

Neural crest cell biology shapes lizard skull evolution across evolutionary time scales

Quentin Horta-Lacueva¹, Tobias Uller¹, Morris Flecks², Mariam Gabelaia², Christy Anna Hipsley³, Martin Kirchner⁴, Johannes Müller⁴, Nathalie Feiner^{1,5}

¹Department of Biology, Lund University, Lund 223 62, Sweden

²Museum Koenig, Leibniz Institute for the Analysis of Biodiversity Change, Bonn 53113, Germany

³Department of Biology, University of Copenhagen, Copenhagen DK-2200, Denmark

⁴Museum für Naturkunde, Leibniz Institute for Evolution and Biodiversity Science, Berlin 10115, Germany

⁵Max-Planck-Institut für Evolutionäre Biologie, Plön 24306, Germany

Corresponding author: Department of Biology, Lund University, Kontaktvägen 10, 223 62 Lund, Sweden. Email: quentin.horta-lacueva@biol.lu.se

Abstract

The vertebrate skull originates from two embryonic lineages, the mesoderm and the neural crest, offering a unique framework to study how developmental mechanisms connect phenotypic variation and evolutionary diversification. Using 3D geometric morphometrics, we analysed skull shape variation in lacertid lizards. Mesoderm- and neural crest-derived bones formed two distinct, conserved modules at both micro- and macroevolutionary scales. In the common wall lizard (*Podarcis muralis*), rapid evolution of skull shape under sexual selection was primarily driven by neural crest-derived bones. While the primary axis of shape divergence in *P. muralis* aligned with a major axis of variation across lacertids, neural crest-derived bones exhibited overall slower evolutionary rates and lower morphological disparity than mesodermal-derived bones. We propose that this discrepancy between the role of the neural crest for skull evolution on micro- and macroevolution reflects developmental bias imposed by neural crest cell biology. By enabling developmental coupling of skull shape, body colouration and behaviour, the neural crest cells can facilitate rapid, correlated responses under sexual selection but may limit long-term evolvability in the skull.

Keywords: developmental bias, macroevolution, microevolution, evolvability, lacertid

Introduction

Developmental processes structure the morphological variation available to selection (Alberch, 1989; Uller et al., 2018). If developmental processes themselves remain conserved, evolutionary adaptation and diversification will be facilitated in some directions (i.e., “lines of least resistance”), reflecting phenotypic variants that are both readily generated and adaptive (Rohner & Berger, 2025; Schluter, 1996; Tejero-Cicuéndez et al., 2023). Persistent developmental bias may explain why the major axis of phenotypic variation among individuals or between populations of a species is commonly aligned with divergence between species (Jablonski, 2020; Rohner & Berger, 2025; Stansfield & Parsons, 2024; Tejero-Cicuéndez et al., 2023; Tsuboi et al., 2024). Furthermore, developmental processes contribute to macroevolutionary patterns of diversification. For example, models of tooth development improve the explanatory power of comparative studies in primates and rodents (Kavanagh et al., 2007; Machado et al., 2023). However, in the absence of a developmental explanation for why phenotypic variation should be structured in a particular way, the processes underlying major evolutionary trends remain challenging to establish.

Structures with more than one developmental origin are valuable to test the impact of developmental bias on evolution. The

vertebrate skull is one such structure because it develops from two different germ layers: the mesoderm and the neural crest, the latter being derived from the ectoderm (Figure 1; Bronner & LeDouarin, 2012; Hirasawa & Kuratani, 2015). Bones that are mesoderm- or neural crest-derived are partitioned within the skull in a configuration that is largely conserved across vertebrates (Fabbri et al., 2017; Teng et al., 2019). This dual developmental origin of the skull may make bones of the same origin vary consistently together, imposing a certain structure on morphological variation (Wilson et al., 2021). In contrast to the mesoderm, neural crest cells are transient, vertebrate-specific cells that migrate to different parts of the embryo, including the head, and differentiate into a wide range of cell types (e.g., bone, pigmentary, endocrine, mesenchymal, neuronal and glial cells; Barresi & Gilbert, 2023; Bronner & LeDouarin, 2012). That neural crest cells migrate and differentiate into many other cell types in addition to those that make up the skull has been proposed to generate covariance between morphological, behavioural and physiological traits (Brandon et al., 2023; Parsons et al., 2020; Sánchez-Villagra et al., 2016; Wilkins et al., 2014), thereby exercising additional influence over variation and evolution in skull shape. Overall, such differences between mesoderm- and neural crest-derived skull bones should generate structured patterns of covariance (i.e., modularity) that influence morphological adap-

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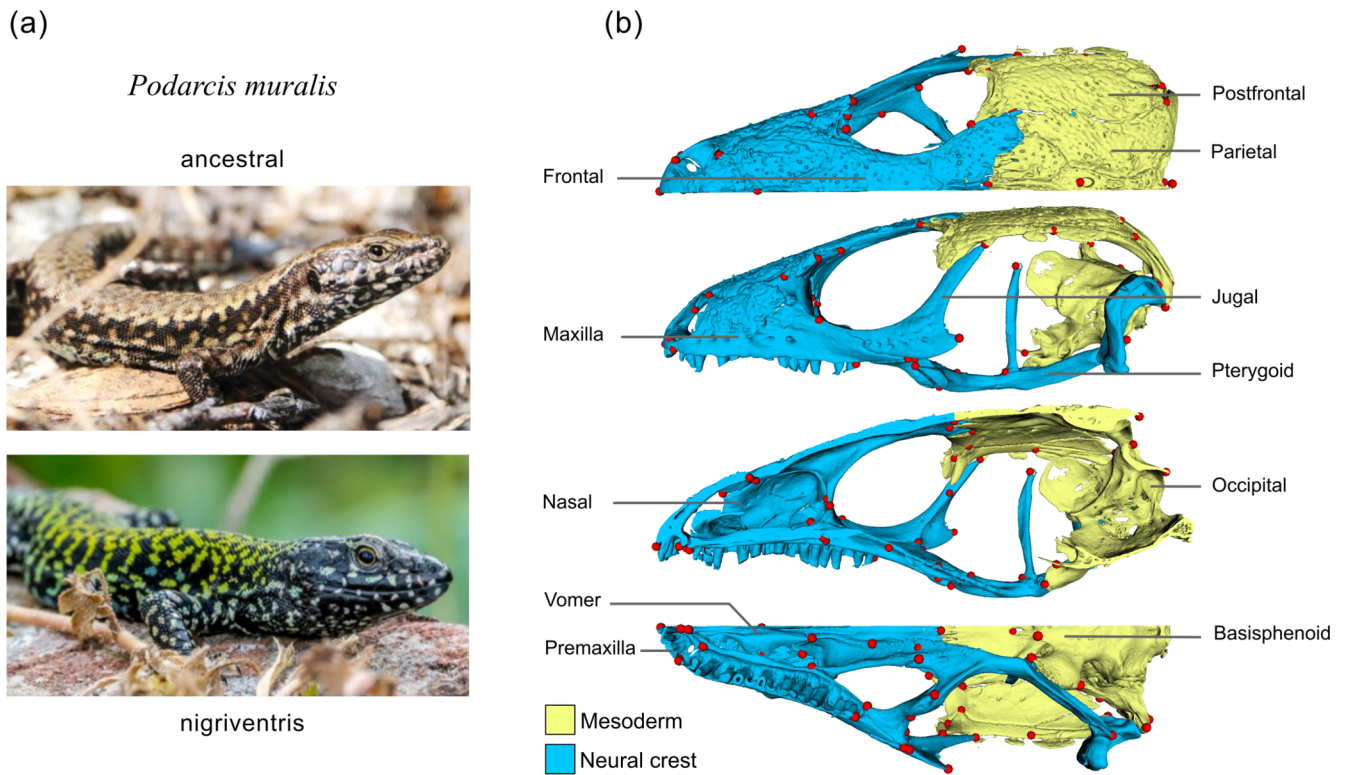


