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COMMENTARY

One Gene Is Not Enough To Explain the Evolution of Homosexuality

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Most mammalian lineages have two distinct modes of olfaction. One is the main olfactory system (MOS), which is specialized for volatile compounds from the environment, such as those associated with food. The other is the vomeronasal system (VNS), which uses a distinct neuroepithelium, the vomeronasal organ (VNO), to sense molecules that mediate conspecific social interactions. These molecules include pheromones that signal the sex, maturity, and reproductive receptivity of another individual. Though both the MOS and VNS were ancestral to placental mammals, they have been reduced in parallel in some lineages. The VNS, in particular, has been lost in the catarrhine primates (i.e., old world monkeys [OWM], apes, and humans), most bats, and the fully aquatic cetaceans (whales and dolphins) and manatees (Bhatnagar & Meisami, 1998; Kishida, Thewissen, Hayakawa, Imai, & Agata, 2015; Mackay-Sim, Duvall, & Graves, 1985). Some platyrrhine primates (i.e., new world monkeys [NWM]) also show highly reduced VNO (Smith et al., 2011).

Mutant mice lacking *TRPC2* function retain a vomeronasal sensory epithelium, but cannot detect or respond to known pheromones (Stowers, Holy, Meister, Dulac, & Koentges, 2002). The resulting impairment of afferent vomeronasal receptor (VR) signaling leads to loss of VNS-mediated behaviors, such as male–male aggression and the limitation of copulation attempts to females, as well as increased same-sex sexual behavior (SSSB). SSSB is also seen in catarrhines and in a subset of platyrrhine monkeys (Dixson, 2010; Vasey, 1995). Pflau, Jordan, and Breedlove (2019) note an intriguing correlation between the absence of a robust VNS and the presence of SSSB. They also point out that null alleles of *TRPC2* were fixed in the catarrhines and coincide (at least roughly) with observable SSSB in that clade. Because the TRP family in mammals is small, and because full-length *TRPC2* pseudogenes exist in catarrhine genomes (Liman, Corey, & Dulac, 1999; Vannier et al., 1999; Wes et al., 1995), orthology and recent loss are not in doubt. The question thus becomes how to interpret this loss.

Noting the essential role of the VNO in mediating sex recognition in rodents, Pflau et al. (2019) suggest that *TRPC2* could be a determiner of sex-specific behavior across mammals more broadly. Further, they propose that its loss may have been the initial trigger that allowed frequent SSSB to emerge in catarrhine primates, including the homosexuality of our own species. Because of its simplicity, this is an attractive hypothesis. However, it rests on three assumptions that each appear to be somewhat shaky.

Assumption 1: Catarrhine Primates Are Like Rodents in Their Dependence Upon the VNS for Reliable Sex Discrimination

Rodents lack conspicuous anatomical sexual dimorphisms and see relatively poorly. As a result, they likely rely on the VNS almost completely for sex discrimination. In contrast, catarrhine primates evolved sexual dimorphisms that do not rely upon on pheromones for recognition. These include adult size dimorphism, sex-specific vocalizations, and sexually selected anatomical features, some of which are extreme and take advantage of primate color vision (Dixson, Dixson, & Anderson, 2005). Humans can even accurately determine sex from an individual's gait when abstracted as a point representation (Kozlowski & Cutting, 1977). In addition, humans can detect sexually dimorphic chemical cues, such as androgen metabolites (e.g., Lundstrom, Hummel, & Olsson, 2003), in a VNS-independent manner (Knecht et al., 2003). The MOS therefore can play some of the historical roles of the VNS. Taken together, catarrhines appear to be cognitively aware of the sex of their conspecifics, even if they do engage in SSSB with some of them. It remains an open question, however, whether SSSB in new world monkeys was enabled by VNS reduction.

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Assumption 2: Loss of TRPC2 Is a Cause, and not a Consequence, of VNS Loss

Assuming that the VNS served as an essential block to SSSB in primates, Pflau et al. (2019) then go further to propose that loss of *TRPC2* is more likely to be a cause, and not a consequence, of VNS loss. This is possible, but a more general alternative is that the VNS or its function was lost first, and later so were many genes whose essential functions were in the VNO. If the loss-as-consequence alternative were correct, we can make two predictions:

> The VNS was lost prior to the fixation of the mutations that disable TRPC2.

