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Review

# Genomic snowflakes: how the uniqueness of DNA folding allows us to smell the chemical universe

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Olfactory receptor (OR) gene choice, the stable expression of one out of >2000 OR alleles by olfactory sensory neurons, constitutes a gene regulatory process that is driven by three-dimensional nuclear architecture. Moreover, the differentiation-dependent process that culminates in monogenic and monoallelic OR transcription represents a powerful demonstration of the rich mechanistic insight that single-cell genomics and multiomics can provide toward the understanding of a biological process. At this review, we describe the latest advances in the understanding of OR gene regulation and highlight important standing questions regarding the emerging specificity of ultra-long-range genomic interaction and the contribution of transcription and noncoding RNAs.

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## Introduction

Olfaction, the detection and identification of volatile chemicals, is a primal sense essential for animal survival, reproduction, and social interactions. As such, it is subjected to immense evolutionary pressure toward combining the widest sensory spectrum with the highest possible sensitivity and specificity. To expand their sensory window, mammals dedicate up to 5% of their gene-coding capacity to olfactory receptor (OR) genes, 7-transmembrane G protein–coupled receptors for volatile chemicals [1]. There are ~1100 functional OR genes in the mouse genome, organized in genomic clusters distributed across most chromosomes. To achieve sensitivity and specificity in odor recognition, mice deploy the 'one receptor per neuron' and 'one receptor per glomerulus' rules [2]. The former is manifested by the strictly monogenic and monoallelic OR transcription in each mature olfactory sensory neuron (OSN) [3], while the latter by the OR-instructed convergence of all the OSN axons with the same OR protein to the same glomerulus of the olfactory bulb [4,5]. These two principles assure that each OSN is only stimulated by volatile chemicals that activate the OR protein they express, transforming the chemical structure of an odorant into odor-specific patterns of glomerular activation in the brain. Thus, because the OR protein identity determines both odorant detection and axon guidance specificity, OR expression in mature OSNs must be strictly singular.

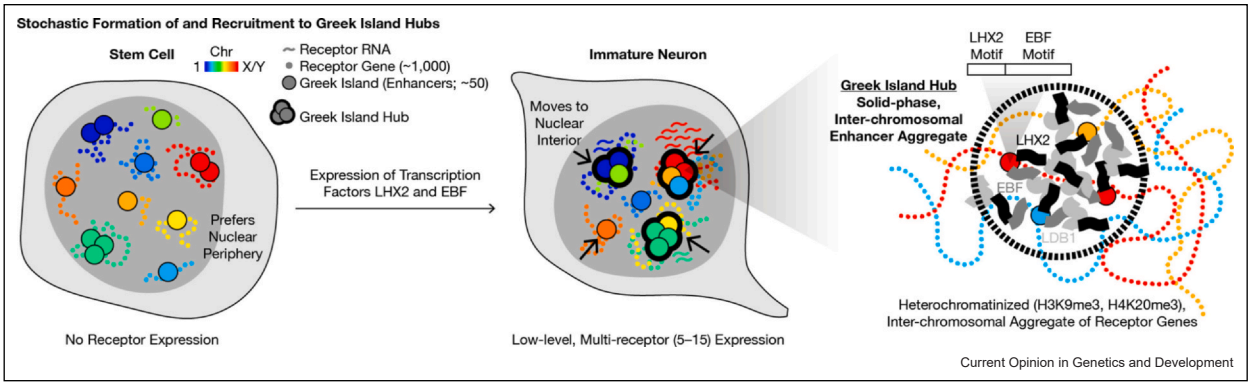
While singular OR expression is essential for vertebrate olfaction, the rapid evolutionary expansion of the OR gene family from ~70 OR genes in fish to >1000 OR genes in amphibia and most terrestrial vertebrates [6] poses extreme regulatory challenges. If combinatorial control of gene expression was solely responsible for the singularity and diversity of OR expression, then each newly evolved OR must be controlled by distinct *cis*-regulatory elements recognized by unique combinations of transcription factors tailored to each OSN subtype [7]. However, both the >1000 OR promoters and >63 intergenic OR enhancers, the Greek Islands [8–10] share numerous common transcription factor–binding motifs recognized predominantly by Lin-11, Isl-1, Mec-3-homeobox transcription factor Lhx2 and members of the Ebf family (Ebf1-4) [11–14]. Moreover, single-cell RNA-seq experiments have convincingly shown that the differentiating OSN progenitors do not have the regulatory precision to activate only a single OR, rather they co-transcribe random combinations of 5–15 different OR alleles before switching to a strictly singular OR transcription [15–19]. Consistent with this, single-cell RNA-seq experiments have yet to identify unique combinations of transcription factors correlating with specific OR identities. Thus, while a deterministic process is restricting the OR repertoire that each OSN can choose