Figure 1. The nigriventris syndrome in *P. muralis* and skull anatomy in lacertids. (a) External appearance of males of the common wall lizards with the ancestral phenotype and the nigriventris syndrome. Top photograph by Nathalie Feiner, bottom photograph by Arnaud Badiane. (b) Skull partitioned into mesoderm- (yellow) and neural crest-derived (blue) bones in different perspectives (first: dorsal, second: lateral, third: sagittal, fourth: ventral). Dots: landmarks used in morphometric analyses.

tation and diversification on both micro- and macroevolutionary time scales (Goswami et al., 2023; Wilson et al., 2021).

Here, we used a comparative approach to test for a germ layer-associated developmental bias in the adaptive evolution of skull shape in lizards, using two levels of comparison. First, in a lacertid species, the common wall lizard (*Podarcis muralis*, family Lacertidae, Squamata), we investigated if changes in skull shape accompany the recent evolution of a sexually selected suite of traits, the “nigriventris syndrome,” which consists of exaggerated coloration, morphological characters including larger relative head size, and aggressive behaviour (Figure 1, Feiner et al., 2024; MacGregor et al., 2017a, 2017b; While et al., 2015). The traits that comprise this syndrome partially originate from the neural crest, and genomic analyses suggest that genes that regulate aspects of neural crest cell biology contributed to its evolution (Feiner et al., 2024). Thus, in *P. muralis*, we expect (i) modularity between putatively mesoderm- and neural crest-derived bones, and (ii) that morphological change associated with the nigriventris syndrome is more pronounced for the parts of the skull with a putative neural crest origin.

Second, we assessed to what extent germ layer-associated developmental bias is maintained and contributes to morphological diversification of skulls within the lacertid lizards. This family includes 387 currently described species (Uetz & Etzold, 1996; accession date 09/07/2025) distributed across Eurasia and Africa and their skull shape diversity has been linked to adaptations to diverse habitats and lifestyles (Hipsley & Müller, 2017). If germ layer-associated developmental bias shaped the diversification of skull morphology in this group, we expect (iii) that shape changes associated with the nigriventris phenotype in *P. muralis* are reflected also in the diversification of skull shape in lacer-

tids, (iv) that modularity of mesoderm- and neural crest-derived bones persist across the lacertid family, and (v) that the tempo of evolution and disparity differ for mesoderm- versus neural crest-derived parts.

Results

Evolution of the nigriventris syndrome is associated with changes in skull size and shape

The nigriventris syndrome of the common wall lizard is composed of a suite of traits including coloration, morphology and behaviour that has been suggested to be associated with neural crest biology (Feiner et al., 2024). To test if skull shape differs between nigriventris and ancestral phenotypes, and if these differences are particularly pronounced for the parts of the skull that putatively originate from the neural crest, we generated 3D scans of skulls of 62 specimens collected on the Italian peninsula using micro-computed tomography (μ CT). We compared the skull shape of male common wall lizards from populations classified along a 1 to 5 ordinal score, ranging from populations fixed for the ancestral phenotype (the “ancestral” group, score 1), populations with intermediate phenotypes ranging from scores 2 to 4, and populations fixed for the most extreme nigriventris phenotype (the “nigriventris” group, score 5; Figure 2). For more details on classification and the analyses of the expression of the nigriventris syndrome across the Italian peninsula, see Methods, Ruiz Miñano et al. (2021) and Feiner et al. (2024).

Consistent with previous findings (Feiner et al., 2024), common wall lizards from populations fixed for the nigriventris phenotype had longer heads relative to body size than specimens

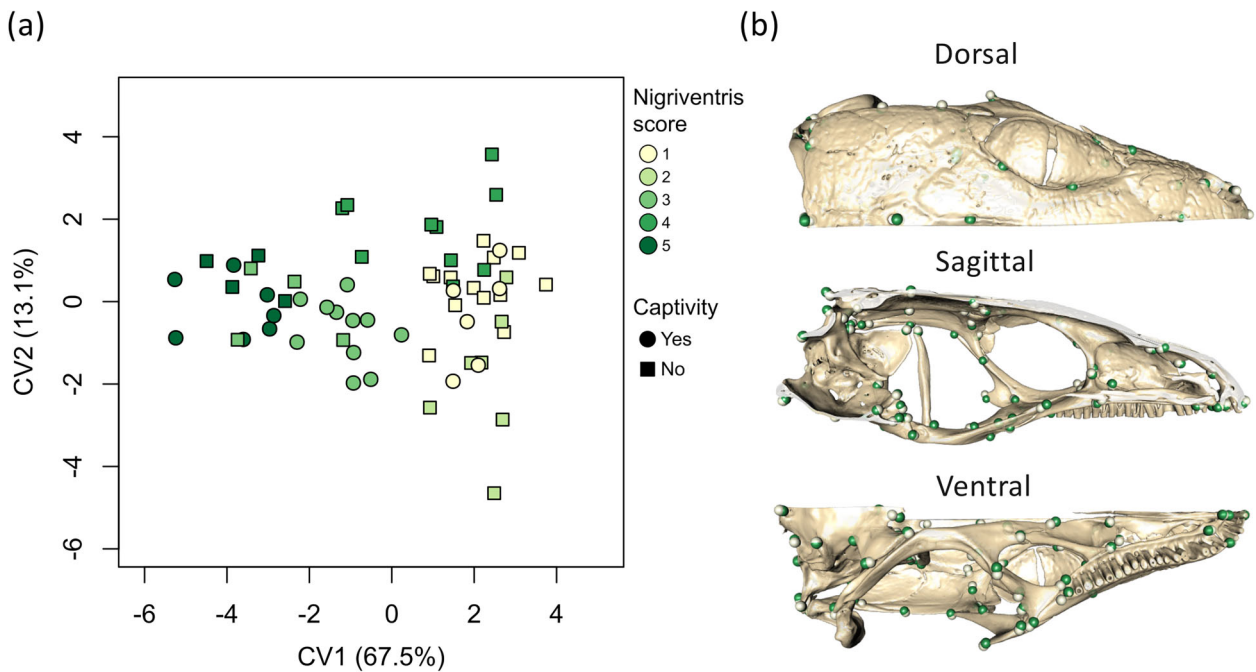


Figure 2. Canonical Variate analysis of landmark configurations on the skull of *Podarcis muralis*. Nigriventris score categories range from populations with ancestral phenotypes to populations with the most extreme expression of the nigriventris syndrome. (a) Projection of the first two canonical variates (CV), (b) landmark displacement between the two extremes of CV1 (minimum: light dots; maximum: dark dots).

