# Molecular recognition and evolution in biological repertoires: from olfaction to the origin of life

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Our research focuses on molecular recognition within biological repertoires. Focusing on the olfactory system, we ask what are the proteins involved in this sensory pathway? How do the relevant protein receptor families evolve and function? What are the environmental and genetic factors that shape our olfactory individuality? Olfactory receptors (ORs) are G-protein coupled receptors, which constitute the largest gene superfamily in the human genome. We use the tools of human genomics, bioinformatics, comparative genomics and population genetics to shed light on this huge repertoire. In parallel, we are interested in the fundamental question of biology – how did life emerge? To begin answering this question, we employ statistical molecular complementarity formalisms to decipher the very early steps in prebiotic self-organization.

### Genome analysis of olfactory receptor (OR) genes

Employing novel technologies for genome-wide OR sequencing and data mining, and as part of the world-wide human genome project, we have completely elucidated the human olfactory sub-genome - the entire collection of OR genes and pseudogenes. The results are accumulated in a unique database (HORDE) equipped with diverse analysis modes, including a nomenclature system, now officially accepted worldwide. The most up to date version of HORDE includes 855 ORs classified into 17 families (Fig. 1). The OR genes are organized in 136 genomic clusters on all but two human chromosomes. To gain insight on OR gene structure and their transcription regulation we collected expression data from a multitude of sources, including cDNAs and mRNAs information as well as microarray data. This effort showed an unexpectedly high degree of ectopic expression

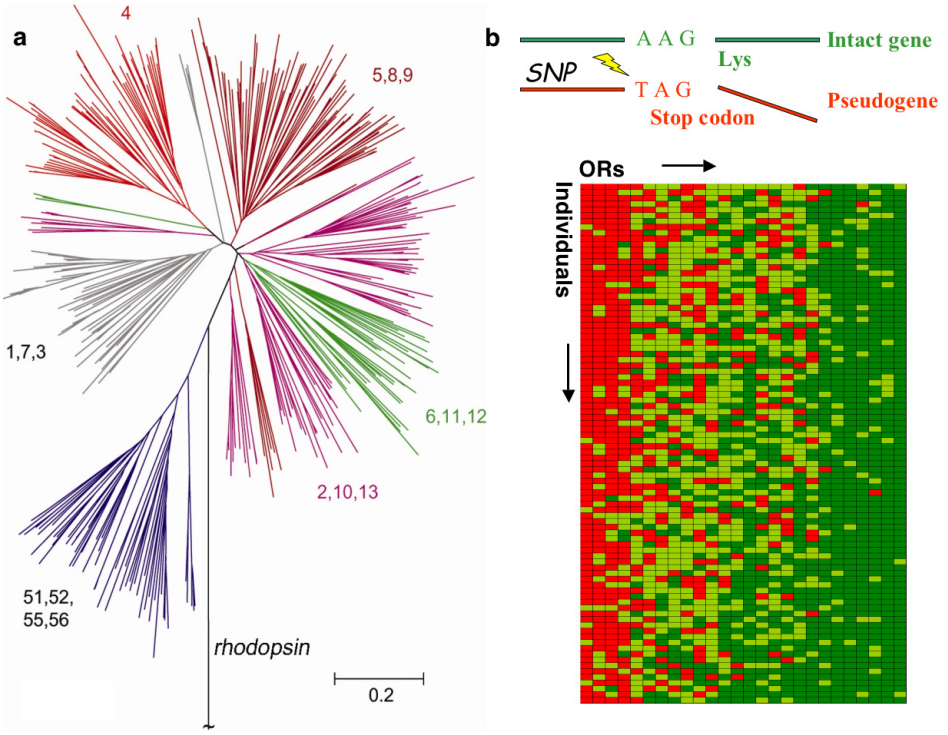


***Fig. 1*** *a. A phylogenetic analysis of the human olfactory receptor repertoire into families, currently expanded to include several other mammals. The families are divided into two classes; Class I (families 51-56) and Class II (families 1-13). See http://bip.weizmann.ac.il/HORDE*
*b. The diagram depicts a pseudogenezation process by a single nucleotide polymorphism, which gives rise to a stop codon instead of an amino-acid coding codon. The "barcode" represents the observed individual olfactory receptor genotypes – each column is a specific olfactory receptor and each line is individual. Red indicates homozygous receptor disruption, dark green denotes homozygously intact olfactory receptor and light green indicates heterozygosity.*

