 6 are only present in the ER, do not traffic to the plasma membrane and specifically interact with the minimal/non-glycosylated forms of Alpha2C via an interaction with its C-terminus (Saito et al. 2004, Bjork et al. 2013). REEPs may function as general modulators of the ER, rather than specifically interacting with GPCRs. Loss of association of REEP2 with membranes leads to hereditary spastic paraplegia (Esteves et al. 2014).

Olfactory receptors (ORs) are present on the plasma membrane of cilia of olfactory sensory neurons located in the olfactory epithelium of the nasal sinus. Each mature neuron expresses only one OR gene (reviewed in Nagai et al. 2016) and each OR binds one particular volatile chemical or set of volatile chemicals, known as odorants. The binding of an odorant to an OR (Mainland et al. 2015) causes a conformational change in the receptor that activates the G alpha subunit (Golf, GNAL) of an associated heterotrimeric G protein complex to exchange GDP for GTP (inferred from mouse homologs in Jones et al. 1990).

GNAL:GTP and the Gbeta:Ggamma subcomplex (GNB1:GNG13) dissociate from the olfactory receptor and GNAL:GTP then binds and activates adenylate cyclase 3 (ADCY3) (inferred from rat homologs in Bakalyar and Reed 1990, reviewed in Boccaccio et al. 2021). Cyclic AMP produced by ADCY3 binds and opens the olfactory cyclic nucleotide-gated channel (CNG channel) composed of CNGA2, CNGA4, and CNGB isoform 1b (inferred from rat homologs in Liman and Buck 1994). The CNG channel translocates sodium and calcium cations from the extracellular region into the cytosol. The resulting cytosolic calcium ions bind ANO2 and increase the transport of chloride ions by ANO2 from the cytosol to the extracellular region (inferred from mouse homologs in Pifferi et al. 2009, Stephan et al. 2009). The translocations of ions across the plasma membrane causes depolarization of the neuron yielding a receptor potential and action potential that is transmitted to the olfactory bulb of the brain.

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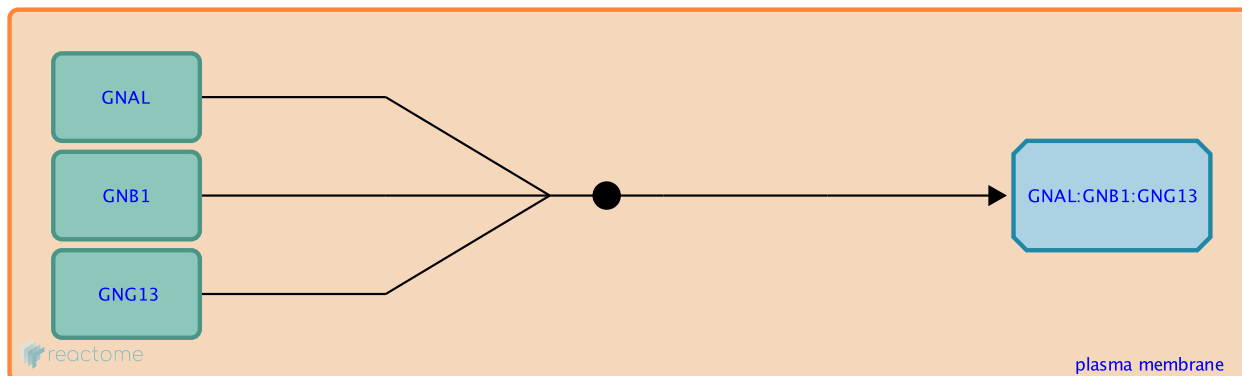
G Protein trimer formation (olfactory) ↗

Location: [Olfactory Signaling Pathway](#)

Stable identifier: R-HSA-381749

Type: binding

Compartments: plasma membrane



The heterotrimeric guanine nucleotide-binding proteins (G-proteins) function to transduce signals from this vast panoply of receptors to effector systems including ion channels and enzymes that alter the rate of production, release or degradation of intracellular second messengers. GPCRs activate the G-proteins, which consist of an alpha-subunit that binds and hydrolyses guanosine triphosphate (GTP), a beta and a gamma subunit.