with the ancestral phenotype (Table S1). The ancestral and nigriventris phenotypes also differed in skull shape, with individuals from populations with intermediate expression of the syndrome tending to fall in between the two extremes (Table 1, Figure 2a). The inferred changes in skull shape from the ancestral to the derived nigriventris phenotype involved several putatively neural crest-derived bones (jugal, epipterygoid and maxilla) being laterally compressed, thus giving a slimmer appearance to the skull. Other bones of neural crest origin tended to converge along the antero-posterior axis on the ventral side of the snout (epipterygoid, pterygoid, premaxilla, vomer) while being extended anteriorly along the dorsal side (frontal, nasal), resulting in relatively shorter snouts with smaller nostrils (Figure 2b). The changes in skull shape that accompanied the evolution of the nigriventris phenotype also involved mesoderm-derived bones, contributing to a lateral compression and a dorsal extension of the skull roof, giving the back of the skull roof a round aspect (parietal, post-frontal), and a relative contraction of the brain case (occipital bones and basisphenoid). Analyses based on shape estimates retaining size information led to the same conclusions (Figure S1). These results indicate that the nigriventris syndrome comprises head shape changes corresponding to a larger skull with elongated appearances and larger skull roofs relative to the snout.

The dual origin of skull bones affects modularity and divergence within species

To test for co-variation between the mesoderm- and neural crest-derived elements of the skull, we partitioned the 77 landmarks by putative developmental origin (neural crest: 40; mesoderm: 35; uncertain: 2, see Methods) and assessed support for modularity within each configuration. We found that bones putatively originating from either the mesoderm or the neural crest formed statistically supported modules in *P. muralis* (Covariance Ratio CR = 0.88; $Z = -4.74$; $P < 0.001$). We tested if

four landmarks placed on the parietal (a putatively mesoderm-derived bone) but which were in contact with putatively neural crest-derived bones influenced the result. Removing these landmarks did not change the observed pattern of modularity (CR = 0.89; $Z = -3.89$; $P = 0.001$). Pairwise comparisons of phenotypic distances between the ancestral and nigriventris group revealed significant and large effect sizes for the neural crest-derived module ($d = 0.015$; $Z = 2.89$; $P = 0.002$), while the mesoderm-derived module showed no statistically significant divergence between ancestral and nigriventris phenotypes ($d = 0.012$; $Z = 0.83$; $P = 0.210$). These results suggest that the germ layer origin structures skull shape variability in *P. muralis*, and that the neural crest-derived part of the skull is mostly responsible for the morphological changes associated with the nigriventris syndrome.

Shape changes in the nigriventris phenotype reflects morphological diversification in lacertid lizards

To assess the relationship between the divergence of ancestral and nigriventris skull shapes in *P. muralis* and macroevolutionary patterns of diversification, we first inspected how skull shape in lacertids varies along the dimensions describing the differences between ancestral and nigriventris phenotypes. We collected data on skull shape for 174 species of lizards from the lacertid family, including species from all but one of the 43 genera (see Methods). When rotating the principal components of lacertid skulls along the axis of the maximum divergence between ancestral and nigriventris phenotypes, we find that 8.68% of the total variation in lacertids was captured by the ancestral-nigriventris axis of divergence (Figure 3). In comparison, the first three principal components capture 26.17%, 17.17% and 6.20% of the total variation. Species with extreme values in the direction of the nigriventris phenotype are lizards with robust skulls, relatively small nostrils and orbits, and large parietal bones, like

Table 1. RRPP mANCOVA for shape changes in *P. muralis* varying in the expression of the nigriventris syndrome.

	Df.	SS	MS	R ²	F	Z	P
Origin (captive, wild) ¹	1	0.0030	0.0030	0.0455	3.326	3.741	<0.001
log(centroid size)	1	0.0066	0.0066	0.1000	7.300	5.549	<0.001
nigriventris score	4	0.0051	0.0013	0.0782	1.428	2.514	0.007
log(centroid size) × nigriventris score	4	0.0051	0.0013	0.0779	1.422	2.546	0.006
Residuals	51	0.0459	0.0009	0.6984			
Total	61	0.066					

¹Fixed effect to correct for specimens that underwent to period of captivity following their capture in the wild.

