

Research



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When morphology does not fit the genomes: the case of rodent olfaction

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Linking genes to phenotypes has been a major question in evolutionary biology for the last decades. In the genomic era, few studies attempted to link olfactory-related genes to different anatomical proxies. However, they found very inconsistent results. This study is the first to investigate a potential relation between olfactory turbinals and olfactory receptor (OR) genes. We demonstrated that despite the use of similar methodology in the acquisition of data, OR genes do not correlate with the relative and the absolute surface area of olfactory turbinals. These results challenged the interpretations of several studies based on different proxies related to olfaction and their potential relation to olfactory capabilities.

1. Introduction

The sense of olfaction is key to the survival of most mammals [1–3]. However, there is still a large gap in our understanding of how olfactory performance relates to its genomic and anatomical bases, and whether and how olfactory genetics and morphology differentially covary among species that have contrasting olfactory capabilities. Olfactory turbinals (turbinals covered with olfactory epithelium) are considered the main olfactory bony system. Olfactory sensory neurons from these areas project posteriorly via olfactory nerves through the cribriform plate and join the glomeruli from the main olfactory bulb [1]. It is assumed that olfactory turbinals are uniformly covered with olfactory receptors (ORs), therefore the absolute surface area of olfactory turbinals may reflect the absolute number of ORs [4–8]. Comparative phylogenetic analyses demonstrated a relation between the relative size of olfactory turbinals and species ecology such as diet [4,7] or lifestyle [4,8]. At the genomic level, OR genes encode the most represented chemosensory receptors in mammals, and constitute the largest multigenic superfamily categorized into about 13 gene families [3,9,10]. Moreover, the number of functional and pseudogenized OR genes and their composition vary highly along mammalian phylogeny [3,9] and with species ecology [9–15]. This is for example the case for diet [10,13,15] or ecological lifestyle [11,14,16,17]. Therefore, OR genes are expected to covary with morphological olfactory-related proxies such as olfactory turbinals.

Linking genes to phenotypes has been a major question in evolutionary biology for the last decades. Few studies focused on olfaction, evaluated the correlation between genetic and morphological proxies and yielded contrasting results [18–20]. However, to date, none of them investigated the potential relation between olfactory turbinals and OR genes. The major obstacles to address these issues have been to access and accurately quantify the internal olfactory organs as

well as the limited number of high-quality, available mammalian genomes. However, in 2022, more than 500 mammalian genomes became mineable, and genome quality has increased exponentially [21]. Similarly, X-ray micro-computed tomography (micro-CT) has become more accessible, resulting in an unprecedented expansion of three-dimensional data for internal anatomical structures [22]. This provides ample opportunities to fill the gap in our understanding of the basis and evolution of olfaction in mammals.

In the most diversified mammalian order, the rodents [23], we investigated the potential relation between the two main proxies for olfaction: (1) OR genes and (2) olfactory turbinals. For this, we used standardized genomics and morphological data, carefully acquired by similar investigators and using identical methods.

2. Results

No significant correlations were found between (i) the number of functional OR genes and the relative olfactory turbinal surface area (figure 2a, $s = 0.33$, $r^2 = -0.01$, $p = 0.35$), (ii) the number of functional OR genes and the absolute olfactory turbinal surface area (figure 2b, $s = 0.04$, $r^2 = -0.01$, $p = 0.39$), (iii) the number of functional OR genes and the skull length (figure 2c, $s = 0.05$, $r^2 = -0.04$, $p = 0.63$), (iv) the total number of OR genes and the skull length (figure 2d, $s = 0.21$, $r^2 = -0.04$, $p = 0.18$), (v) the number of functional OR genes and the number of olfactory turbinals (figure 2e, $s = -0.03$, $r^2 = -0.05$, $p = 0.94$), (vi) the total number of OR genes and the number of olfactory turbinals (figure 2f, $s = 0.07$, $r^2 = -0.05$, $p = 0.90$), (vii) the relative olfactory turbinal surface area and the number of olfactory turbinals (figure 2g, $s = -0.08$, $r^2 = -0.04$, $p = 0.72$), and (viii) the absolute olfactory turbinal surface area and the number of olfactory turbinals (figure 2h, $s = 3.06$, $r^2 = 0.11$, $p = 0.07$). Conversely, there is a significant correlation between: (i) the total turbinal surface area and the skull length (figure 2i, $s = 2.82$, $r^2 = 0.96$, $p = 7.01 \times 10^{-16}$), (ii) the absolute olfactory turbinal surface area and the skull length (figure 2j, $s = 2.41$, $r^2 = 0.94$, $p = 3.25 \times 10^{-14}$), and (iii) the absolute olfactory turbinals surface area and the total turbinal surface area (figure 2k, $s = 0.86$, $r^2 = 0.98$, $p = 2.20 \times 10^{-16}$). The inclusion or exclusion of the lamina semicircularis (ls) did not change the results (electronic supplementary material, tables S1–S15). This reinforces the relevance of our results given the current available genomes and scanned specimens.