Followed by: [Olfactory Receptor - G Protein olfactory trimer complex formation](#)

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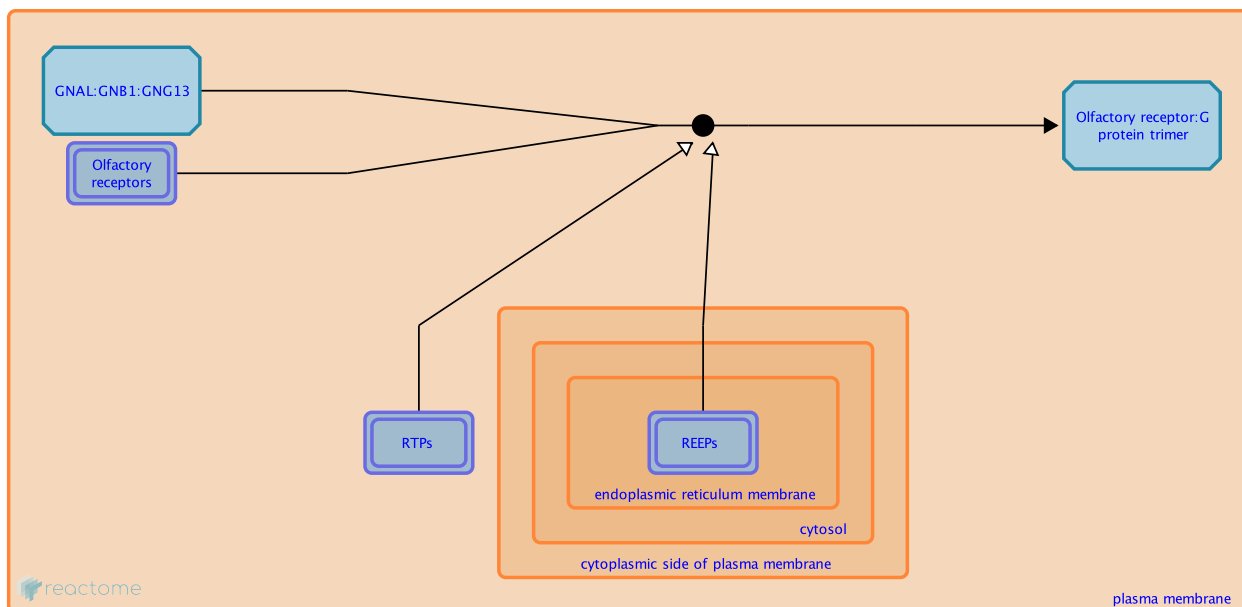
Olfactory Receptor - G Protein olfactory trimer complex formation ↗

Location: [Olfactory Signaling Pathway](#)

Stable identifier: R-HSA-381750

Type: binding

Compartments: plasma membrane



Olfactory receptors (ORs) have diverse protein sequences but can be assigned to subfamilies on the basis of sequence relationships. Odorants and pheromones bind to these 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. Members of the same subfamily have related sequences and are likely to recognize structurally related odorants.

Of the 960 human OR genes and pseudogenes, there is experimental evidence which indicates that at least 437 actually are expressed in human olfactory epithelium; this includes 357 OR genes, and 80 OR pseudogenes (Zhang, 2007). These 357 olfactory-expressed OR genes are therefore expected to be functional in the Olfactory Signaling Pathway, and to interact directly with human G alpha olf in human olfactory cells.

(Note: A subset of 200 of these 357 OR genes are shown as components of OR-G Protein reaction. The others will be added to Reactome later.)

Preceded by: [G Protein trimer formation \(olfactory\)](#)

Literature references




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