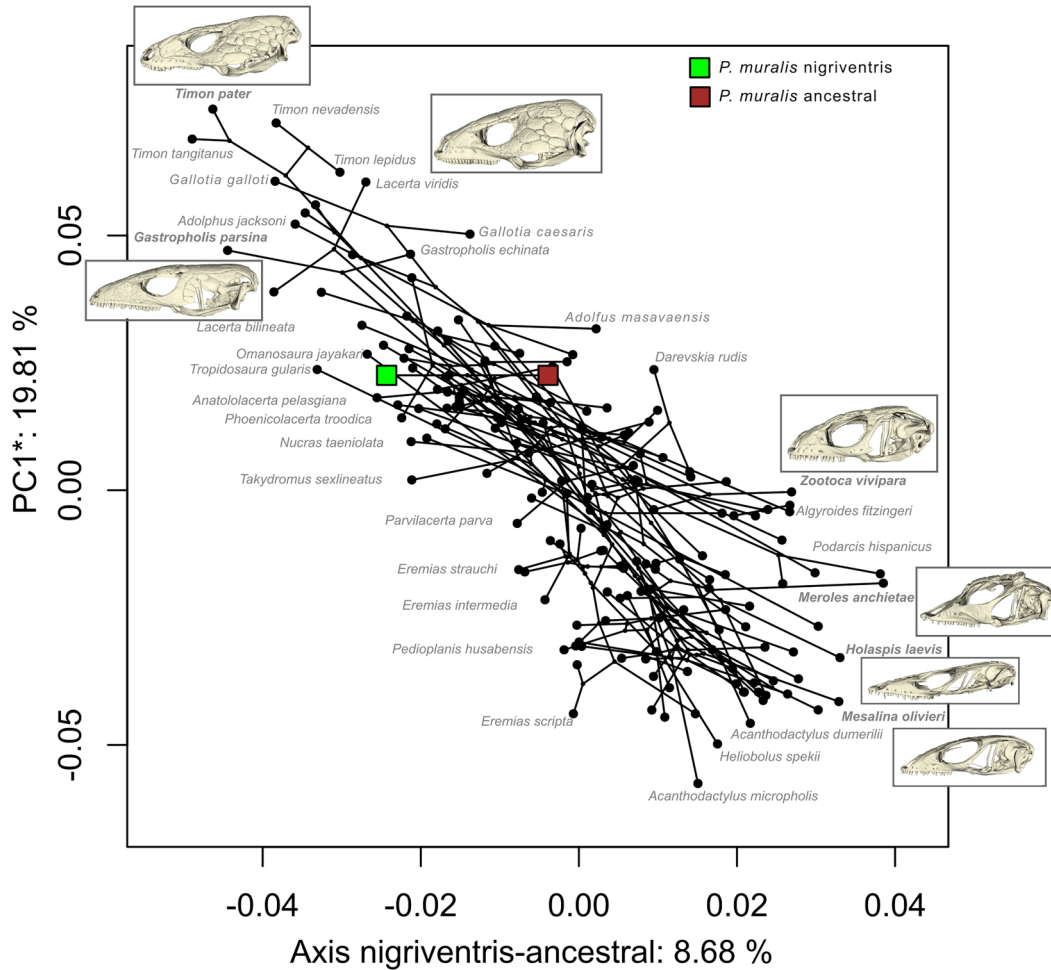


Figure 3. Morphological variation in lacertids with regard to the ancestral-nigriventris axis of divergence. Phylomorphospace of 174 species of lacertids (black dots) aligned with the axis of divergence between the ancestral and the nigriventris average shapes in *P. muralis* (shown as brown and green squares). The y-axis is the first principal component minus the variation from the rotated axis. To provide examples of the morphologies at the extreme ends of the ancestral-nigriventris axis, we show skull morphologies of selected species (highlighted in bold text).

large-bodied species from the *Timon*, *Gastropholis*, *Gallotia* and *Lacerta* genera, but also the smaller forest dwelling species *Adolphus jacksoni*. Species with extreme values towards the ancestral shape of *P. muralis* possess slender snouts, large dorsally exposed nostrils and large orbits, reminiscent of a previously described pedomorphic appearance in some lacertids (Hipsley & Müller, 2017; Urošević et al., 2013). These species include small-bodied, sand or desert dwelling species (genera *Acanthodactylus*, *Heliobolus*, *Meroles* and *Mesalina*) as well as the tree gliding *Holaspis laevis*. We conclude that the divergence between ancestral and nigriventris phenotypes in *P. muralis* spans an axis that captures variation in skull shape also across lacertid lizards.

Germ layer-associated modularity persists at the macroevolutionary scale

If the contrasting variational properties induced by the dual developmental origin have a persistent effect on diversification beyond the species level, we expect modularity between the mesoderm- and neural crest-derived regions of the skull in lacertids, in agreement with our observations in *P. muralis*. Further, we expect differences between modules in their evolutionary rates and in morphological variation (i.e., disparity). Despite 50–70 million years of adaptive divergence to meet a diversity of functional demands (Čerňanský et al., 2020; Hipsley et al., 2009), patterns of covariation between skull bones are consistent: as for

P. muralis, configurations of mesoderm- and neural crest-derived bones formed statistically supported modules within lacertids (CR = 0.967; $Z = -4.15$; $P = 0.002$). These results suggest that the dual origin of the lacertid skull structures morphological variation at the population level within *P. muralis* as well as in deep evolutionary time, at the level of the lacertid family.

Considering the tempo of evolution for the two modules, we find that the neural crest-derived module shows an overall slower evolutionary rate relative to the mesoderm-derived module ($\sigma^2_{\text{mult neural crest}} = 5.11 \times 10^{-6}$; $\sigma^2_{\text{mult mesoderm}} = 7.95 \times 10^{-6}$; $Z = 11.98$; $P < 0.001$). Consistent with this, phylogenetic signal is higher for the neural crest- relative to the mesoderm-derived module ($Z_{\text{neural crest}} = 28.63$; $Z_{\text{mesoderm}} = 23.73$; pairwise $Z = 28.63$; $P < 0.001$). We also find that the neural crest-derived module overall shows reduced disparity (Procrustes variance, PV, neural crest module: 0.0017; PV mesoderm module: 0.0023; average per-landmark variance: neural crest = 4.32×10^{-5} ; mesoderm = 6.47×10^{-5} ; $t = 3.23$; d.f. = 64.68; $P = 0.002$). Thus, in contrast to the morphological divergence associated with the nigriventris syndrome in *P. muralis*, the neural crest-derived part of the skull shows lower realized evolvability relative to the mesoderm-derived part at the level of the family, both in terms of evolutionary rate and disparity.

Finally, we tested at the landmark-level whether the specific regions of the skull that showed high divergence between ancestral and nigriventris phenotypes in *P. muralis* exhibit particularly high variation and evolutionary rates across species. We found that landmarks describing the largest phenotypic distances between the ancestral and the nigriventris phenotypes in *P. muralis* were indeed associated with higher disparity (i.e., per-landmark variance) within lacertids (Figure 4a, adjusted $R^2 = 0.23$). However, this effect was stronger for landmarks placed on mesoderm- than neural crest-derived bones, as indicated by a tendency for differences between the slope estimates for each type of landmark (slope estimates [95% Confidence Intervals]: $\beta_{\text{neural crest}} = 0.004$ [-0.007; 0.016]; $\beta_{\text{mesoderm}} = 0.015$ [0.006; 0.024]; $t = -1.82$; d.f. = 71; $P = 0.072$). Furthermore, while we observed an overall positive relationship between per-landmark evolutionary rates and their associated phenotypic distances between the ancestral and nigriventris phenotypes (Figure 4b; adjusted $R^2 = 0.18$), comparisons of slopes suggested that this effect was driven by mesoderm-derived bones ($\beta_{\text{neural crest}} > 0.001$ [-0.005; 0.006]; $\beta_{\text{mesoderm}} = 0.006$ [0.002; 0.010]; t-test: d.f. = 71; $t = -2.11$; $P = 0.038$).

Altogether, these results suggest that while the putatively neural crest-derived part of the skull contributed disproportionately to the evolution of the nigriventris syndrome within *P. muralis*, it is less evolvable than the mesoderm-derived part of the skull in lacertids. That the parts of the skull putatively derived from the neural crest are highly conserved but can be associated with rapid phenotypic divergence is supported by the observation that rare and localised shifts in the evolvability of the neural crest-derived module accumulate in the genus *Podarcis* (Figure 5). However, we did not find support for an overall faster rate of skull evolution in *Podarcis* relative to other lacertids ($\sigma^2_{\text{Podarcis}} = 1.25 \times 10^{-6}$; $\sigma^2_{\text{other lacertids}} = 7.24 \times 10^{-6}$; $Z = 0.13$; $P = 0.49$).

