Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 884–888, January 1996
Genetics

The chromosomal distribution of mouse odorant receptor genes

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Communicated by Frederick W. Alt, Children's Hospital, Boston, MA, October 23, 1995

ABSTRACT **Odorant receptors (ORs) on nasal olfactory sensory neurons are encoded by a large multigene family. Each member of the family is expressed in a small percentage of neurons that are confined to one of several spatial zones in the nose but are randomly distributed throughout that zone. This pattern of expression suggests that when the sensory neuron selects which OR gene to express it may be confined to a particular zonal gene set of several hundred OR genes but select from among the members of that set via a stochastic mechanism. Both locus-dependent and locus-independent models of OR gene choice have been proposed. To investigate the feasibility of these models, we determined the chromosomal locations of 21 OR genes expressed in four different spatial zones. We found that OR genes are clustered within multiple loci that are broadly distributed in the genome. These loci lie within paralogous chromosomal regions that appear to have arisen by duplications of large chromosomal domains followed by extensive gene duplication and divergence. Our studies show that OR genes expressed in the same zone map to numerous loci; moreover, a single locus can contain genes expressed in different zones. These findings raise the possibility that OR gene choice may be locus-independent or involve consecutive stochastic choices.**

Mammals can discriminate a myriad of different odors. This ability depends on a multigene family that encodes 500–1000 different odorant receptors (ORs) (1–3). ORs are expressed by nasal olfactory sensory neurons; each neuron may express only one allele of a single OR gene (4–9). In the nose, different sets of ORs are expressed in distinct spatial zones (5, 7, 10). Neurons that express the same OR gene are located in the same zone; however, in that zone, they are randomly interspersed with neurons expressing other ORs. This distribution suggests that, when the cell chooses an OR gene for expression, it may be restricted to a specific zonal gene set, but it may select from that set by a stochastic mechanism.

Proposed models of OR gene choice fall into two classes: locus-dependent and locus-independent (5–7). Locus-dependent models posit that OR genes are clustered in the genome, perhaps with members of different zonal gene sets clustered at distinct loci. In such models, a cell might select a single OR gene in a cluster for expression by gene rearrangement (11, 12) to a cluster-specific expression site or by juxtaposition, via DNA looping (13, 14), of a cluster-specific enhancer with the promoter of a single OR gene. In contrast, locus-independent models do not require that OR genes be clustered. For example, gene conversion events might place a copy of a single OR gene at a unique, unlinked expression site (15). Alternatively, stochastic activation of a single OR gene might involve a complex of transcriptional regulatory proteins present at a limiting concentration during a brief developmental period.

To assess the feasibility of these models, we determined the expression zones, sequences, and chromosomal locations of a number of mouse OR genes. Our studies mapped OR genes to 11 different loci on 7 chromosomes. The chromosomal distributions of OR genes expressed in different zones, sequence relationships among OR genes found at various loci, and the chromosomal locations of OR gene loci have implications for the mechanisms underlying OR gene regulation and for the evolution and possible functions of multiple OR gene loci.§¶

MATERIALS AND METHODS

Cloning and Analysis of Mouse OR Genes. Coding region segments of mouse OR genes were isolated and cloned as described and subjected to DNA sequence analysis (5, 16). The sequence comparisons and the dendrogram were generated using the PILEUP computer program of the sequence analysis software package from the Genetics Computer Group (GCG package).