from [18], additional nondeterministic mechanisms refine this choice and assure that every mature OSN will stably express only one OR allele for the life of the OSN.

## Greek Island Hubs: a common transcriptional complex for ~1000 competing olfactory receptor genes

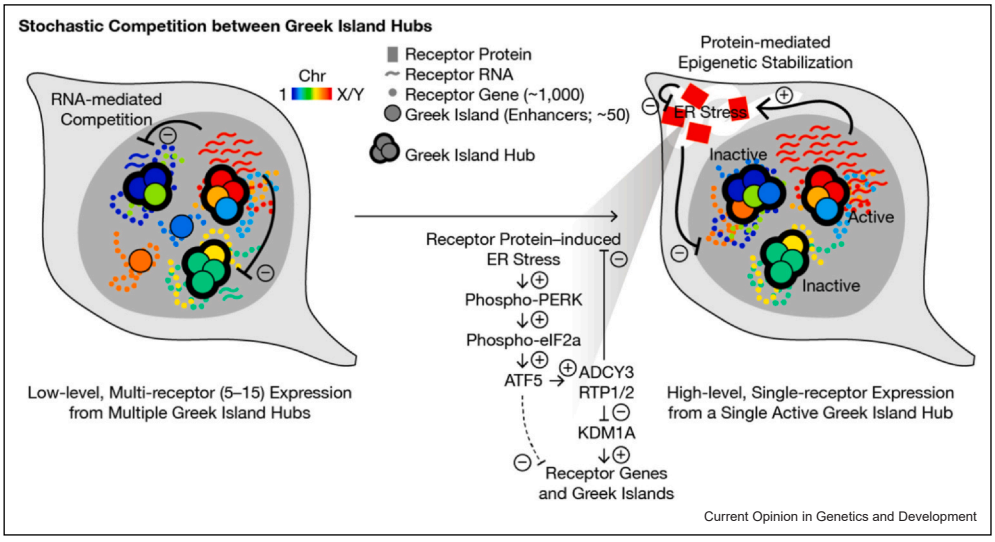
Transcription factors Lhx2 and Ebf1-4, together with adaptor protein Ldb1, constitute a tripartite protein complex that is expressed in most OSNs and regulates transcription of most OR genes [20,21]. These three proteins bind on the Greek Islands at the early stages of OSN differentiation [9,22], instructing the assembly of specific and frequent long-range *cis* and *trans* interactions between them [8,10,22–24], regardless of the identity of the chosen OR allele [22] (Figure 1). Downregulation of lamin B receptor (Lbr), which occurs simultaneous with the onset of Lhx2/Ebf/Ldb1 expression, allows the detachment of OR clusters and Greek Islands from the nuclear lamina, and their interchromosomal convergence toward the interior of the nucleus [25,26] (Figure 1). A recent preprint suggests that the 'composite' Lhx2/Ebf-binding motif that is highly enriched in the Greek Islands [9,10] promotes high-affinity interactions and solid-phase transitions that provide specificity and stability in Greek Island genomic contacts [27] (Figure 1). These interactions have regulatory importance because *in situ* HiC experiments in OSN populations revealed specific and robust *cis* and *trans* interactions between Greek Islands and the transcriptionally active OR allele [22,28] (Figure 1). These OSN-specific genomic contacts are abolished upon conditional deletion of Lhx2 and Ldb1 in mature OSNs, resulting in strong and widespread downregulation of OR transcription [22]. Taken together, these observations proposed that OR enhancers form a multi-enhancer hub, the Greek Island Hub (GIH), that acts as the 'executor' of singular OR gene expression [22]. Indeed, diploid chromosome conformation capture [29], a high-resolution, single-cell Hi-C method that distinguishes maternal from paternal haplotypes at ~20 Kb resolution, confirmed the interchromosomal convergence of Greek Islands into distinct multi-enhancer hubs [23] (Figure 1). Subsequent single-cell Hi-C experiments in fluorescence-activated cell sorting OSNs that express green fluorescent protein-tagged OR alleles, showed that GIHs are in close spatial proximity with the active OR allele in the vast majority of individual OSNs analyzed [24] (Figure 2). This observation was further expanded to many additional OR alleles by linking mRNA to chromatin architecture [10], a high-sensitivity single-cell Hi-C/RNA-seq multiomic technology [10,30], that provides information for the transcriptionally active OR without the use of genetically modified mice. However, while single-cell Hi-C and DNA fluorescence in situ hybridization experiments and their RNA co-assays support the role of the GIH in OR transcription, they also revealed that transcriptional singularity cannot be explained exclusively by the multichromosomal convergence of OR enhancers into a single hub. This is because each one of these single-cell experiments reveals the existence of multiple GIHs in each OSN, with similar enhancer constitution and contact specificity between active and inactive hubs [10,23,24] (Figure 2). In fact, the GIH with the highest number of enhancers is rarely the one that is transcriptionally engaged in each OSN [10], excluding the possibility that the most complex hub is the one that defines the chosen OR. That said, transcriptionally active and inactive GIHs are not identical; both single-cell Hi-C and its RNA co-assay detect highly specific genomic contacts between the resident OR enhancers and the chosen OR, whereas in transcriptionally inactive hubs, Greek Island–OR contacts have significantly lower genomic specificity [10,24]. Why only one GIH can associate specifically with a single OR