A direct test of this hypothesis is difficult in catarrhines. The relevant stem lineages that diverged before the last common ancestor of living OWM and apes, such as the Pliopithecoidea (Begun, 2017) and *Aegyptopithecus* (Simons, 1992), lived tens of millions of years ago (Seiffert, 2006). Their fossil remains would thus not be expected to retain ancient DNA. Demonstration that loss of the VNS greatly predated the last common ancestor of extant catarrhines would at least be consistent with *TRPC2* loss as a consequence, and here there is some hope for an answer. The size of the main olfactory system can be inferred in fossil mammal skulls from the cribriform plate (Bird et al., 2018), and similar inferences about the vomeronasal organ in fossil primates can be made from the vomeronasal groove (Garrett, 2015, Ch. 7).

As a less direct test of whether loss of the VNS can precede that of *TRPC2*, we can take advantage of the fact that the VNS has been lost multiple times in mammals (Hecker, Lachele, Stuckas, Giere, & Hiller, 2019). This offers a chance to examine the relation between gene loss and VNO loss across replicated natural experiments. The most relevant case is that of NWM species. As Pflau et al. (2019) note, those that exhibit SSSB generally have reduced VNS, but retain intact *TRPC2* genes. This suggests *TRPC2* loss can indeed *follow* VNO loss and that other mutations targeting VNO-specific aspects of neural development may be often the "tip of the spear" for selection.

> TRPC2 should not be unique in its pattern of retention and loss.

If *TRPC2* loss were a correlated consequence of VNO loss and SSSB, then other VNO-enriched genes from rodents and NWM should become pseudogenes in the OWM clade. Fortunately, much has been learned about VNS-specific gene evolution in the last decade. Over 500 vomeronasal receptors (VRs) are annotated in the mouse genome, and the VNO transcriptome has been determined (Ibarra-Soria, Levitin, Saraiva, & Logan, 2014). One of the two VR receptor classes, Class 1, is indeed remarkably contracted in catarrhine primates (Yoder & Larsen, 2014; Young, Massa, Hsu, & Trask, 2010). These include a VR gene that has otherwise remained as a stable ortholog across 400 million years of vertebrate evolution, *ancV1R*. Similar to *TRPC2, ancV1R* was lost in OWM and apes (Suzuki et al., 2018), as well as in bats and cetaceans, which also lack a VNO. Hecker et al. (2019) have recently performed an extensive screen for genes consistently associated with VNO loss and found several others. These include the calcium-binding protein *S100z*, the aldehyde oxidase *Aox2* involved in odorant degradation, and an uncharacterized gene, *Mslnl*, which is expressed in both the VNS and MOS. These studies underscore that while *TRPC2* is an important player in vomeronasal physiology, it is far from unique in its association with loss of pheromone signaling.

Assumption 3: Human Homosexuality Is Homologous with Non-Human Primate SSSB

As noted by Dixson (2010), SSSB in non-human primates appears to be motivated by both hedonism (i.e., pleasure-seeking) and the maintenance of dominance hierarchies. As such, it exists alongside procreative sexual activity. In our own species, hedonic roles for SSSB surely exist alongside a primarily heterosexual orientation, especially during adolescence (Parkes et al., 2011). However, from the pioneering work of Kinsey and coworkers (Kinsey, Pomeroy, & Martin, 1948; Kinsey, Pomeroy, Martin, & Gebhard, 1953) and subsequent larger surveys (e.g., Chandra, Mosher, & Copen, 2011), it has become clear that roughly 2% of adult men and slightly fewer women have a strong orientation toward exclusive homosexuality. Further, for men homosexual orientation is more frequent than bisexuality. The bimodal distribution of orientation is inconsistent with opportunistic hedonism as the sole mechanism. Rather, the early-developing, disincentive-resistant form of SSSB exhibited by some humans (e.g., Green, 1987) resembles a behavioral polyphenism, one not shared with other catarrhine primates.

In conclusion, while there is clear evidence of a dramatic ablation of VNS function at the base of the extant catarrhines, it is premature to conclude that *TRPC2* inactivation was the first step in that process. It is also unlikely that VNS loss is sufficient to trigger SSSB in catarrhine primates in general and human homosexuality more specifically. Nevertheless, many lines of evidence do suggest that human homosexuality is an innate trait that develops no later than early childhood, and thus, there is a biological basis for it (Bailey et al., 2016). We therefore should keep searching and keep our eyes wide open in the process.

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