***In Situ* Hybridization.** *In situ* hybridizations were performed as recently described (5).

Genetic Crosses. Two sets of multilocus genetic crosses were analyzed for inheritance of OR related sequences: (NFS/N or C58/J × *Mus mus musculus*) × *M. m. musculus* (17) and (NFS/N × *Mus spretus*) × *M. spretus* or C58/J (18). DNAs from the progeny of these crosses have been typed for ≈800 markers, which map to all 19 autosomes and the X chromosome (17, 18). Hybridization probes and assay methods have been described for the following markers: *Sag, C4bp, Mtap2, Sfpi1, Abl, Grp78, Gad1, Cyct, Mtap1, Cyp2a, Apoe, Gpi1, Tyr, Zp2, Fli1, Cbl2, Pfp, Tra1, Ifg, Gli, D10H12S53E, Evi2, Gabra1, Mgat1, Il3, Ahd4, Shbg*, and *Tcrg* (19–28). Additional markers not previously described include *Plf* (proliferin), which was typed as a *Bam*HI restriction fragment length polymorphism (RFLP) in the *M. m. musculus* cross and an *Apa* I RFLP in the *M. spretus* cross using as probe a 780-bp *Pst* I fragment from the clone PLF-1 (American Type Culture Collection) (29); *Ugt1a1* (dioxin inducible glucuronyltransferase, member 1), which was typed after digestion with *Bam*HI in the *M. m. musculus* crosses and *Hin*dIII in the *M. spretus* crosses using a mouse probe obtained from D. Peterson (University of Cincinnati) (30); and *Cd3g* (Cd3g antigen, γ polypeptide), which was typed after *Hin*dIII digestion in both crosses using as probe the 750-bp insert of clone pB10 AT3 γ-1 obtained from G. Krissansen (University of Auckland, New Zealand) (31). Data were stored and analyzed using the program LOCUS designed by C. E. Bockler (National Institutes of Allergy and Infectious Diseases, Bethesda) Percentage recombination and standard errors between specific loci were calculated from the number of recombinants according to Green (32). Loci were ordered by minimizing the number of recombinants.

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Abbreviations: OR, odorant receptor; AASI, amino acid sequence identity; NSI, nucleotide sequence identity; RFLP, restriction fragment length polymorphism; cM, centimorgan(s); Chr, chromosome.

§The mapping data reported in this paper have been deposited in the Mouse DataBase (accession nos. MGD-CREX-285–298).

¶The sequences reported in this paper have been deposited in the GenBank data base (accession nos. U28767–28784).

RESULTS

Preliminary Studies. We previously cloned coding region segments of a number of mouse OR genes (5). Most of these genes hybridized to multiple bands on Southern blots of genomic DNA, indicating that the OR multigene family can be divided into subfamilies of highly related genes (16). *In situ* hybridization experiments were then used to determine the patterns of expression of genes belonging to different subfamilies. These studies identified three distinct spatial zones that express different sets of OR genes and suggested that there could be a fourth zone (5). For the chromosome mapping studies, it was critical that the zones of expression of individual OR genes be precisely defined. To do this, we compared the expression patterns of genes assigned to the same zone on adjacent tissue sections by *in situ* hybridization.

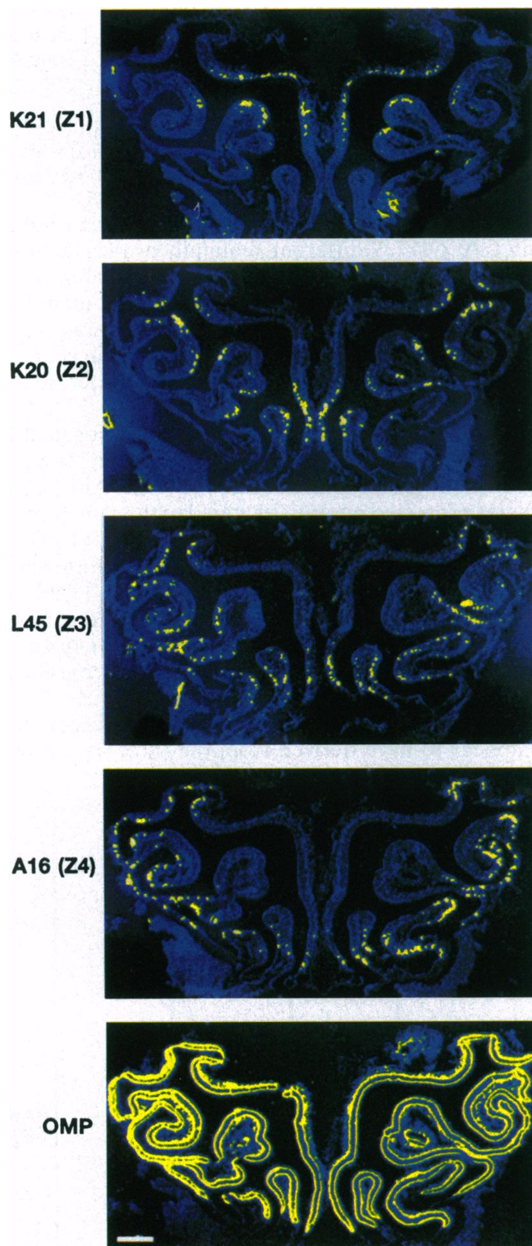

FIG. 1. Coronal sections of mouse nose were hybridized with radiolabeled OR gene probes (K21, K20, L45, and A16) or an OMP probe. The OMP probe hybridizes to all olfactory neurons, whereas each OR probe hybridizes to dispersed neurons within only one of four spatial zones (Z1–Z4). Images were processed with Adobe Photoshop. (Bar = 400 μm.)