Discussion

In this study, we show that the evolution of the lacertid skull reflects the developmental origins of its bones, which arise from either migratory neural crest cells or mesodermal tissue. Skull

shape variation within and among species of lacertid lizards is partitioned into two distinct modules corresponding to these developmental origins. The contributions of each module to phenotypic variation differ across evolutionary time scales. At the microevolutionary level, among common wall lizards, the neural crest-derived module accounts for most of the cranial variation associated with the sexually selected nigriventris syndrome. In contrast, at the level of the family Lacertidae, this same module exhibits lower evolutionary rates and reduced morphological disparity. As discussed below, we propose that these contrasting patterns are consistent with the idea that neural crest cells can enable rapid response to correlational sexual selection by generating covariation of coloration, head morphology and behaviour, but that this pleiotropy also limits its role for the adaptive divergence of skull shape at a macroevolutionary scale.

The capacity of the neural crest to structure morphological variability at the species level has been most extensively explored in relation to the so-called domestication syndrome. Correlated changes in coloration, behaviour and craniofacial morphology observed in domesticated animals have been hypothesized to arise from their shared developmental origin in neural crest cells (Sánchez-Villagra et al., 2016; Wilkins et al., 2014). Evidence remains equivocal regarding the contribution of neural crest cells to variation relevant for the domestication syndrome, and regarding their role in structuring cranial variation as part of the suite of correlated traits (Johnsson et al., 2021; Pendleton et al., 2018; Rubio & Summers, 2022; Wilkins et al., 2021; Le Verger et al., 2024). For example, a study in domesticated chickens reports a lack of modularity among mesoderm- and neural crest-derived bones, although the most variable cranial regions among breeds likely include neural crest-derived bones (Stange et al., 2018). This demonstrates that empirical evidence for or against the neural crest cell hypothesis of the domestication syndrome can be difficult to interpret. In addition, given that signatures of domestication events may have been superseded by subsequent selection for extreme phenotypes (Sánchez-Villagra et al., 2017), the hypothesis may apply more directly to wild populations (Brandon et al., 2023). Our previous work has identified the evolution of the sexually selected nigriventris syndrome in *Podarcis muralis* as a promising case. The nigriventris syndrome can be considered a “reverse” to the domestication syndrome because it involves a similar suite of exaggerated traits. Genomic regions associated with the nigriventris syndrome are enriched for genes with a described function in neural crest cell regulation (Feiner et al., 2024), and coloration, morphology and behaviour remain integrated during introgression into a distantly related lineage (Feiner et al., 2024; While et al., 2015). Here, we report that the neural crest-derived module contributed more to the divergence in skull shape between ancestral and nigriventris phenotypes than the mesoderm derived module. This finding supports the hypothesis that the neural crest plays a pivotal role in the evolution of the nigriventris syndrome and provides evidence that morphological variation generated by neural crest cells can shape evolutionary trajectories in natural populations.

Our finding of conserved modularity between mesoderm- and neural crest-derived bones across lacertids as well as within *P. muralis* is broadly consistent with the conserved patterns of modularity between the rostrum and the posterior cranium at multiple levels (during ontogeny, within species, and across species) reported in the same family by a different study (Lacertidae; Urošević et al., 2019). In contrast, patterns of modularity in skulls appear to be highly variable between different species of Anolis lizards, even though most of the morphological variation

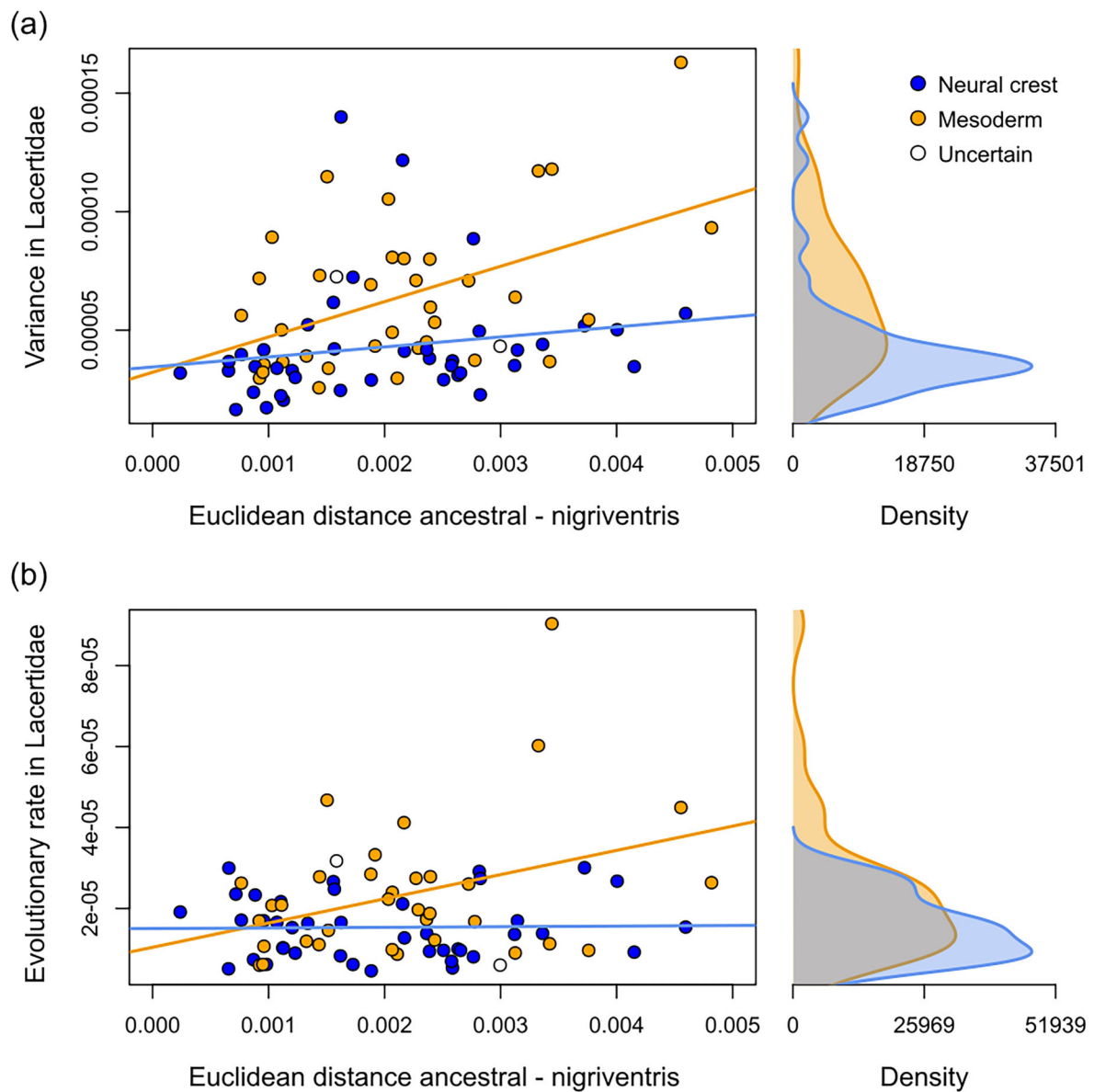


Figure 4. Relationship between per-landmark magnitude of change in the nigriventris phenotype and the variation at the macroevolutionary level. Kernel densities of variances and evolutionary rates of the two types of landmarks are shown on the right insets. (a) Per-landmark Euclidean distances between the ancestral versus nigriventris groups over per-landmark variances in lacertids (adjusted $R^2 = 0.22$). (b) Per-landmark Euclidean distances between the ancestral vs nigriventris groups over per-landmark evolutionary rates in lacertids (adjusted $R^2 = 0.18$).

