

Minireview

## Nose thyself: individuality in the human olfactory genome

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### Abstract

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A recent study using cell-based assays together with an olfactory psychophysical survey in humans has established a link between a genetic polymorphism in an odorant receptor and variability in perception of the smell of the steroid androstenone.

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Different people have different noses. Not just on the outside, it turns out, but inside as well. Indeed, there may be more variation in olfactory abilities among humans than in any other sense. We have all had the experience of being in a room where everyone seems to smell some odor, good or bad, that we simply do not perceive, no matter how much we sniff. Detection thresholds - the ability to detect a given odor at a particular concentration - vary over several orders of magnitude of concentration in different people. There are also many cases of selective anosmia, the inability to detect a particular odor, in the human (and mouse) population, and many of these seem to sort along genetic lines. One of the best known is a selective anosmia to isovaleric acid. This is socially important because isovaleric acid is the main noxious component of body odor. About 6% of the human population appears to have this anosmia, and they tend to self identify [1].

The high level of variation in the sense of smell may be related to the large family of genes that encode the odor receptors. Odor receptors are G-protein-coupled receptors that are expressed in specialized cilia on the tips of olfactory sensory neurons located in a layer of epithelium at the back of the nasal cavity. The odor receptor genes were first identified in 1991 by Linda Buck and Richard Axel [2], who predicted that they might comprise a very large gene family. We now know that they form the largest gene family known in mammals, numbering more than 1,000 genes [3], or more than 5% of the typical mammalian genome. Even humans, whose sense of smell is thought to be less good than that of many other animals,

have some 350 odor receptor genes, comprising more than 1% of the coding genome [4]. For comparison, the next largest family of GPCRs is that of the serotonin receptors, with just 15 members. Given all the genetic material in the odor receptor genes, there are presumably many opportunities for polymorphisms and other variations with phenotypic effects.

A recent report in *Nature* by Keller *et al.* [5] now establishes a specific connection between a particular genetic polymorphism and olfactory ability in humans - in this case, the detection of the steroids androstenone and androstadienone. This work makes use of two different and complementary techniques: functional assays in cells containing introduced receptor genes and a psychophysical survey of human subjects. The extensive genetic mapping information in human populations and the fact that humans can report their olfactory experiences makes for a powerful collaboration.

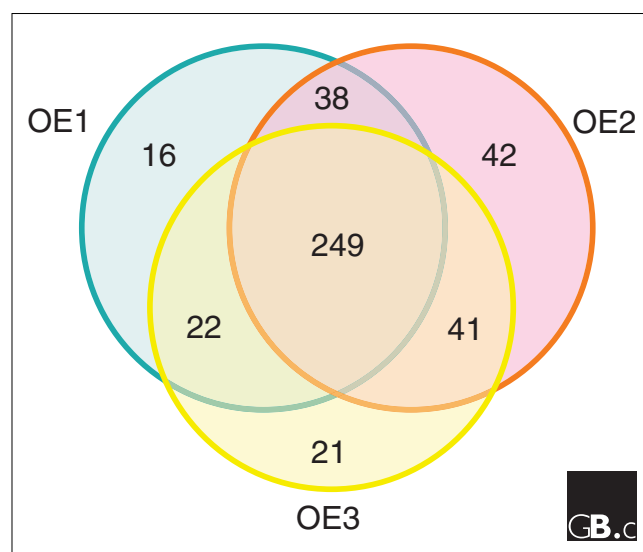
Androstenone is well established as a pheromone in pigs; it is also found in truffles and accounts for the ability of boars to sniff them out. Androstenone and the closely related steroid androstadienone have been suggested, though never proven, to act as pheromones in humans. Different people report a wide range of perceived odors from these chemicals, from unpleasant and urinous to sweaty, woody or even pleasantly floral, and nearly 30% of the human population claims not to be able to smell them at all [6,7]. These two chemicals therefore represent an interesting example of genetic variation in the human population, and one that is relatively easy to document.

There are numerous possible causes for differential olfactory abilities, including age, gender, environment, health status and experience. Between the receptor and the change in membrane voltage that signals the presence of an odor to the brain lies a complex biochemical pathway, and mutations in any of the proteins in this pathway can also result in olfactory abnormalities. An example is Kallmann syndrome [8], which is caused by mutation of a G protein that happens to be expressed in olfactory neurons as well as in other tissues. Along with hypogonadism, caused by a deficiency in pituitary hormones, patients with this condition also have anosmia.