**Figure 1**




Stochastic formation of GIHs during neuronal differentiation. At the stem cells of the olfactory epithelium, OR gene clusters are located at the nuclear periphery due to interactions with Lbr. At the onset of neuronal differentiation, Lbr is downregulated, releasing the OR clusters, which converge toward the interior of the cell. Lhx2/Ebf/Ldb1 binding on the composite motif of the Greek Islands enables highly specific homotypic interactions between Greek Islands and assembly of multiple interchromosomal GIHs that remain attached due to composite motif-induced solid-phase transitions.

**Figure 2**




Transcriptional competition between GIHs and protein-elicited feedback mediate stable transition to transcriptional singularity. Lowly transcribed OR alleles are recruited to GIHs, resulting in their transcriptional upregulation. The OR that will first reach a transcriptional threshold will prevail while OR alleles transcribed in competing hubs will be 'dropped', resulting in their transcriptional silencing. If the prevailing OR produces intact OR protein, ER stress-induced downregulation of lysine demethylase Kdm1a will assure that no other OR allele can be de-silenced, preserving the singular choice for the life of the neuron. ER, endoplasmic reticulum.

allele and what is the purpose of having additional hubs if only one is utilized?

## An RNA-mediated transition from polygenic to singular olfactory receptor transcription

High-sensitivity single-cell Hi-C/RNA co-assay, which can detect co-transcribed OR alleles in OSN progenitors, revealed that each one of the co-transcribed OR alleles interact with one of the additional GIHs, which form early during OSN differentiation [10]. Moreover, Greek Islands from the hub associated with the most highly transcribed OR make significantly more specific contacts with that OR, compared with the hub that contains the second most highly transcribed OR [10]. This immediately suggests that the extra GIHs detected in mature OSNs are remnants from their engagement in polygenic OR transcription in OSN progenitors [24] (Figure 2). Moreover, differences in Greek Island–OR genomic contacts between the hubs with the highest and second highest