Species with a similar number of functional OR genes may have different values of the relative olfactory turbinal surface area (figure 2a). Conversely, species with comparable values of the relative olfactory turbinal surface area may have a different number of functional OR genes (figure 2a).

When the 13 different families of functional OR genes are independently analysed, none of them significantly correlates with the relative olfactory turbinal surface area that used total turbinal surface area for sizing (electronic supplementary material, tables S1–S15). When skull length is used for sizing, the relative olfactory turbinal surface area significantly correlates with the number of functional OR genes of the following families: 1S55, 2S11, 2S1.3.7 and 2S4 (electronic supplementary material, figure S1). However, r squared values are very low (less than 0.29) and these significant correlations are only based on the relative olfactory turbinals

surface area that used skull length for sizing (see electronic supplementary material, Methods S1.).

3. Discussion

(a) Lack of link between genomic and morphology

Despite their key function in olfaction, functional OR genes and the relative surface area of olfactory turbinals did not significantly correlate with each other in Rodentia (figure 2a). Interestingly, species with a similar number of functional OR genes may have different values of the relative (or absolute) olfactory turbinal surface area, and conversely (figures 1 and 2a,b). The absolute surface area of olfactory turbinals mostly reflects allometry (figure 2b,h,j, [5–8]). The smallest taxa (*Heterocephalus*, *Microtus*, *Mus*, *Muscardinus*) have the lowest values while the largest species (*Castor*, *Hydrochoerus*, *Hystrix*, *Myocastor*) have the highest ones. Indeed, absolute olfactory turbinal surface area is significantly correlated with skull length (figure 2j, [7,8]). The number of functional OR genes and the total number of OR genes are independent of species size since they did not correlate with skull length (figure 2c,d). This pattern may be the result of different selective pressures, such as drift, phylogenetic inertia as well as environmental constraints [3,13,14]. As an example, the amphibious mammals were largely studied in the light of their olfactory turbinal reductions [4,8] and their large number of OR pseudogenes and/or different OR gene compositions [11–13,16,24–27]. When amphibious and terrestrial species are compared, their patterns differ depending on whether we look at the functional OR genes or the relative surface area of olfactory turbinals. For example, the amphibious *Castor*, *Hydrochoerus* and *Ondatra* have the lowest values for the relative olfactory turbinal surface area while they have an intermediate number of functional OR genes (figures 1 and 2a). According to the ecological lifestyle, when the mean value of the sampled species is considered, there is a tendency for the reduction of the number of functional OR genes in amphibious species for ORs class I, ORs class II and all ORs (electronic supplementary material, figure S3). However, our dataset lacks closely related terrestrial species to go further in our interpretation. Indeed, the more phylogenetically distant the species are, the more likely it is that the observed differences are due to this distance and not to ecology. Such an accurate comparison can be approached with the amphibious *Ondatra* and the terrestrial *Microtus*, both species from the subfamily of the Arvicolinae. Again, when amphibious and terrestrial species are compared, their patterns differ depending on whether we look at the genomics or morphological proxies. The relative surface area of olfactory turbinals is markedly lower in *Ondatra* than in *Microtus* (figures 1 and 2a). This is a complete opposite pattern for the number of functional OR genes, which are higher in *Ondatra* than in *Microtus* (figures 1 and 2a). Our results contrast with the significant correlation between the relative surface area of the cribriform plate and the number of functional OR genes across Mammalia [19]. This is surprising knowing that the absolute and the relative surface area of olfactory turbinals significantly correlated with different proxies of the cribriform plate of carnivora and some myrmecophagous mammals [28,29]. The cribriform plate is often described as a potential proxy for olfactory function [28]