These experiments demonstrated that there are four distinct spatial zones (zones 1–4) of OR gene expression in the nasal olfactory epithelium (Fig. 1). Of 30 OR genes tested, 25 hybridized to neurons in one of these zones, 4 hybridized to more than one zone, and 1 hybridized to parts of two zones. Thus, individual OR genes, as well as members of the same subfamily, are usually, but not always, expressed in one of four zones. For the mapping studies, we selected 21 of the genes that are expressed in only one zone.

The Chromosomal Organization of Mouse OR Genes. The chromosomal locations of OR genes were determined by Southern blot analyses of DNAs from the progeny of two sets of multilocus crosses (see *Materials and Methods*). Most of the probes identified a number of different restriction fragments in parental mouse DNAs. Most of these fragments are expected to represent different genes that belong to the same OR subfamily (5, 16). Since progeny mouse DNAs were screened by using restriction enzymes that produced the greatest number of polymorphic fragments, the 21 OR probes could be used to follow the inheritance of 39 fragments (a maximum of 39 distinct genes) (Table 1). The map location of each fragment was established by comparing its inheritance to the inheritance of >800 markers previously mapped in the mouse crosses used (17, 18).

Table 1. RFLPs used to map OR genes to individual loci

Locus	OR	Zone	Enzyme	NFS/N	*M. spretus*
Olfr1	M5	Z1	*Sst* I	4.3*	
			Pst I		11.5/4.8
Olfr3	K10	Z1	*Hin*dIII	12.5	9.0
Olfr4	A16	Z4	*Pst* I	8.9/8.6	10.1/7.6
	K17	Z1	*Apa* I	15.5*	
			*Hin*dIII	5.2	4.6
	K20	Z2	*Eco*RI	11.5/5.5/4.3*	
			*Bam*HI	10.0/7.2/4.2 and 3.8	10.8/1.7
Olfr5	M41	Z4	*Bam*HI	>28/8.6	19.4/3.3
			Xba I	16.0/5.6*	
Olfr6	M50	Z4	*Bst*EII	26*	
Olfr7	K4	Z2	*Pst* I	2.9*	
			Pvu II		16.4/4.0/1.7
	K18	Z1	*Eco*RI	9.2	14.5
	K21	Z1	*Sac* I	23.1	
	M3	Z1	*Pst* I	11.8	5.4
	M15	Z1	*Eco*RI	8.8	4.4
	M30	Z1	*Eco*RI	22.8/4.0*	
			Pvu II	12.8/7.8	>28/8.4/3.9
	M31	Z1	*Sac* I	11.5*	
	M71	Z1	*Bam*HI	17.5/13.0	13.3
	M93	Z1	*Hin*dIII	8.4/7.6	4.6
Olfr8	M64	Z3	*Xba* I	12.4/8.2/3.8*	
			*Hin*dIII	17.2/9.8	14.5
Olfr9	M25	Z1	*Xba* I	12.2/5.0*	
			*Hin*dIII	5.8	7.5
Olfr10	L45	Z3	*Sst* I	1.9*	
			Bgl II	5.5	9.4/7.5/4.7
Olfr11	M49	Z2	*Hin*dIII	8.2	3.2
			Pvu II	4.0*	
Olfr12	M76	Z3	*Sst* I	19.0*	
			*Eco*RI	>28	7.8/0.7

Approximate sizes (in kb) of restriction fragments identified with each OR probe in Southern blot analyses are given for the parental mice of the two genetic crosses—the wild mouse species *M. spretus* and the inbred strain NFS/N. Only those fragments that were informative and followed in the crosses are shown. Spatial zones of expression of the different OR genes are indicated.

*Fragments were followed in the *M. m. musculus* crosses; all other fragments were followed in the *M. spretus* crosses.