transcriptional output proposed that transcription rates *per se* may determine which will be the prevailing hub during transition to singularity [10]. Indeed, artificial induction of robust OR transcription of OR Olfr17 at the polygenic stage of OR transcription results in preferential recruitment to a GIH in most OSN progenitors and eventual singular choice of this OR allele in most mature OSNs [18,24]. In fact, if Olfr17 is induced in an OSN that has already chosen a different OR, there is a transient stage whereby both OR alleles are associated with two different hubs, followed by release of the originally chosen OR from its cognate hub, and singular transcription of the Olfr17 allele [24]. These observations propose that differentiating OSNs can form numerous transcriptionally engaged GIHs, but they cannot support strong OR transcription from multiple hubs [10,24]. As the transcriptional output from each GIH increases with differentiation, the number of transcriptionally engaged hubs decreases, resulting, eventually, in strong OR transcription from only one hub.

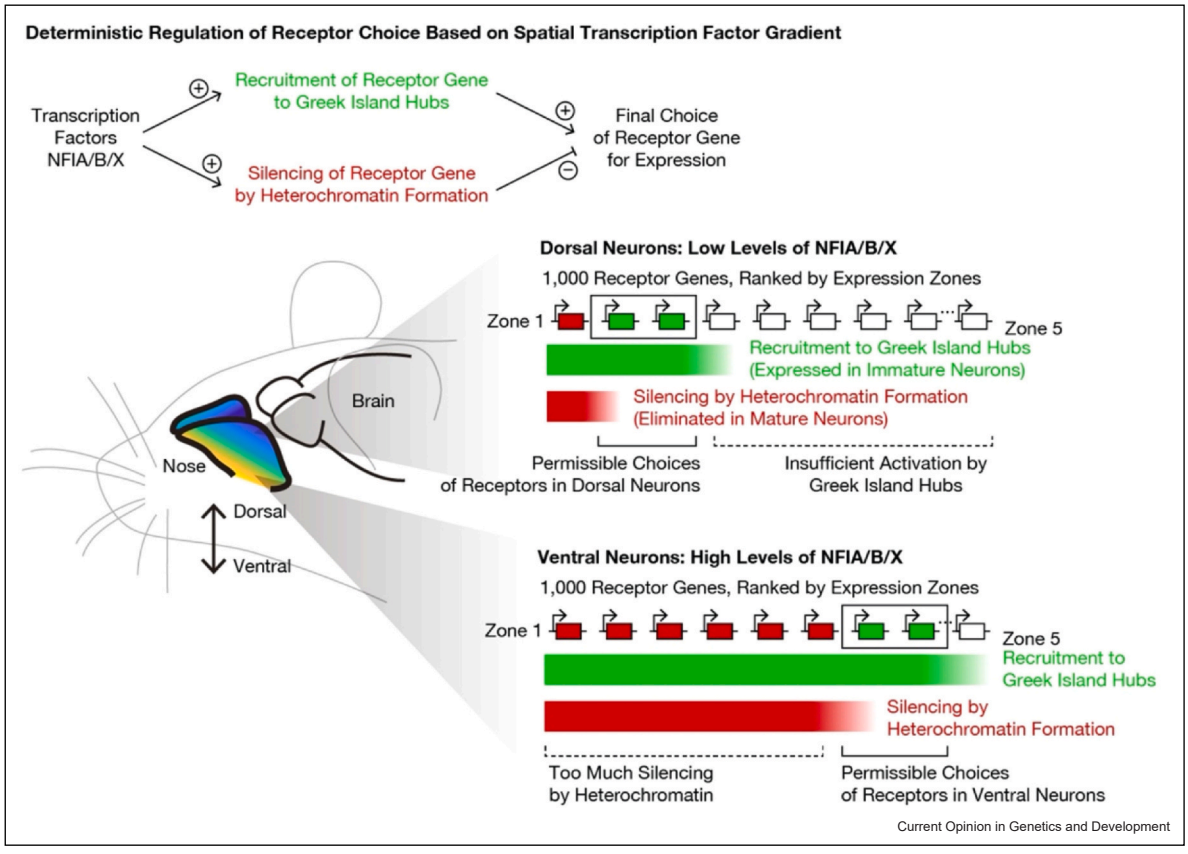
A mechanistic explanation for a transcriptional competition between GIHs is that the nascent OR mRNA recruits a limited RNA-binding protein that facilitates GIH–OR interactions and thus enhances the transcription of the underlying OR allele [24]. If OR transcription from a GIH becomes stronger than the rest, more of this protein will be recruited to this hub, and less will be available for the competing hubs, resulting in 'symmetry breaking' [31] and incapacitation of all but one GIH [24]. Consistent with this hypothesis, introduction of a premature stop codon to OR Olfr17, which prevents OR protein synthesis while the nascent OR mRNA is intact, does not interfere with the ability of the noncoding Olfr17 OR allele to associate with GIHs upon transcriptional induction and to silence the expression of the competing OR alleles in each OSN [24]. Thus, while multichromosomal convergence of Greek Islands into a few transcriptionally competent hubs limits the maximum number of co-transcribed OR alleles from a theoretical maximum of > 2000 to an experimentally observed 5–15, an RNA-mediated