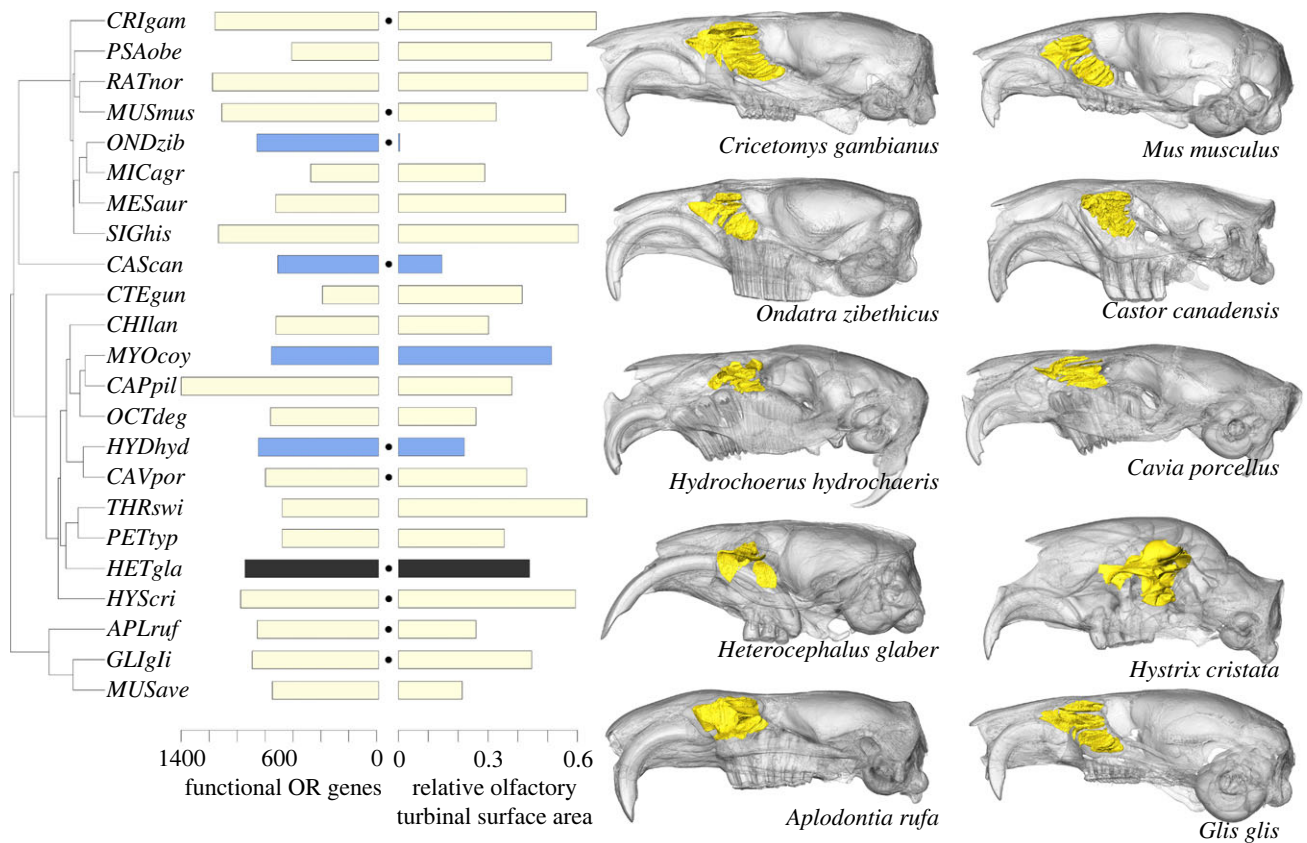


Figure 1. Inconsistent pattern between the functional OR genes and the relative olfactory turbinal surface area. Phylogeny of the sampled species with bar plots of their functional OR genes and relative olfactory turbinal surface area as well as three-dimensional representations of their skull and olfactory turbinals. The relative olfactory turbinal surface area corresponds to the residuals of the PGLS between the absolute olfactory turbinal surface area and the total turbinal surface area. Black dots represent the illustrated species. Bar plot colours: beige = terrestrial, blue = amphibious, black = subterranean species.

because it is a proxy for the cross section of olfactory nerves that originate from the olfactory turbinals and join the olfactory bulb through this plate. Similarly, olfactory turbinals are described as a potential proxy for olfactory function [4,8] because it is assumed that they reflect olfactory epithelium surface area and therefore ORs.

The absence of significant correlations between the two main genomics and morphological proxies for olfaction may be explained by several factors. First, it is possible that olfactory turbinals are not uniformly covered by ORs [30] and/or that their degree of receptive range varies [31]. Second, the degree of neural connectivity may also vary between organs and species [32]. Third, the olfactory epithelium cover may vary between species and mammalian orders [30,33,34]. Also, some evidence in Carnivora suggested that some parts of the olfactory turbinals may be selected for respiration [35]. However, in rodents, such variation is mostly discussed for the lamina semicircularis (ls) and we demonstrated that with our current dataset, its inclusion or exclusion did not change the results (electronic supplementary material, tables S1–S15, see also electronic supplementary material, Methods S1.). Finally, it is possible that OR genes do not represent the different expression levels leading to different olfactory capabilities [36]. A recent study in phyllostomid bats demonstrated that there is no relation between the evolutionary rates of OR genes extracted from transcriptomes and diet whereas there may exist a relation between olfactory epithelium and diet [37]. In addition, whereas classes I and II of OR genes have been postulated to bind mostly water-borne and air-borne

odorant molecules [9,38], the different OR gene families have mostly been distinguished on the basis of their DNA sequence alignment and phylogenetic analysis, and await for more functional characterization.