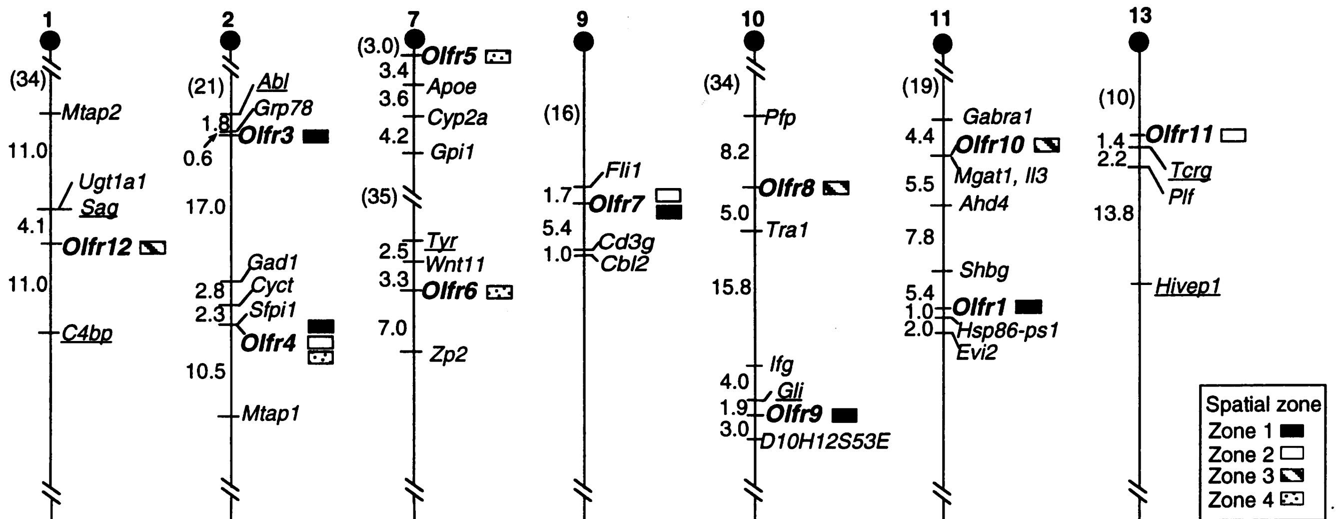

FIG. 2. Chromosomal locations of OR gene loci. Loci typed in this work are shown on the right of each chromosome, and distances (in cM) between OR gene loci and other loci are indicated on the left. Approximate distance between the centromere and the most proximal marker used is given in parentheses for each chromosome. Expression zones of OR genes mapped to each locus are indicated by patterned boxes (see key).

Our experiments revealed that OR genes are widely distributed in the genome; the restriction fragments analyzed mapped to 11 distinct sites on 7 different chromosomes: Chromosome (Chr) 1, 2, 7, 9, 10, 11, and 13. Four of these chromosomes (Chr 2, 7, 10, and 11) contain two OR loci that are separated by at least 15 centimorgans (cM). We have designated the OR gene loci *Olfr1* and *Olfr3–Olfr12* (Fig. 2; Table 1). Another mouse OR gene locus, *Olfr2*, has previously been identified on Chr 9, ≈5 cM from the centromere (33). The locations of 3 of 4 OR gene loci previously seen by chromosomal *in situ* hybridizations are not known (6). Given that the probes we used identify only 5–10% of mouse OR genes, it seems likely that there will ultimately prove to be more than 12 OR gene loci.

There are clearly clusters of OR genes at individual loci. In each of 12 cases in which we mapped multiple fragments with a single probe, all of the fragments mapped to the same chromosomal locus (Table 1). Thus, OR genes that belong to the same subfamily (i.e., are highly related in sequence) are located at the same site. However, a single locus (e.g., *Olfr4* and *Olfr7*) can also contain members of different subfamilies (Table 1). At *Olfr7*, 9 different subfamily probes identified 15 fragments (≈15 OR genes); at *Olfr4*, 3 subfamily probes identified 7 fragments. No recombinants were identified between the fragments mapping within these clusters in up to 106 mice for *Olfr4* and 199 mice for *Olfr7*, indicating that at the 95% confidence level the OR genes in these clusters are within 2.8 and 1.5 cM, respectively.