symmetry-breaking process reduces this number to 1 (Figure 2). Future single-cell 3D genome technologies that integrate chromatin–RNA interactions will offer novel insights into how OR-transcribed RNA influences competition among multiple transcriptionally involved enhancer hubs during the transition from multigenic to singular OR expression under physiological conditions. Although a decline in Greek Island accessibility has been observed from late progenitors to mature OSNs and was inferred as the reflection of the inactivation of most enhancer hubs with only one remaining active [10,24], this still needs to be confirmed at the single-cell level. Emerging single-cell 3D genome approaches incorporating epigenomic profiling (e.g. histone modifications and chromatin accessibility) offer the potential to distinguish active and inactive GIHs and elucidate their dynamics during OSN differentiation. If this singularly transcribed OR allele expresses a full-length OR protein, then Perk signaling elicited during OR translation in the endoplasmic reticulum will stabilize this singular transcriptional choice for the life of the OSN [32,33] (Figure 2); if, however, the transcriptionally prevailing OR was a pseudogene, this process will reset [24,34–36] until an intact OR gene is stably chosen. Intriguingly, variations on the levels of Perk signaling related to variations in OR protein sequence also instruct the convergence of the OSN axons with the same OR protein to the same glomerulus of the olfactory bulb [37], explaining how the probabilistic choice of a single OR is transformed into a stereotypic axon guidance process (Figure 2).