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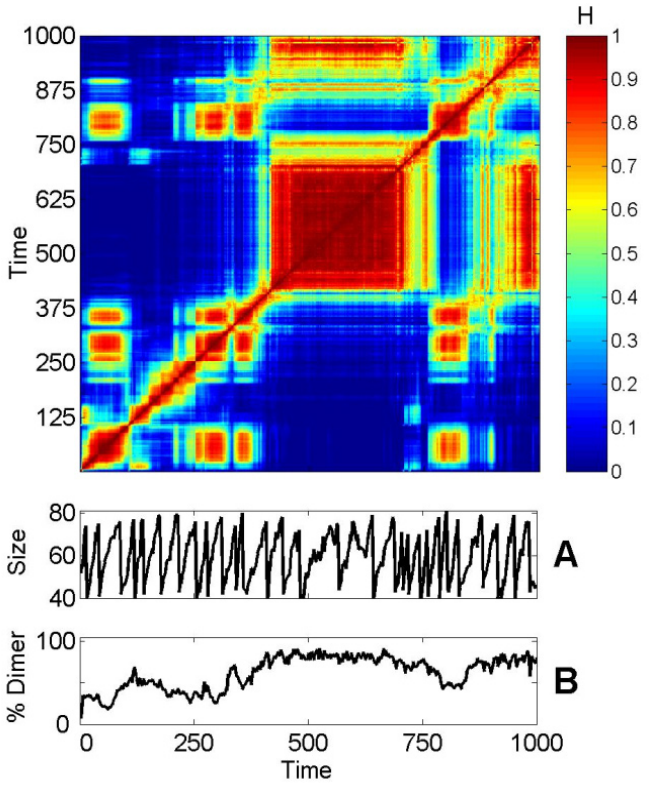


***Fig. 2*** *Time auto-correlation matrix from a Polymer-GARD simulation. Red squares (high mutual similarity H) are "composomes" with high efficiency of inheritance across splits (panel A). Dimers takeover is seen in panel B. See: http//ool.weizmann.ac.il*

in non-olfactory tissues. ESTs and mRNA genomic placements were further explored to reveal new information on the 5'- and 3'-untranslated regions of 154 ORs. This is a fundamental step for analyzing OR gene structure promoter regions.

### Genetics of human olfactory variability

Olfaction, though not absolutely essential to humans, is highly important for our quality of life. Humans exhibit high variability of both general olfactory thresholds and sensitivities towards specific odorants, which is attributed in part to genetic variation. We strive to identify the genes underlying such variation.

Previously we showed that humans and apes have undergone a recent and massive OR gene loss, that correlates with the acquisition of full (trichromatic) color vision. In addition we identified OR genes that underwent recent pseudogenization in humans. Such genes constitute an unusual phenomenon of segregating pseudogenes (SPG), i.e. genes showing both functional and inactive alleles in the population. Importantly, OR SPGs are natural knockouts, perfect candidates to underlie the long known phenomenon of odor blindness (specific anosmia) - diminished sensitivity towards one or more odorants, with otherwise normal olfactory acuity. Individualized SPG combinations generate an olfactory "barcode", whereby every human nose is genetically different. In our ongoing research with hundreds of volunteers, using high-throughput Single Nucleotide Polymorphism (SNP) analysis, we show preliminary association of two of such SPG loci with specific anosmia to isolvaleric acid. Our data also supports the existence of "general olfactory sensitivity trait", as implied by the concordance of sensitivities to different odorants in a given individual. In our laboratory we strive to identify the genetic basis of this trait in humans and mice, utilizing the recently described in silico genetic mapping method, automated olfactometry and Affymetrix 500k whole genome SNP microarray scans.

### A lipid world scenario of the origin of life

In the 'lipid world' scenario for origin of life we have suggested that life emerged from primordial assemblies of lipid-like amphiphilic molecules. Based on our Receptor Affinity Distribution model, developed by us to understand ligand binding in the olfactory system, we devised an artificial chemistry formalism, the Graded Autocatalysis Replication Domain (GARD) model. This describes by computer simulations the catalytic interactions in large molecular repertoires of prebiotic molecules. GARD depicts the kinetics of molecular assemblies that are kept far from equilibrium by occasional fission. Our simulations demonstrated the capacity of primordial transfer of "compositional genome" information (Fig. 2). This implies a primitive self-replication mechanism, simpler than the ones suggested by scenarios that invoke nucleic acid sequence templating. Extensions of GARD portray development of polymers, and the formation of metabolism-like networks. A model of the assemblies along with a finite environment has shown processes akin to life-like open-ended evolution. GARD networks help shed light on quantitative Systems Biology aspects of present-day cellular networks.

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