Importantly, consistent with previous chromosomal *in situ* hybridization studies (6), OR genes that are expressed in the same nasal zone are not clustered at one locus. Although 8 OR subfamilies expressed in zone 1 mapped to the same site on Chr 9, other zone 1 genes mapped to four other loci (Table 1; Fig. 2). In addition, each of the three probes tested for each of the other zones identified genes at a different locus (Table 1; Fig. 2). Our results also show that a single locus can contain OR genes expressed in different zones. For instance, *Olfr4* contains genes expressed in zones 1, 2, and 4 while *Olfr7* contains genes expressed in zones 1 and 2.

In mouse and human, large domains of different chromosomes appear to have derived from the same ancestral chro-

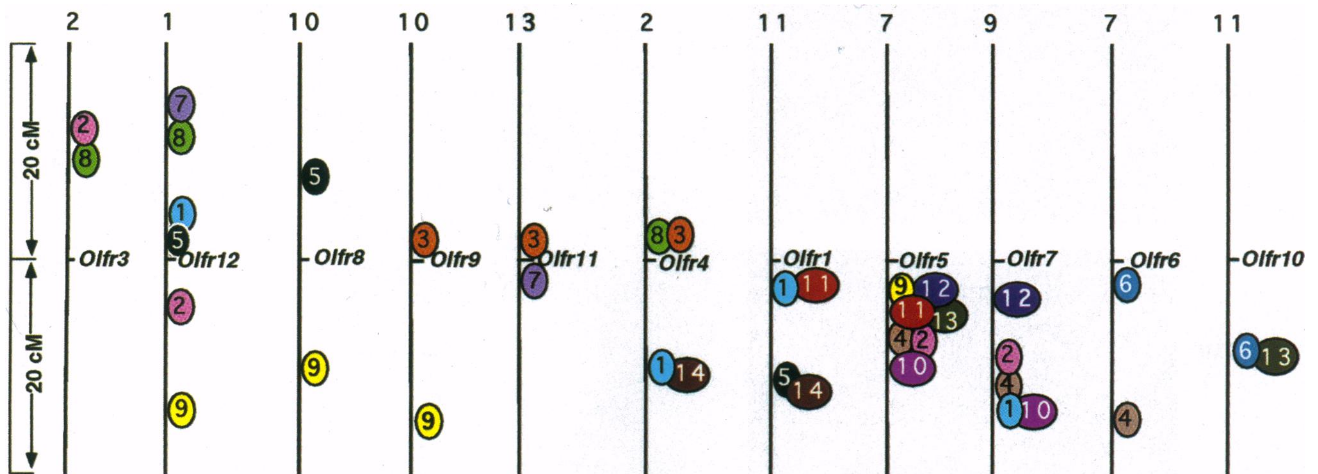

FIG. 3. OR gene loci are located in paralogous regions of the genome. Shown here are approximate locations of paralogs of 14 different gene families (see below) that map within 20 cM of two or more OR gene loci. Map positions were obtained from ref. 35. Chromosomes are oriented to clarify relationships among paralogous regions. Circled numbers refer to the following gene families: 1, acetylcholine receptor subunit genes; 2, octamer binding transcription factor genes; 3, Gli family of transcription factor genes; 4, cytochrome P450 genes; 5, collagen genes; 6, hemoglobin genes; 7, inhibin genes; 8, paired box genes; 9, peptidase genes; 10, phosphate isomerase genes; 11, ATPase polypeptide genes; 12, serine protease genes; 13, creatine kinase genes; 14, homeobox genes.

mosome by duplication (34). The different domains contain homologous members (paralogs) of the same gene families. The OR gene loci we identified lie within such paralogous regions (Fig. 3). For example, paralogous members of two gene families (*Acr* and *Otf*) are linked to 4 of the OR gene loci, while members of other families are linked to 2 or more OR gene loci (Fig. 3). Taken together, these linkages establish evolutionary relationships among all 11 of the OR gene loci identified and suggest that multiple OR gene loci have arisen, during evolution, via duplications of large chromosomal regions in which linkage relationships between OR genes and other gene families have been maintained. The finding that members of the same OR subfamily map to the same locus further suggests that considerable duplication and divergence subsequently occurred within individual loci.

