De-Orphanizing Olfaction

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Cliff and C. diff - Smelling the diagnosis
How can he do it?
A broad-, sensitive and fine-tuned chemical detector
The mammalian olfactory system

1. Odorants bind to receptors
2. Olfactory receptor cells are activated and send electric signals
3. The signals are relayed in glomeruli
4. The signals are transmitted to higher regions of the brain

Nasal Mucous

Olfactory Bulb

Olfactory Sensory Neurons

Olfactory Cilia
One olfactory neuron – one receptor rule

OR genes

Neuron I

Neuron II

Neuron III

Stochastic expression, negative feedback

Individual A

Individual B

Individual C
monophosphate (cAMP). Finally, this increase in cAMP opens cyclic nucleotide
gated cation (CNG) channels, causing ... single OR can
be activated by multiple odors (Fig. 1-4) (Firestein, 2001; B Malnic, et al., 1999; 
Mombaerts, 2004a).
Number of ORs
Human    396
Mouse   1130
Rat        1207
Dog         811
A combinatorial odor coding

1. How many and which ORs are activated by a given odor?
2. How does each OR contribute odor perception?
Functional expression of ORs in heterologous cells: Importance of Receptor-Transporting Proteins (RTPs)

Cell Surface Expression

Saito et al., 04, Zhuang et al., 06
Large-scale in vitro screening with human and mouse ORs
OR functional variation affects odor perception in humans
## Individual OR genes and odor perception

<table>
<thead>
<tr>
<th>OR</th>
<th>variant type</th>
<th>odor</th>
<th>natural source</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR7D4</td>
<td>missense</td>
<td>androstenone, androstadienone</td>
<td>pork</td>
<td>Keller et al., 07, Lunde et al., 12</td>
</tr>
<tr>
<td>OR11H7P</td>
<td>segregated pseudogene</td>
<td>isovaleric acid</td>
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<td>Menashe et al., 07</td>
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<tr>
<td>OR cluster</td>
<td></td>
<td>urine after eating asparagus</td>
<td></td>
<td>Eriksson et al., 10</td>
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<tr>
<td>OR cluster</td>
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<td>soapy flavor of cilantro</td>
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<td>Eriksson et al., 12</td>
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<tr>
<td>OR2J3</td>
<td>missense</td>
<td>cis-3-hexen-1-ol</td>
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<td>McRae et al., 12</td>
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<tr>
<td>OR5A1</td>
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<td>beta-ionone</td>
<td>juice</td>
<td>Jaeger et al., 13</td>
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<td>OR cluster</td>
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<td>2-heptanone</td>
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<td>McRae et al., 13</td>
</tr>
<tr>
<td>OR cluster</td>
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<td>beta-damascenone</td>
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<td>guaiacol</td>
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<td>Mainland et al.,</td>
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</tbody>
</table>
Each individual has a unique set of functional OR repertoire.
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