(b) Estimating and linking olfactory capabilities with morphology and genomes

Our study demonstrated that at the taxonomic scale of rodents, the number of olfactory turbinals does not correlate with potential proxies for olfactory functions such as the number of functional OR genes, and the relative and the absolute olfactory turbinal surface area (figure 2*e,g,h*). This finding matches with the general hypothesis that the number of turbinals is mostly related to phylogenetic inertia while their relative size and complexity is related to species ecology and olfactory performance [4,6–8,33,34,39,40].

Olfactory capabilities are commonly divided in two major components: (1) sensitivity, the ability to detect odours at low concentration and (2) discrimination, the ability to distinguish between two similar odours [4,41]. Van Valkenburgh *et al.* ([4] citing [42,43]) hypothesized that the relative surface area of olfactory turbinals may neither correlate with olfactory discrimination nor with sensitivity. Therefore, they suggested that it may characterize the diversity of odorants that can be perceived. However, Martinez *et al.* [7] demonstrated that highly specialized worm-eating rodents have significantly higher relative surface area and complexity of olfactory turbinals as compared to their close omnivorous and carnivorous relatives. This may be also the

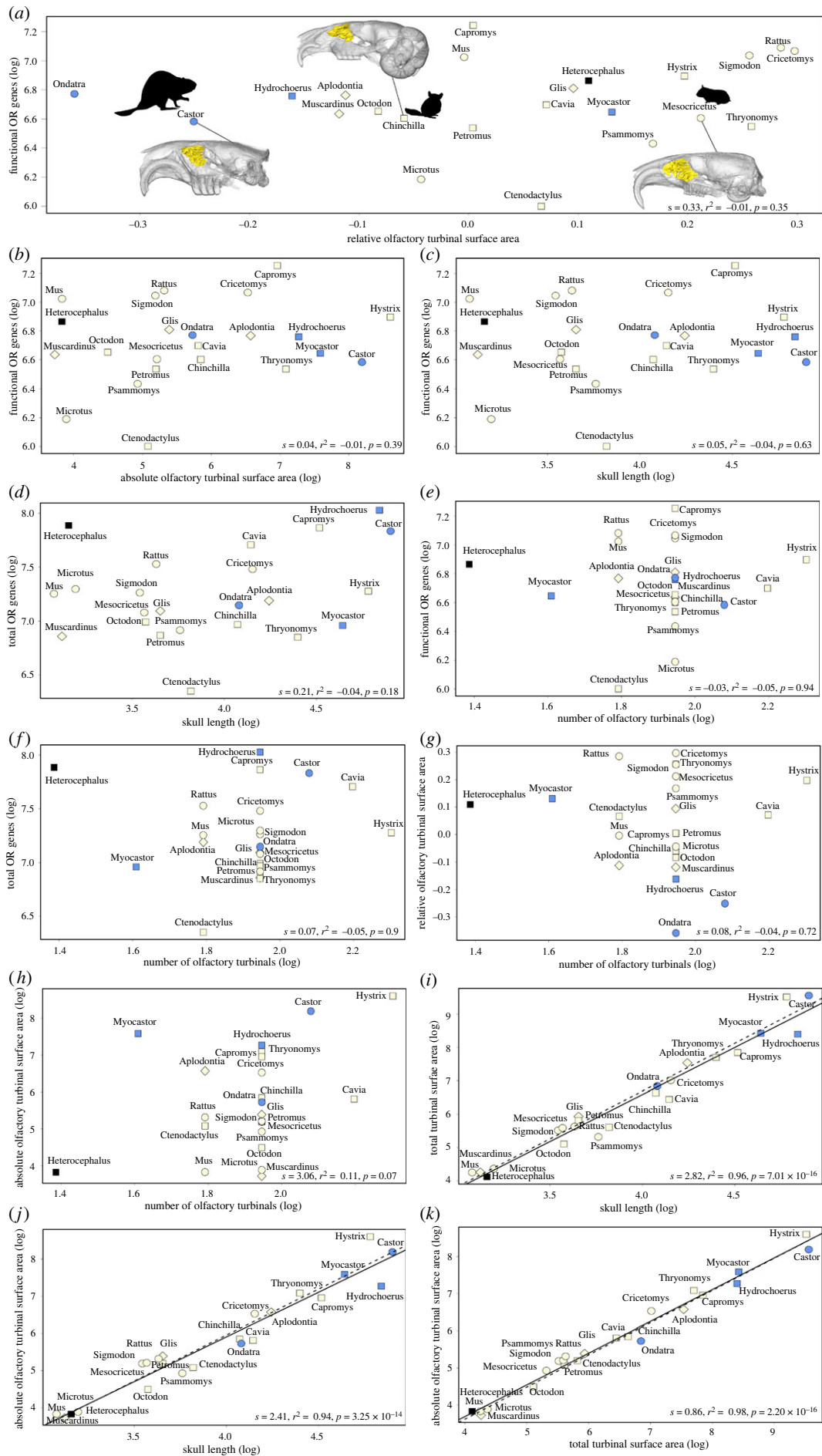


Figure 2. Absence of significant correlations between the morphology and the genomes. Linear regressions (continuous lines) and PGLS (dashed lines) between genomic and morphological proxies for olfaction. Species silhouettes and three-dimensional representations of the skull and the olfactory turbinals in *Castor*, *Chinchilla* and *Mesocricetus*. Symbols: circle = mouse-related clade, square = Ctenohystrica clade, diamond = squirrel-related clade.

case in Carnivora where large-bodied hypercarnivores such as wolf (*Canis lupus*) and wolverine (*Gulo gulo*) have very large olfactory turbinals [6]. These results suggest that the relative size of olfactory turbinals may be linked to olfactory sensitivity. However, the very small number of studies linking olfactory performance with the relative size of olfactory organs leaves many open questions [44]. In addition, the mechanisms of olfaction are still not fully understood [45]. For example, a single odorant molecule can be detected by a specialized receptor, or by multiple receptors operating independently or in combination. Conversely, a single olfactory receptor can also bind to several odorant molecules [10,46–48]. To complicate things further, odorant molecules with different structures may be perceived as a single odour and different odorant molecules with a similar structure may be perceived as the same odour, while odorant molecules with similar structure may be perceived as different odours [10,46–48]. However, as an example, the millions or even trillions of olfactory stimuli that humans can detect cannot be