## A deterministic axis of olfactory receptor gene choice

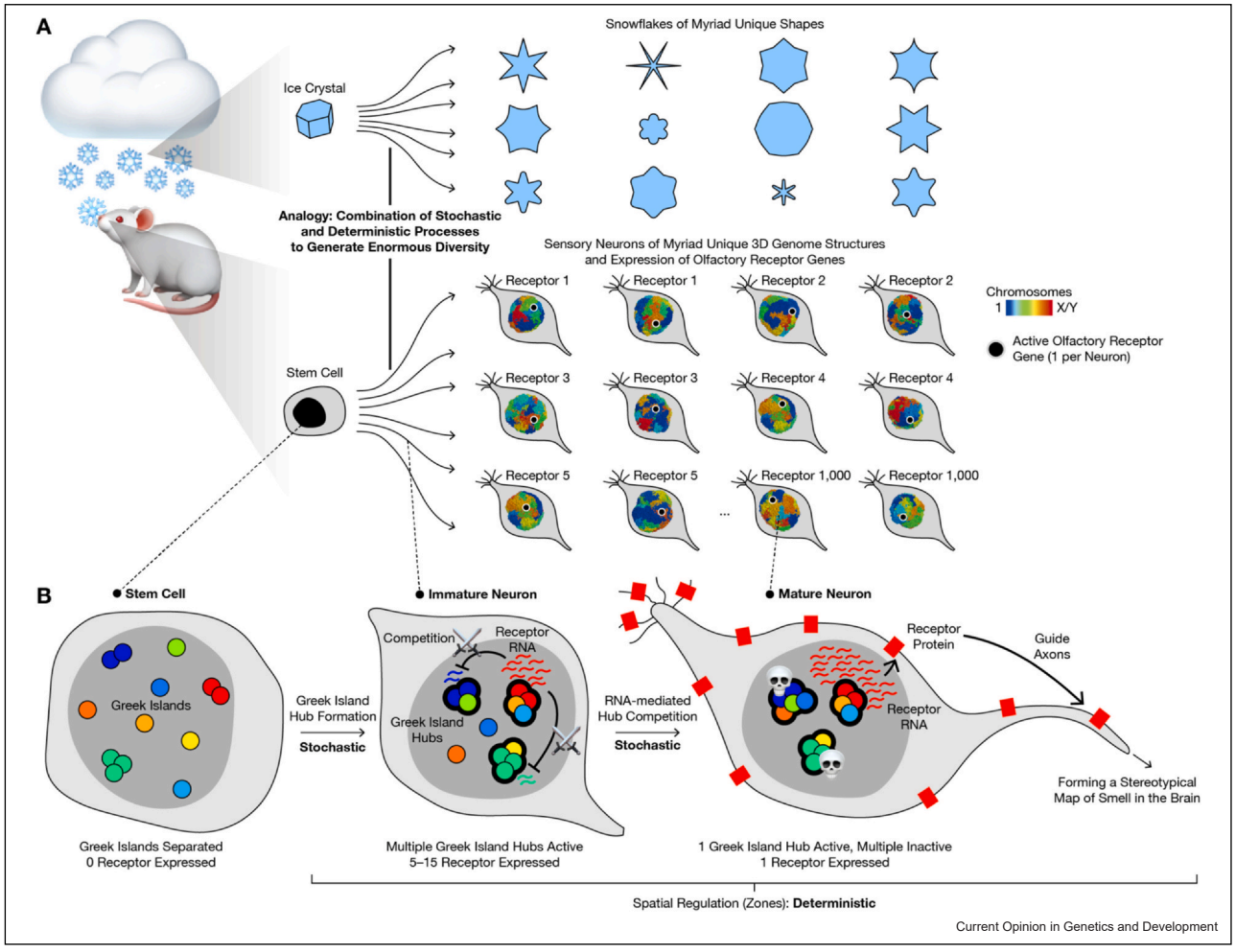
Soon after the discovery of the OR gene family, it became apparent that OR gene expression is restricted in defined 'zones' of expression along the dorsoventral (DV) axis of the main olfactory epithelium (MOE) [38,39]. Single-cell RNA-seq [19,40], spatial transcriptomic [18,41], and imaging experiments [42] have since defined the zonal expression pattern of most OR genes at high spatial resolution, revealing that each OR is expressed at stereotypic segments of the MOE. Genetic experiments revealed that DV gradients of transcription factors nuclear factor I (NFI)A, B, and X

**Figure 3**




NFI gradients define the 'selectable' OR repertoire across the DV axis of the main olfactory epithelium. Differences in NFI protein levels in OSN progenitor cells determine which OR alleles will be heterochromatinized and which can be recruited to the GIHs of each OSN, biasing OR gene choice in spatially influenced fashion. NFI, nuclear factor I.

