

Dispatches

Olfaction: It Makes a World of Scents

Mutations in odorant receptor genes predict olfactory perception of common compounds in foods and flowers. Through recombination they can generate extensive combinatorial variation in sensory ability among individuals.

Stephen Wooding

“The first condition of understanding a foreign country is to smell it.”

T.S. Eliot

Scent is an essential aspect of life and its many pleasures. From the comforting aroma of warm bread to the nauseating reek of rotten meat, olfaction reveals an invisible landscape around us, shaping both our immediate reactions and broader likes and dislikes. One of the most striking aspects of these sensations is that they can vary from person to person. It happens every day: we smell one thing, our friend smells another or nothing at all. But why? The answer is complex. Age and sex influence olfactory processes, as do some drugs, tobacco use, and other factors [1]. However, mounting evidence suggests that mutational polymorphism in odorant receptors (ORs) — a specialized family of over 350 G protein-coupled receptors mediating odorant recognition — is among the most important. Over the past five years, associations between polymorphism in genes encoding ORs and olfactory variation have been pinpointed for a variety of compounds relevant to daily life, including isovaleric acid (found in cheese; *OR11H7P*), cis-3-hexen-1-ol (a grassy smell; *OR2J3*), and androstenone (found in ham and pork, as well as human sweat; *OR7D4*) [2–4]. However, response profiles remain unknown for the vast majority of ORs, and little is known about correlations in perception across compounds, which are predicted to arise from OR genes' genomic clustering. In this issue of *Current Biology*, a pair of papers by McRae *et al.* [5] and Jaeger *et al.* [6] provide a compelling new installment in efforts to dissect these complex relationships, together detecting five new associations between OR mutations and olfactory phenotypes and describing, for the first time, their combinatorial properties.

The importance of odorant receptors in shaping olfactory sensitivity is emphasized by their role at the interface between the body and the external environment [7,8]. As in other vertebrates, human OR genes are expressed in immotile cilia of olfactory sensory neurons (OSNs), on the surface of the olfactory epithelium, where they are exposed to ambient odorants. Upon exposure, they trigger a G protein-mediated transduction cascade, depolarizing the cell and generating a neural signal. Remarkably, each individual OSN expresses just a single allele of a single OR gene, such that the sensory interface as a whole is composed of as many as ~700 OSN subtypes, each responsive to a different set of odorants. When scents are detected, signals from the OSNs are transmitted to the olfactory bulb, which integrates their output and acts as a hub for downstream processing. This organization allows the discrimination of complex odors at a high level of resolution, painting a detailed portrait of the fragrant world around us. It also strongly suggests that mutational variability in different ORs affects responses to different scents, giving each of us a unique perspective on the same scene.

The potentially direct relevance of polymorphism in ORs to sensory experiences in day-to-day life has led to a cottage industry aimed at uncovering one-to-one relationships between specific odorant compounds and allelic variants, which is making rapid progress. Among the specific associations pinpointed to date, two connect OR variation with perception of compounds common in foods (isovaleric acid in cheeses, and androstenone in ham and pork) [9]. Additional associations have been localized to OR gene clusters though not yet completely mapped, such as effects on sensitivity to aldehydes in cilantro [10]. However, many questions remain unanswered. Most pressing are questions about the overall mapping

between OR genes and odorants in the environment: fewer than ten specific interactions between odorants and OR alleles have been identified to date, yet the odorant receptor family as a whole in humans includes more than three hundred members. The genomic organization of the OR genes, which reside in clusters, raises additional questions. For instance, linkage disequilibrium among OR loci is expected to be high, resulting in correlations in individual sensitivity to some scents. However this aspect of olfaction remains poorly investigated.

In their new contribution, McRae *et al.* [5] take us another step forward in understanding OR-driven variation in olfaction and its place in day-to-day life. Their approach was straightforward. To provide a meaningful vantage point, McRae *et al.* [5] focused on a series of compounds that possess distinct scent characteristics contributing to a variety of familiar odors such as blue cheese (2-heptanone), onion (dipropyl disulfide), and apple (β -damascenone). For each of these, phenotypes were assessed for each compound using serial dilution tests, which challenged subjects to detect each odor at varying concentrations to determine the lowest concentration at which an odorant could be perceived. Genotype–phenotype association tests were then performed using ~900,000 genome-wide SNPs. McRae *et al.* [5] did not come up empty-handed. Across a battery of compounds, highly significant associations were present for four: 2-heptanone (found in blue cheese), isobutyraldehyde (malt), β -damascenone (apple), and β -ionone (floral). As predicted by olfaction's mechanistic basis, all associated variants are located near (albeit not actually in) OR genes (*OR5H14*, *OR6B2*, *OR7E14P*, and *OR4D6*, respectively). These results again underscore the broad importance of ORs in helping us navigate the rugged terrain of the olfactory world.

Jaeger *et al.*'s [6] contribution delves deeper into the functional underpinnings of variation in olfaction



Figure 1. Are freesias fragrant?

Left: A freesia flower. β -ionone, one of the odorants examined by McRae *et al.* [5], is an important constituent of freesias' bouquet [13]. Photo © 2013 Tony Hisgett. Right: Voting station for Blakeslee's freesia scent surveys at the 1935 International Flower Show in New York City [12].

and their connection to real-world experiences. Building on the discovery of McRae *et al.* [5] that variants somewhere in a 12-gene cluster on chromosome 11 explain variation in β -ionone sensitivity, Jaeger *et al.* [6] took the unusually aggressive approach of completely sequencing all 12 OR genes in subjects and testing for associations. This strategy netted a high-frequency non-synonymous (asparagine to aspartic acid) variant in *OR5A1* that strongly alters the response of the receptor to β -ionone *in vitro* and explains more than 95% of observed variance in threshold response — an extremely high value representing nearly perfect single-gene Mendelian inheritance. Remarkably, the variant also predicted subjects' preferences for foods (such as chocolate) and drinks containing added β -ionone. This finding, though intuitive, is crucially important. Because consumed foods are mixtures of a myriad molecules, genetic effects on the perception of just one might have negligible effects on overall sensory response. In the case of β -ionone, Jaeger *et al.*'s [6] results were clear cut: a single nucleotide in a single gene significantly shaped individual preferences for a variety of foods, beverages, and other products. Given the massive genetic diversity in human ORs and the range of possible odorants around us, numerous similar associations undoubtedly remain to be discovered.

