The human olfactory receptor repertoire

ABSTRACT

The identification and cloning of all functional human odorant receptor genes is an important initial step in understanding receptor-ligand specificity and combinatorial encoding of odorant stimuli in human olfaction.

INTRODUCTION

Background Olfaction is a major neurosensory function by which mammals investigate the external chemical environment. The initial step in odor identification is interaction of an odorant molecule with olfactory (odorant) receptors (ORs) expressed at the surface of cilia of chemosensory olfactory neurons in the olfactory epithelium. Seven-transmembrane ORs, first identified in 1991, are the largest vertebrate gene family, comprising as many as 1,000 genes (reviewed in). Mammalian ORs are classical G-protein-coupled receptors belonging to Class I or A, which also includes opsins and catecholamine receptors. Each olfactory neuron appears to express a single type of OR implying a sophisticated mechanism of OR gene choice. Another intriguing feature of olfaction is combinatorial recognition of odorants. Each receptor recognizes multiple odorants, and each odorant binds to multiple receptors to generate specific activation patterns for each of a vast number of distinct smells. The genes encoding ORs are devoid of introns within their coding regions. Mammalian OR genes are typically organized in clusters of ten or more members and located on many chromosomes. The repertoire of human OR (hOR) genes contains a large fraction of pseudogenes, suggesting that olfaction became less important in the course of primate evolution. Recent studies indicate that some 70% of all hOR genes may be pseudogenes, compared with fewer than 5% in rodents or lower primates. Analyses of incomplete compilations of hORs, in particular approximately 150 full-length receptor genes, have recently been published. A larger annotated set of hOR genes is available as an online database. The very recent milestone publication of the first draft of the human genome sequence by two groups opens up the possibility of detailed and complete identification, mapping and analysis of OR genes and their products in the near future. One of these groups reported that the human genome contains 906 OR genes, of which approximately 60% appear to be pseudogenes. Many alternative nomenclatures for hORs, including a comprehensive phylogenetic classification developed at the Weizmann Institute, have been proposed by various labs over the past few years. The identification, cloning and sequence-based classification and analysis of candidate hORs are essential prerequisites for rational structure-function studies of this vast receptor family. Our goal was to identify the complete repertoire of hOR genes encoding full-length receptors. The approach was to carry out reiterative homology-based searches of GenBank DNA, particularly recently available unannotated raw sequences, and to compile hOR sequences already present in other public databases. We report here the identification and cloning of 347 putative full-length hOR receptor genes, which we believe accounts for nearly the entire repertoire of functional hORs. We also present a comparative sequence analysis of the predicted OR gene products and propose a new nomenclature for candidate hORs.

CONCLUSION

Conclusions Identification and cloning of the functional hOR repertoire

creates a basis for addressing many unresolved issues in human olfaction. Most importantly, in conjunction with robust heterologous expression and assay systems and high-throughput screening of odorant libraries, it will ultimately lead to understanding of structure-function relationships and small-molecule recognition by this large group of G-protein-coupled receptors. The impact of genetic polymorphism of ORs on differential olfactory perception in the human population is another exciting topic. Global comparative analysis of functional hOR candidate gene and pseudogene repertoires, as well as of repertoires of human and murine ORs will shed light on the evolution of the human olfactory apparatus and its biological consequences.