The 350 or so genes for odor receptors would, however, seem to be the most likely targets for mutations affecting olfaction. Single-nucleotide polymorphisms (SNPs) occur at considerable frequency in the human genome and are thought to constitute the genetic basis for most of the variability in human traits. SNPs that modify a particular odor receptor could lead to significant differences in threshold sensitivity towards particular odorants or to odorant-specific olfactory deficits. The most obvious candidates for generating a functional effect are the 600 or so non-synonymous SNPs that change amino-acid residues that might be crucial to protein function of odorant receptors [9]. In addition, polymorphisms in the promoter or other regulatory regions of odor receptor genes might result in altered expression patterns that modify olfactory function [10].

There is an enormous diversity in the repertoire of functional odorant receptor genes among different people. Roughly 60% of human odor receptor genes have mutated into non-functional pseudogenes in a relatively recent genomic process; thus a substantial fraction of human odor receptors might be expected to segregate between an intact and a pseudogene form in different individuals. Menashe *et al.* [11] genotyped 51 odor receptor loci in 189 individuals of several ethnic origins to screen for SNPs that distinguish the intact and pseudogenic forms. Remarkably, of the 189 individuals, 178 functionally different genomes were found. These and earlier findings suggest that differing evolutionary pressures may have shaped the chemosensory repertoire in different human populations. Additional variation in the population may come from differences in gene expression. Experiments with custom microarrays specialized for detecting odor receptor genes have found that the expressed receptor repertoires of any pair of individuals differ by at least 14% [12], suggesting that polymorphisms exist not only in coding regions but also in promoter and other regulatory regions (Figure 1).

Despite many anecdotal reports and numerous population screens that indicate heritable olfactory traits, a definitive connection has never been made between single-gene mutations and olfactory abilities. Now combined work from two laboratories [5], those of Leslie Voshall at Rockefeller University, New York, and Hiro Matsunami at



**Figure 1**

The diversity of odor receptor gene expression in humans. The numbers refer to the number of genes whose expression was detected (at  $P < 0.05$ ) in one or more of three samples of olfactory epithelium [12]. As can be seen, there is a substantial difference in the odor gene repertoire expressed in the three samples.

Duke University School of Medicine in Durham, North Carolina, provides this evidence. This study combined a cell-based assay technique to identify ligands for human odor receptors with an olfactory psychophysical study of a diverse population of human volunteers. The authors cloned a panel of 335 putative human odor receptors and expressed them in Hana3A cells, which were then screened for androstenedione-mediated stimulation. A receptor called OR7D4 gave the strongest response, suggesting that this is the high-affinity androstenedione receptor in humans. Polymorphisms in OR7D4 were then identified in 391 individuals and two non-synonymous substitutions that occurred at the highest frequency were identified. These substitutions gave two receptor variants of OR7D4, called RT and WM, which differed in one amino acid. The authors investigated the ligand specificity of the two variants in the cell-based assay and found that the RT form responded to androstadienone whereas the WM form did not.

To correlate this variation in OR7D4 with variation in the actual perception of androstenedione and androstadienone, olfactory psychophysical studies were carried out with 391 human volunteers. Subjects were asked to rate the perceived intensity, valence (the emotional reaction associated with a stimulus) and detection threshold of androstenedione and androstadienone, compared with control odors. Statistical analysis showed that the OR7D4 genotype had a significant effect on the perception of androstenedione odor intensity. Heterozygous RT/WM individuals as a group had higher detection thresholds than RT/RT individuals, that is, they

were less sensitive to the odor. Variation in OR7D4 genotype also affected the perception of odor quality. The RT/WM group rated the smell of both androstenone and androstadienone as less unpleasant than did the RT/RT group. In this study, non-parametric regression analysis showed that OR7D4 genotype explained 19% and 39% of the variance in the valence and intensity rating, respectively, of the steroid odors. Thus, although there must be some additional receptors or non-genetic effects involved, OR7D4 genotype was clearly identified as a significant heritable factor influencing the perception of androstenone and androstadienone. This study provides the first link between an identified genetic polymorphism in an odor receptor gene and altered perception of an odor compound.

GPCRs are estimated to account for some 50% of the targets for drugs in current use. As the odor receptors are GPCRs, the demonstration of polymorphic variation in their function by Keller *et al.* [5] provides strong support for the likelihood that polymorphic variation in other GPCRs has important effects on drug efficacy and side effects. Non-synonymous SNPs in GPCRs can clearly have large effects on function, and further investigation of the odor receptors is likely to unearth more information on variation and its effect on function in this important receptor class.

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