An additional enlightening aspect of McRae *et al.*'s [5] findings is that the discovered associations appear to be driven by variants with a broad genomic distribution, residing in different OR gene clusters and freely recombining. As a result, individuals carry varying combinations of alleles, predicting that phenotypes also vary independently from compound to compound. This is exactly what McRae *et al.* [5] observed: among the compounds with significant observed genotype–phenotype associations, ability to perceive one compound was only weakly correlated with ability to perceive the others. However, this trend is not expected to carry across all loci. Because OR genes reside in genomic clusters, it is likely that ability to perceive many odors is in fact correlated in proportion to their genomic proximity. Deciphering the scents for which this is true, and the strength of the correlations, remains an important problem. Thus, McRae *et al.*'s [5] findings provide the most explicit evidence to date that genetic diversity in OR genes has combinatorial properties that send each of us to our own 'scent world', but many details remain to be worked out.

Beyond shedding light on both the mechanistic underpinnings of variable olfactory sensitivity and their likely relevance to preferences, both papers' [5,6] findings touch on an intriguing historical footnote.

Several of the most important findings in early studies of variation in olfaction were made by Albert Blakeslee, an American botanist and fellow of the US National Academy of Sciences, who also made key contributions in elucidating the genetic underpinnings of taste perception [11]. One of Blakeslee's favorite observations was that individuals appear to vary in ability to perceive the fragrance of freesia (*Freesia* spp.) flowers: while some people find freesia to have a lovely fragrance, others are indifferent, appearing not to perceive the smell at all (Figure 1). He even performed a public demonstration to this effect at the 1935 International Flower Show in New York City, where he surveyed more than 8000 attendees, assessing both the strength of perceived scent of potted freesias and its pleasantness using voting machines [12]. In contrast to his earlier success demonstrating a strong genetic component to taste perception, Blakeslee was unable to identify such an effect with scent, possibly as a result of its less clear-cut phenotypes. However, a hidden clue lay in freesia's floral chemistry. Unbeknownst to Blakeslee, one of the major scented constituents of freesia is β -ionone — a compound Jaeger *et al.*'s [6] results now tell us is strongly influenced by mutations in *OR5A1* [13]. Thus, 80 years on, Blakeslee appears finally to have his answer.

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Evolution: One Thread to Unite Them All

Mitochondria play important roles in the overall metabolism of eukaryotes. Traditionally, they have played a secondary role to the nucleus in the origin of eukaryotes. However, their relative positions in this crucial event for eukaryotic evolution might be reversed.

Mark van der Giezen

In true reflection of their name, eukaryotes are generally considered to be united via the presence of their genetic overlord, the nucleus. However, over the last decade or so, the mitochondrion, which is thought to be derived from an enslaved bacterium, has come to the fore to perhaps challenge the importance of the nucleus in the origin of the eukaryotes. Traditional views envisaged a gradual rise of complexity from prokaryotes, via a primitive eukaryote, to cells containing fully fledged oxygen-respiring mitochondria. Several candidates had been put forward as possible offspring of this primitive eukaryote that never gained a mitochondrion [1]. However, it has now been convincingly shown that mitochondria are actually present in all these lineages but in disguise [2–5]. As the classic eukaryogenesis view needed a eukaryotic lineage that does not require mitochondria, these unusual mitochondria were most ‘unwelcome’ discoveries but did prompt novel theories to explain the origin of eukaryotes. However, there are still some eukaryotes of uncertain

taxonomic affinity that do not seem to contain mitochondria. The oyster parasite *Mikrocytos mackini* is one such eukaryote [6] and it could have perhaps rekindled the primitive eukaryote theory. However, a new study by Burki et al. [7] reported in this issue of *Current Biology* has dashed that hope as well. Another study in this issue by James et al. [8] also discusses the evolution of unusual mitochondria.

Most eukaryotes are taxonomically well characterized and belong to one of the so-called eukaryotic supergroups [9]. However, several ‘orphan’ lineages exist that are difficult to place. Burki et al. [7] clearly demonstrate that *M. mackini*, the causative agent of the disastrous Denman Island Disease in oysters (Figure 1), is a Rhizarian. Although Rhizaria are well known because of Ernst Haeckel’s amazing drawings over a century ago, they are also the least well-studied eukaryotic supergroup due to the near impossibility of culturing them. Similarly, another group of organisms known from environmental studies but not well characterized in the laboratory are the Cryptomycota [10]. James et al. [8] show that these Cryptomycota are actually related to the microsporidia, a group of obligate intracellular



Figure 1. New threats to food security.

Fish and shellfish are increasingly important sources of animal protein. Oyster pathogens such as *Mikrocytos* sp. as described by Burki et al. [7] in this issue of *Current Biology* are becoming more important threats to food security. Shown is a *Mikrocytos* sp. infected Pacific Oyster (*Crassostrea gigas*) (left). Note the characteristic green pustules on the adductor muscle (arrow) which is normally cream coloured. A non-infected oyster is shown on the right for comparison. (Images kindly provided by Dr. Matt Longshaw, Cefas, UK.)