Sequence Relationships Among Linked and Unlinked OR Genes. Structurally related ORs may recognize the same odorants or odorants that share certain structural features. The identification of multiple OR gene loci and the mapping of members of the same OR subfamily to the same locus raised the possibility that individual loci might be functionally distinct. To assess this possibility, we sequenced the 21 OR gene segments used in the mapping experiments and analyzed the extent to which OR genes mapped to individual loci are related. The regions compared cover ≈40% of the coding region and include highly variable regions proposed to be involved in odorant binding (4, 16).

The 21 OR sequences show an average nucleotide sequence identity (NSI) of 49% (range, 40–71%) and an average amino acid sequence identity (AASI) of 37% (range, 25–64%). ORs showing >57% NSI invariably mapped to the same locus (Fig. 4). For example, M30 and M31 (58% NSI; 47% AASI) both mapped to *Olfr7*, and A16 and K20 (66% NSI; 58% AASI) both mapped to *Olfr4*. However, a single locus can also encode more structurally diverse ORs: M30 and K4 (41% NSI; 26% AASI) and M31 and K18 (43% NSI; 31% AASI) all mapped to the same locus on Chr 9. This suggests that, if a particular odorant is detected only by a single subfamily, or a group of highly related subfamilies, the ability to perceive that odorant might rely on a single OR gene locus. However, that locus may encode ORs capable of recognizing a variety of odorants.

Are different spatial zones specialized to detect different structural classes of odorants? If so, structurally related ORs might be expressed in the same zone. This is generally true for ORs that belong to the same subfamily (5, 7). However, among the sequences examined, AASI among ORs expressed in the same zone averaged 40%, 35%, 31%, and 42% for zones 1–4, respectively, similar to the average AASI among all of the sequences examined (37%). Moreover, some ORs were most similar to an OR expressed in a different zone (e.g., K4 and A16). This suggests that an odorant that is recognized by members of a single subfamily may be detected by neurons in only one spatial zone while odorants recognized by members of different, but related, subfamilies may be detected by neurons in more than one zone.

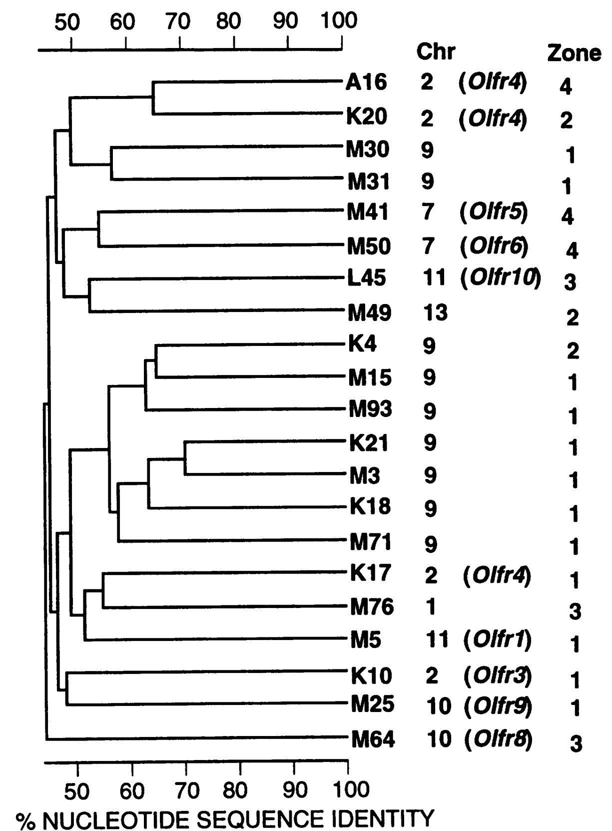

FIG. 4. Nucleotide sequence relationships, chromosomal locations, and zones of expression of OR genes mapped. Dendrogram was generated by using coding region segments of each gene. Percentage nucleotide sequence identity between connected pairs of genes is indicated. Chromosomal location (Chr) of each gene and spatial zone in which it is expressed (Zone) are indicated on the right. Locus assignments are shown in those cases in which there are two OR gene loci on a chromosome.

DISCUSSION

In the studies reported here, we defined the expression patterns of a number of mouse OR genes, analyzed sequence relationships among these genes, and determined their chromosomal locations. Our experiments show that OR genes are widely distributed in the genome: we identified 11 distinct OR gene loci on 7 different chromosomes. Multiple genes were found to map to 8 of the loci, indicating that many, if not all, of the loci contain clusters of OR genes.