is concentrated in the rostral part of the skull, and hence in putatively neural crest-derived bones (Sanger et al., 2012). Cranial modularity has been proposed to be an intrinsic determinant of evolvability, for example explaining patterns of adaptive radiation of Hawaiian honeycreepers and Darwin's finches (Tokita et al., 2017). However, how modularity relates to evolvability, especially with regards to the relative evolutionary rates of modules, is difficult to establish because phenotypic diversification is not simply a function of evolutionary rate (Felice et al., 2018; Starr et al., 2024). In placental mammals for example, mesoderm-derived bones are as prone as neural crest-derived bones to generate disparity despite their slower evolution (Goswami et al., 2023). Here we report slower evolutionary rates, reduced disparity and stronger phylogenetic signal for a neural-crest derived module across lacertids, which is opposite to the patterns described in placental mammals and birds (Felice & Goswami, 2018; Goswami et al., 2023). Furthermore, the neural crest-derived landmarks

that contributed most significantly to the nigriventris syndrome did not exhibit accelerated rates of evolution, indicating that the neural crest-derived module does not contribute disproportionately to skull shape diversification at a broader phylogenetic scale. That our results contrast with the patterns observed in other clades, and differ between micro- and macroevolutionary scales within lacertid lizards, indicates that even though development structures variability, the realised variation within each portion of the skull can be complex to predict.

A possible explanation for the greater importance of the mesoderm in the diversification of the lacertid skull is that functional morphology related to feeding performance and ecological specialization could depend more heavily on mesoderm-derived skeletal elements. However, this idea is not supported by studies on *Podarcis melisellensis* showing that the shapes of several neural crest-derived bones (e.g., pterygoid, jugal, premaxilla) covary with diet and bite force (Taverne et al., 2021).

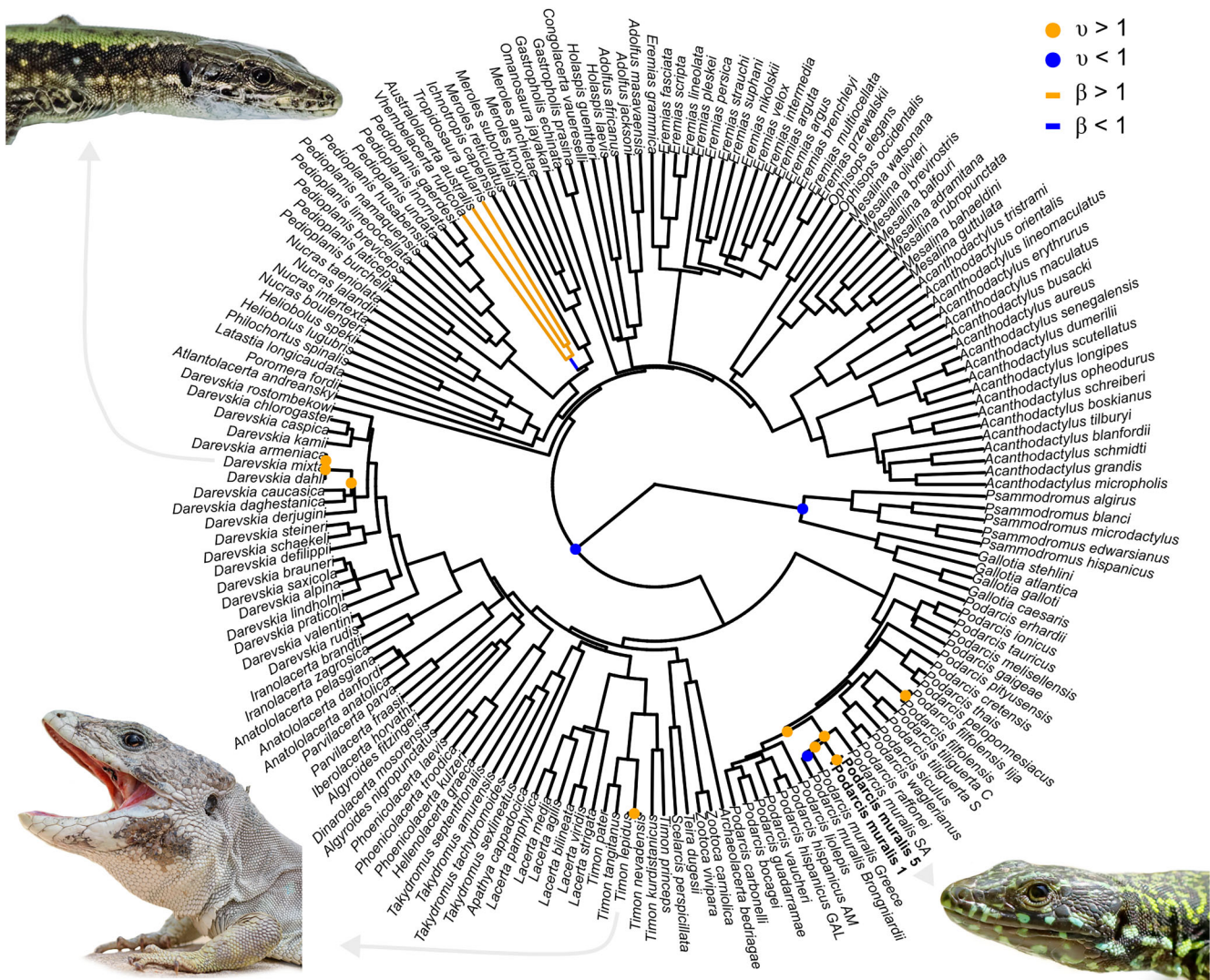


Figure 5. Shifts in evolvability of the neural crest-derived part of the skull across the phylogeny of lacertids. Shifts in evolvability (v) and in selection (β) were obtained with phylogenetic modelling (Fabric model), using the first five principal components of the phylomorphospace of the landmarks placed on the putative neural crest-derived bones. Only the shifts with posterior probability > 0.8 are shown. The Central Italy lineage of *P. muralis* features two tips, one for each average shape of the nigriventris scores 1 (ancestral phenotype) and 5 (most pronounced nigriventris phenotype). Insets show representative males of species within clades where shifts in evolvability occur. Photographs by Giorgi Iankoshvili (*D. mixta*), Pedro Luna Guillen (*T. nevadensis*) and Quentín Horta-Lacueva (*P. muralis*, nigriventris phenotype).

