

Poster C-8

Molecular recognition and evolution in the olfactory receptor gene superfamily



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Short Abstract: We compared five mammalian repertoires of olfactory receptors (ORs), including the marsupial opossum,. We identified 48 CLICs (CLusters In Conservation) containing most of the mammalian ORs. Human and mouse OR expression data were collected from a multitude of sources. Data showed an unexpectedly high degree of ectopic expression in non-olfactory tissues.

Long Abstract:

Olfaction, the sense of smell, detects and discriminates millions of odorant molecules. This capacity is made possible by the olfactory receptors (ORs) protein superfamily, belonging to the hyperfamily of G-protein coupled receptors. ORs are expressed on the dendritic membrane of olfactory sensory neurons, and enable the transduction of the chemical signal to neuronal action potentials. Employing novel technologies for genome-wide OR sequencing and data mining we have completely elucidated the human and dog OR repertoires. These OR sequences are catalogued in HORDE, the Human Olfactory Receptor Data Exploratorium (<http://bip.weizmann.ac.il/HORDE>). The most up to date version of HORDE includes 855 human Ors, classified into 17 families. The OR genes are distributed in clusters on all but two human chromosomes.

Incorporation of non human OR repertoires into HORDE

The completion of several mammalian and other vertebrate genomes allowed the identification of entire OR repertoires in several species. These are constantly integrated into HORDE, and are compared to the human OR repertoire. Currently, HORDE contains the complete OR repertoires of mouse, dog, rat, chimpanzee and chicken. Some OR sequences of primates, reptiles and amphibian are available as well.

Recently we have elucidated the complete OR repertoire out of the opossum *Monodelphis domestica* genome, the only published marsupial genome. Employing computational methodologies we identified 1519 ORs, of which 40.7% are pseudogenes. This highcount of pseudogenes in the opossum OR repertoire is twice than in other macrosmatic species such as mouse or dog, and comparable to that of primates. Phylogenetic analyses revealed that more than half of the opossum ORs have common ancestry with eutherian ORs, in contrast to only 22 when comparing to chicken. This result indicates on a great expansion of the OR superfamily which occurred in the early mammalian era.

We identified a unique marsupial specific expansion classified as a novel OR family (family

14). Perhaps this OR family contributes to yet unidentified unique chemosensory capacities of this species.

Ancient Genomic Architecture for Mammalian OR Clusters

We studied the common evolutionary origin of the mammalian OR repertoires, highlighting inter-species differences. To this end, we developed a novel and general algorithm to identify CLICs (CLusters In Conservation), which allows a comprehensive comparison of gene clusters in multiple species. This algorithm progresses from the intra-species identification of genomic clusters, through the pairwise comparison of individual ORs from different species, to their integration in the multi-species framework of CLICs. To discover CLICs, privileged orthologs, defined as gene pairs showing conservation of both syntenic genomic location and coding sequence similarity, were subjected to a graph theory algorithm. When applied to ORs in five mammals, including the marsupial opossum, more than 90% of the genes were found within a framework of 48 multi-species CLICs, invoking a general conservation of gene order and composition. A detailed analysis of individual CLICs revealed multiple differences among species, interpretable through species-specific genomic rearrangements and reflecting a complex mammalian evolutionary dynamics. One significant instance involves CLIC #1 which lacks a human member, implying the human-specific deletion of an OR cluster, whose mouse counterpart has been tentatively associated with Isovaleric acid odorant detection.

Our results demonstrate that most of the mammalian olfactory receptor clusters have a common ancestry, preceding the split between marsupials and placental mammals. In contrast, only two of these CLICs were capable of incorporating chicken OR genes, parsimoniously implying that all other CLICs have emerged subsequent to the avian-mammalian divergence.

Widespread ectopic expression of olfactory receptor genes

ORs are expected to be specifically expressed in olfactory tissues. However, some OR were reported previously to be ectopically expressed in non-olfactory tissues. Most of these reports were related to Ors in testis and germ cells, leading to the hypothesis that the relevant gene products are involved in mammalian sperm chemotaxis.

To obtain a comprehensive view of OR ectopic expression, we analyzed the expression patterns of hundreds of human and mouse OR transcripts, via deposited EST and microarray data, in several dozens human and mouse tissues. Different tissues had specific, relatively small OR gene subsets which had particularly high expression levels. In testis, average expression was not particularly high, and it had very few highly expressed genes, none corresponding to ORs previously implicated in sperm chemotaxis. Higher expression levels were more often seen for genes with a non-OR genomic neighbor. Importantly, no correlation in expression levels was detected for human-mouse orthologous pairs. Also, no significant difference in expression levels was seen between intact and pseudogenized ORs, except for the pseudogenes of subfamily 7E which has undergone a human-specific expansion.

The OR superfamily as a whole shows widespread, locus-dependent and heterogeneous expression, in agreement with a neutral or near neutral evolutionary model for transcription control. These results cannot reject that small OR subsets might play functional roles in different tissues, however considerable care should be exerted when offering a functional interpretation for ectopic OR expression based only on transcription information.

Publications

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