Our experiments suggest that mouse OR genes are organized into paralogous clusters in the genome. Each OR gene locus appears to be related to other OR gene loci by linkage to members of one or more gene families. Together, these linkage relationships suggest that all of the OR gene loci identified are evolutionarily related. It appears that multiple OR gene loci have arisen during evolution via duplications of large chromosomal regions rather than by the retrotransposition and duplication of individual OR genes. The diversity of OR genes mapped to one OR gene locus (*Olfr7*) further suggests that a primordial OR gene cluster may have been composed of a diverse set of OR genes. Sequence analyses of OR genes on human Chr 17 also support this possibility (36).

The wide distribution of OR genes in the genome is likely to protect against catastrophic losses of OR genes by unequal crossing over or gene slippage that might occur if OR genes were clustered at a single locus (37). The existence of multiple OR gene loci might also promote the development and maintenance of structural, and therefore functional, diversity in the OR family. For example, within individual OR gene clusters, gene conversion mechanisms may help to diversify OR genes via the intermixing of short sequence motifs (16). On the other hand, gene conversion mechanisms could also homogenize clustered OR genes (37, 38). The segregation of OR genes into multiple loci would prevent such homogenization from occurring across the entire family.

Sequence analyses of the OR genes that we mapped show that members of the same OR subfamily, as well as highly related subfamilies, map to the same chromosomal locus. Thus, if the ability to recognize an odorant depends on a particular OR subfamily or a group of related subfamilies, detection of that odorant may rest upon the integrity of a single OR gene locus. This may be relevant in specific anosmias, in which an

individual exhibits a deficit in the ability to detect a specific odorant (39). Specific anosmia could conceivably result from mutation of a single OR gene or loss of a group of related OR genes at a single locus by unequal crossing over or gene conversion.

OR genes that belong to the same subfamily are generally expressed in the same spatial zone in the nose (5, 7). However, we found no further correlation between the relatedness of OR genes and their patterns of expression. OR genes that belong to different, but related, subfamilies can be expressed in different zones. Further studies are required to elucidate the relationship between OR homology and ligand specificity; however, this finding suggests the possibility that zones may, to some extent, be functionally redundant.

Recent studies suggest that each olfactory neuron selects for expression only one allele of a single, zonally appropriate OR gene from among ≈1000 candidates (4–7). A number of possible mechanisms of OR gene choice have been proposed. Some are locus-dependent mechanisms that would require colocalization of OR genes in the genome (5–7). For example, by analogy with some other gene families (11–14), if OR genes expressed in the same zone were all clustered at one locus, a single gene in the cluster might be selected for expression by a DNA looping mechanism involving a single zone-specific enhancer associated with the locus or by movement of the gene by gene rearrangement into a unique expression site associated with the locus.

Our studies rule out locus-dependent models of OR gene regulation that would require the colocalization of all OR genes or of OR genes expressed in the same zone. Not only are there more than 11 different OR gene loci, but a single locus can contain genes expressed in different zones. A locus-dependent mechanism could conceivably operate at each OR locus. However, since gene expression within a zone appears to be random, this arrangement might require that the cell make two consecutive stochastic choices, first a locus choice and then a receptor choice of a zonally appropriate gene from the chosen locus.

The wide distribution of OR genes in the genome suggests the possibility that OR genes might be regulated by locus-independent mechanisms. For example, by analogy with trypanosome VSG genes (15), a single OR gene might be copied into an unlinked expression site via gene conversion. Alternatively, a combination of transcriptional regulators, present at low concentration, might initiate transcription of only a single OR gene during a brief critical period in the cell's development (5).

We would like to thank Roger Brent, Nobuki Nakanishi, and members of the laboratory for critically reading the manuscript. This work was supported by grants from the National Institutes of Health [1-R01-DC01662-01 and PO1 DC000347-10 (L.B.B.), 5-F32-DC00188-01 (S.L.S.), and 2-T32GM07753-14 (K.J.R.)], the W. M. Keck Foundation, the McKnight Endowment Fund for Neuroscience (L.B.B.), the Alfred P. Sloan Foundation (L.B.B.), and the John Merck Fund (L.B.B.). L.B.B. is a Howard Hughes Medical Institute investigator.

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