Stronger and bigger head muscles were described as being associated with shorter snouts as well as taller skulls, likely from the increased curvature of the pterygoid, a neural crest-derived bone (Taverne et al., 2021). Furthermore, skull kinesis in lizards requires articulated movements between bones of both mesoderm and neural crest origins (Gans et al., 2008), suggesting that biomechanical factors may play a limited role in explaining germ layer-associated differences in skull diversification. Instead, the mesoderm-derived part of the skull may show greater evolvability since several of these bones ossify relatively late in ontogeny (Barahona & Barbadiillo, 1998). Late ossification has been proposed to explain the evolution of more prominent posterior parts of the skull in males of *Podarcis bocagei* and *P. carbonelli* (Kaliontzopoulou et al., 2008), and might confer higher variability to the mesoderm-derived part of the skull across lacertids.

The lower disparity observed in neural crest-derived regions across lacertid lizards may give the impression that the rapid cranial divergence associated with the nigriventris syndrome reflects a release from developmental constraint within *P. mu-*

ralis. However, we suggest that developmental linkage induced by the biology of neural crest cells instead facilitates coordinated changes in head morphology, coloration, and behaviour in response to correlational sexual selection (for a discussion on the relationship between covariation and responses to correlational selection, see Rossoni et al., 2024). In *P. muralis*, this is supported by evidence of selection acting on multiple sexually selected traits (e.g., coloration and relative head size; MacGregor et al., 2017b; While et al., 2015), many of which partially originate from the neural crest (Feiner et al., 2024). Cranial adaptations reflecting ecology and diet might primarily involve the mesoderm-derived module if this region is more readily modified without affecting other traits, thereby driving the ecological specialization that is responsible for much of the diversity of lacertid skull shape. Yet, the axis of divergence associated with the nigriventris phenotype does align with one of the major directions of morphological variation in lacertids. Moreover, the skull regions contributing most to the evolution of the nigriventris syndrome also exhibit elevated variability and evolutionary rates across

species. This suggests that the nigriventris phenotype evolved along a major axis of cranial variation shared within lacertids, with sexual selection acting as a key driver of morphological divergence along this axis. Consistent with this view, we find that shifts in evolvability of neural crest-derived regions appear to have occurred independently in other lacertid lineages: in other *Podarcis* species, in *Timon* species with pronounced sexual dimorphism (*T. nevadensis*), and in *Darevskia*, which includes parthenogenetic, all-female species (Freitas et al., 2022; see Barateli et al., 2024 on parthenogenesis and head shape in *Darevskia*). Together, these patterns suggest that changes in correlational sexual selection may repeatedly shape the evolvability of neural crest-derived traits across lacertids. Future comparative studies including both sexes or a measure of sexual dimorphism may shed light on the interplay between sexual and natural selection in shaping covariation of skull shape with other neural crest-derived features (e.g., Sanger et al., 2013).

The contrasting modular patterns of skull variation across evolutionary levels provide insights on the relationship between population-level trait variabilities and long-term evolutionary trends. This pattern resonates with inconsistencies between evolutionary scales in head shape divergence and the effects of sexual selection reported in another wall lizard species, *P. pityusensis* (Woodgate et al., 2025). Yet, across the tree of life, macroevolution seems to be predictable from for patterns of traits covariation (Holstad et al., 2024; Houle et al., 2017; Rohner & Berger, 2025; Schluter, 2024; Tsuboi et al., 2024). While the consistency of correlational structures imposed by the dual developmental origin of the skull supports this view, our results illustrate why a persistent developmental bias need not result in alignment between major axes of variation within and among species.

Methods

Data collection

We studied skull morphology using high-resolution, μ CT scans of the skulls of 263 ethanol-preserved specimens. Scanning was performed on SkyScan1173 and FF20 CT—Comet Yxlon scanners (voxel sizes 7.45–28.04 μ m), image stacks were reconstructed with NRecon and CERA, the resulting volumes were segmented with manual thresholding and editing tools before being converted to meshes, and decimated using 3D Slicer (Fedorov et al., 2012) and SlicerMorph (Rolfe et al., 2021). When overly rugged surfaces were observed by visual inspection, surfaces were smoothed.

The data contained two subsets of specimens dedicated to micro- and macroevolutionary questions. One subset contained 62 adult male *Podarcis muralis* (the “microevolutionary data”). Despite that the nigriventris syndrome is under sexual selection caused by male-male competition (MacGregor et al., 2017b), females also express the same suite of traits (Feiner et al., 2024; While et al., 2015). To facilitate comparisons with the macroevolutionary dataset, we restricted our comparison of ancestral versus nigriventris phenotypes to males. The specimens belonged to the Central Italy lineage, in which the nigriventris phenotype originated (Yang et al., 2018, 2020, 2022). The *P. muralis* specimens belonged to collections from Museum Koenig Bonn ($n = 30$) and Natural History Museum Vienna ($n = 8$), and from captive maintenance of wild-caught individuals at Lund University (Feiner et al., 2024; Pranter & Feiner, 2025) ($n = 24$). The expression of the nigriventris syndrome could not be

quantified directly on museum specimens because the ethanol-preservation alters pigmentation. Therefore, we attributed an ordinal score to every specimen by reporting their capture locality to the map of the gradient of green dorsal coloration established in previous studies (MacGregor et al., 2017a; Ruiz Miñano et al., 2021) as a proxy for the nigriventris phenotype (Figure S2). We defined as “ancestral” the populations that did not express the nigriventris syndrome, generating a nigriventris score ranging from 1 (no exaggerated trait, “ancestral” phenotype) to 5 (most extreme values of the syndrome of exaggerated traits, typical “nigriventris” phenotype).

The other subset contained one specimen for each of 174 species and major lineages with unresolved taxonomic status from the family Lacertidae (the “macroevolutionary data,” ~44% of the described species, 42 of the 43 genera, the genus with the single species *Dalmatolacerta oxycephala* missing). We considered as major lineages: the Corsican and Sardinian lineages of *Podarcis tiliguerta* (Salvi et al., 2017), three lineages of *Podarcis muralis* described as “Southern Alps,” “Southern Balkan” and “Western Europe” (Yang et al., 2022), two lineages of *P. filfolensis* from Malta and Linosa (Salvi et al., 2014), and the “Galera” and “Albacete/Murcia” lineages of *P. hispanicus* (Kaliontzopoulou et al., 2011; Yang et al., 2021). All specimens were males except for three parthenogenetic, female-only species (*Darevskia rostombekowi*, *D. armeniaca* and *D. dahl*).

For the macroevolutionary dataset, we generated μ CT scans of 147 specimens, to which we added 25 previously scanned specimens from Hipsley and Müller (Hipsley & Müller, 2017) and two scanned specimens from MorphoSource (UF: Herp:130038 ark:/87602/m4/486159; UF: Herp:91747 ark:/87602/m4/604781).

The phylogenetic analyses relied on the ultrametric tree from Title and colleagues (Title et al., 2024). We used *phytools* (Revell, 2012) to preprocess the phylogenetic data and append the tree with additional species or major lineages according to the divergence times given in the following references: *Acanthodactylus erythrurus lineomaculatus* (Rancilhac et al., 2023), *Eremias fasciata* (Orlova et al., 2023), *Gastropholis echinata* (Tonini et al., 2016), *P. thais* (Kiourtsoglou et al., 2021), *P. ionicus* (Psonis et al., 2021), *Zootoca carniolica* (Cornetti et al., 2015) and the major lineages of *P. filfolensis*, *P. hispanicus*, *P. muralis* and *P. tiliguerta* (Salvi et al., 2014).