**Figure 4**




Genome architecture 'snowflakes' enable probabilistic and singular OR expression. Depending on the arrangement of each chromosome at the end of the last cell division, postmitotic olfactory neurons assemble multichromosomal GIHs and heterochromatic OR compartments with different constitutions in each cell. This assures that no enhancer complex has a genetically determined advantage over others, preventing strong biases toward specific OR alleles.

control zonal OR expression by regulating the polygenic expression patterns, heterochromatic silencing, and genomic compartmentalization of OR genes across the DV MOE axis [18,19] (Figure 3). Briefly, the expression levels of the 3 NFI genes increase toward the OSN progenitors of the ventral MOE, enabling more ventral OR gene identities to participate in the polygenic stage of OR transcription, and, thus, to be recruited to a GIH [18]. In the same OSN progenitors, more dorsal OR gene identities are rapidly silenced by heterochromatin, also in an NFI-dependent fashion, and thus, become eliminated from the competition for singular choice [18]. More ventral OR gene identities, on the other hand, are not privy to polygenic transcription; thus, they do not have a chance to be recruited to a GIH [18] at this segment of the olfactory epithelium (Figure 3). Thus, by controlling both heterochromatic silencing, polygenic transcription, and genomic compartmentalization, NFI protein concentrations define a small fraction of OR genes that is both 'accessible' and 'recruitable' to the GIH, reducing the problem of OR gene choice from a random choice of 1 out of > 2000 OR alleles to the biased and probabilistic choice of 1 out of a maximum of 50–200 OR alleles [18]. Intriguingly, although the OR repertoire that can be expressed in each OSN is defined by its DV coordinates, each OSN from a specific DV segment has unique patterns of interchromosomal interactions between OR gene clusters and Greek Islands [10,18,23] that is never recapitulated even between OSNs that express the same OR allele [24]. In other words, from a genome folding perspective, OSNs are 'snowflakes' that deploy stochastic combinations of interchromosomal enhancer contacts to accomplish highly diverse but highly reproducible gene expression programs (Figure 4).

## Conclusions and remaining questions

Without a doubt, additional transcription factor combinations may further reduce the number of OR alleles that can be chosen by each OSN [43,44]. The challenge, however, is not only to robustly activate a single OR promoter with the optimal fit for a transcription factor regime but also to keep tens of highly homologous OR promoters, including the identical promoter allele from the other chromosome, completely silent. To solve this problem, evolution deployed regulatory mechanisms that *a priori* incapacitate some of these 'like' promoters before they are recruited to a hub, and *a posteriori* eliminate the ones that escaped. Heterochromatic silencing [45,46] and repressive genomic compartmentalization [25,47] first eliminate 'activatable' OR promoters from the competition; convergence of intergenic OR enhancers into a few GIHs [8,22,23] reduces the number of transactivation complexes that can then associate with the remaining OR promoters by 10-fold; DV axis–influenced activation of weak and polygenic OR transcription subsequently enables recruitment of some of the nonsilenced OR promoters to a GIH; an OR transcription–mediated competition culminates into a single, prevailing GIH [24]; and an OR protein-elicited feedback that stabilizes this choice for the life of the neuron [32–36] (Figure 4). While these observations provide a conceptual solution to the remarkable problem of choosing 1/2000 alleles, many mechanistic questions remain. The answers will not only provide mechanistic understanding of the process of OR gene choice but will also give insight into processes that shape genome architecture and transcriptional diversity across organisms and cell types. For example, chromatin looping also drives the stochastic choice of antigen receptor genes [48] and clustered protocadherin genes [49,50], the latter of which bears further resemblance to OR genes because of RNA-mediated competition [51]. Beyond gene choices, highly stable and specific long-range chromatin interactions may represent a unique gene regulation strategy of postmitotic cells, which is capable of continuously strengthening ultra long-range contacts over decades in the brain [52,53], in sharp contrast to short-lived and transient genome architecture in rapidly dividing cells.

## Data Availability

No data were used for the research described in the article.

## Declaration of Competing Interest

Stavros Lomvardas reports financial support was provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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