explained solely by our approximately 400 functional OR genes, even with combinatorial models [49,50]. In this context, other theories have re-emerged like the highly debated vibration theory of olfaction based on quantum physics [45,51–56]. This implies that olfactory molecules could be detected thanks to their vibration frequency instead of their shape [57]. In this context, it is challenging to interpret how the number of OR genes impact the olfactory capabilities. For this, it will be critical to map the level of gene expression and their composition on the olfactory turbinals [15,58].

4. Material and methods

In this study, we used the same methodology of data acquisition both for morphological data and genomic pipeline to extract OR genes (see discussion in the electronic supplementary material, Methods S1). Undamaged specimens of 32 individuals belonging to 23 species were selected from museums (electronic supplementary material, table S16) and scanned using high-resolution X-ray micro-computed tomography. Left respiratory and olfactory turbinals were segmented following Martinez *et al.* [7,8] with AvizoLite 2020.1 (VSG Inc.). Mean values were used when multiple individuals of a species were sampled. OR genes were extracted from genomic assemblies *in silico*, using

the same bioinformatic procedures for each species (electronic supplementary material, Methods S1). The total number of OR genes is the sum of functional and pseudogenes OR genes. We performed linear regression and phylogenetic generalized least squares (PGLS) between the different variables (figure 2, electronic supplementary material, figures S1 and S2, electronic supplementary material, tables S1–S15). This was performed with the *gls* function from the package nlme [59]. We plotted linear regressions (continuous lines) and PGLS lines (dashed lines) when a significant correlation exists. The relative olfactory turbinal surface area corresponds to the residuals of the PGLS between the absolute olfactory turbinal surface area and the total turbinal surface area. The total turbinal surface area corresponds to the sum of respiratory and olfactory turbinal surface area. We used the phylogeny from Upham *et al.* [60] and pruned to match the species in our dataset.

Data accessibility. All data are available in the main text or the supplementary materials. We provided an online link for the Data S1.

The data are provided in the electronic supplementary material [61].

Authors' contributions. M.Q.: conceptualization, data curation, formal analysis, investigation, methodology, writing—original draft; M.C.: conceptualization, data curation, formal analysis, investigation, writing—original draft; E.D.: conceptualization, data curation, formal analysis, investigation, writing—original draft; P.-H.F.: conceptualization, data curation, formal analysis, investigation, writing—original draft.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

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