Geometric morphometrics

We digitized 77 landmarks on the right side of skull models of every specimen with the Markups module in 3D Slicer 5.2.1. (Fedorov et al., 2012). In cases where bones were deformed or broken, we mirrored the model and digitized what was originally the left side. The landmark data were imported into R with SlicerMorphR (Rolfe et al., 2021). All landmark configurations were then superimposed to a common coordinate system through Generalised Procrustes Analyses (GPA) in *geomorph* (Adams & Otárola-Castillo, 2013; Adams et al., 2013). We conducted the GPA after producing two-sided landmark configurations by mirroring the right-side to avoid inflated landmark variations along the midline (Bardua et al., 2019). The artificially produced left-side was discarded after the GPA, and the analyses were conducted on the aligned configuration of the original side.

Microevolution 1: shape changes in *P. muralis* as part of the nigriventris syndrome

We first tested for differences in skull shape within *P. muralis* based on ordinal scores for the nigriventris syndrome. We performed np-MANCOVA using Randomized Residual Permutation

Procedure (RRPP) with 10 000 permutations and type I sum of squares (Adams & Otárola-Castillo, 2013). We accounted for the effects of the extended periods of captivity, centroid size, and for potential variation in allometry among ordinal categories by adding fixed effect in sequential order as in the full model:

Coordinates \sim captivity + log (Centroid size) \times nigriventris score

Although our main model suggested unique allometries among groups (Table 1), pairwise comparisons returned statistical support for allometric differences only between the ancestral group and the three groups of intermediate categories (Table S2). We therefore considered it appropriate to use size-regressed residuals of shape changes for downstream analyses of differences between the ancestral versus nigriventris phenotype.

Finally, we studied the patterns of shape changes among ordinal categories of the nigriventris syndrome by conducting Canonical Variate Analyses (CVA) adapted to multidimensional data, using *Morpho* (Schlager, 2017). We visualized the 3D changes in landmark configuration along the covariate axes as a deformation of the cubic grid (thin-plate spline interpolation) and as displacement of the average locations of landmarks between groups, using *Morpho* and *rgl* (Adler et al., 2020).

Microevolution 2: importance of the neural crest in the nigriventris-associated shape variation

We tested whether variational properties of putative neural crest-derived bones (NC) relative to mesoderm-derived bones (MES) explained the skull shape changes observed in *P. muralis*. Given that our aim was to test the support for this a priori hypothesis of modularity, we did not investigate other patterns of modularity related to other functional or developmental properties of the skull. We proceeded in two steps, as follows. First, we conducted modularity analyses to test for separate patterns of shape variation related to either tissue type. We partitioned the landmark data into two subsets according to their germ layer of origin: NC bones (40 landmarks) and MES bones (35 landmarks). We attributed a NC or MES origin to each bone by relying on fate-maps produced in mouse, chicken, axolotl and *Xenopus* (synthesised in Maddin et al., 2016; Piekarski et al., 2014). While the developmental origins of most bones appear to be conserved across tetrapods, the status of some bones remains contentious in specific clades, as for example the parietal bone in birds (Teng et al., 2019). Therefore, we referred to paleontological and comparative studies establishing homology across tetrapod groups to verify the conserved state of bones in lacertids (Fabbri et al., 2017; Smith-Paredes et al., 2018). The status of the squamosal bone could not be ascertained from sources, and we therefore designated the two landmarks placed on it as “uncertain.” We evaluated modularity between the two sets of landmarks with Covariance Ratio (CR) coefficients (Adams & Collyer, 2016).

Since we observe modularity between neural crest- and mesoderm-derived bones (see Results), we tested whether the NC module explained shape changes associated with the nigriventris syndrome. We proceeded by reanalysing head shape variations based on ordinal scores with RRPP MANCOVA (see Microevolution 1), this time only considering the landmark either from the NC or from the MES module. We performed pairwise group comparisons between the two most extreme ordinal categories (“ancestral” or “nigriventris”) and assessed the effect size and significance of the differences between groups for each module.

Macroevolution 1: importance of the neural crest in the evolution of lacertids

We tested for modularity in lacertids by estimating Covariance Ratio coefficients (CR) between the NC and MES modules that were defined on the same subset of landmarks as for *P. muralis*. Furthermore, we tested for differences in phylogenetic signal, evolutionary rates and disparity between the two modules by comparing Z estimates (Collyer et al., 2022) and multivariate evolutionary rate ratios R (Denton & Adams, 2015), respectively.

We visualized morphological diversity in lacertids in relation to the nigriventris phenotype by rotating the phylomorphospace (rigid rotation) along the vector describing shape changes between the two extreme (1 and 5) ordinal nigriventris categories in *P. muralis*. To test whether the anatomical regions responsible for shape changes for the nigriventris syndrome in *P. muralis* were responsible for higher variation and evolutionary rates in lacertids, we estimated the magnitude of landmark location changes associated with the nigriventris syndrome by calculating the Euclidean distances of each homologous pair of landmarks between the mean landmark configuration of the “ancestral” (Ordinal score 1) and the “nigriventris” group (Ordinal score 5) in the *P. muralis* data. We evaluated per-landmark variances and per-landmark evolutionary rates in lacertids by following Fabre and colleagues (Fabre et al., 2020). Finally, we assessed the effect of the NC and the MES origin in the relationship between per-landmark effect sizes in the nigriventris phenotype and per-landmark variances or evolutionary rates in lacertids by using linear regressions. Note that highly influential landmarks had little effect on these results (e.g., Cook’s distances of all landmarks were below 1, and the removal of a landmark with relatively high Cook’s distance did not change the results of either regression).

We investigated the possibility of shifts in evolvability in the NC by performing phylogenetic modelling with the Fabric model in BayesTrait (Pagel et al., 2022). For the NC and MES modules, we used the first five and four principal components of the phylomorphospace as shape variables (the subsequent components individually explained 4% of the variance or less), which described 57.8% and 65.9% of the total variation, respectively. Model convergence was assessed by visually inspecting trace plots for adequate mixing and stationarity, and by examining posterior density plots to ensure consistent and unimodal distributions.

Supplementary material

Supplementary material is available online at [Evolution Letters](#).

Data and code availability

Landmark data, skull models, metadata and scripts are available on Zenodo, <https://doi.org/10.5281/zenodo.15855204>.

Author contributions

Q.H., N.F., T.U. designed the research; Q.H. performed the research; Q.H. performed the analyses; Q.H., N.F., T.U. interpreted the data; Q.H., N.F., T.U. wrote the paper; C.H., M.G., M.F., J.M., M.K. contributed data; C.H., M.G., M.F., J.M. critically revised the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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