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RESEARCH ARTICLE

Bite Force Performance from wild Derived mice has Undetectable Heritability Despite Having Heritable Morphological Components

Samuel Ginot[1,3] · **Benedikt Hallgrímsson**[2] · **Sylvie Agret**[1] · **Julien Claude**[1,4]

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Abstract

Fitness-related traits tend to have low heritabilities. Conversely, morphology tends to be highly heritable. Yet, many fitness-related performance traits such as running speed or bite force depend critically on morphology. Craniofacial morphology correlates with bite performance in several groups including rodents. However, within species, this relationship is less clear, and the genetics of performance, morphology and function are rarely analyzed in combination. Here, we use a half-sib design in outbred wild-derived *Mus musculus* to study the morphology-bite force relationship and determine whether there is additive genetic (co-)variance for these traits. Results suggest that bite force has undetectable additive genetic variance and heritability in this sample, while morphological traits related mechanically to bite force exhibit varying levels of heritability. The most heritable traits include the length of the mandible which relates to bite force. Despite its correlation with morphology, realized bite force was not heritable, which suggests it is less responsive to selection in comparison to its morphological determinants. We explain this paradox with a non-additive, many-to-one mapping hypothesis of heritable change in complex traits. We furthermore propose that performance traits could evolve if pleiotropic relationships among the determining traits are modified.

Keywords Quantitative genetics · performance · Rodentia · geometric morphometrics · half-sib design

Introduction

It is generally assumed that the morphology of the musculoskeletal systems evolves in response to selection on performance (Herrel et al., 2005; Van Daele et al., 2008; Becerra et al., 2011; Ginot et al., 2017, 2019; Aerts et al., 2000; Vanhooydonck & Van Damme, 2001). For this to occur, morphological variation must covary with performance (Arnold, 1983). For appendicular traits, relevant measures of performance might be speed (Blumstein et al., 2010, Zamora et al. 2014), endurance (Vanhooydonck et al., 2001) or range and durations of positional behaviors (Bezanson, 2017). For the morphology of the face and, in particular, the rodent skull, bite force is the performance measure most commonly thought to be relevant to fitness. Among species of mammals, bite force covaries with craniofacial morphology (Aguirre et al., 2002; Herrel et al., 2008; Freeman & Lemen, 2008; Van Daele et al., 2008; Becerra et al., 2011), presumably due, at least in part, to the morphological response to selection on this key performance parameter. Within species, however, the relationship between craniofacial morphology and bite force performance is often less clear (e.g. Herrel et al., 2005, Van Daele et al., 2008, Becerra et al., 2011, Ginot et al., 2017) and even more so within age-cohorts of a population (Van Daele et al., 2008; Becerra et al., 2011; Ginot et al., 2017, 2020). These results suggest that bite force is a multi-factorial trait, and that intra-specific variation in bite force is not only due to variation in morphology, but also depends on behavioural or environmental variation.

For performance traits such as bite force to evolve, they must be heritable. Theory and quantitative genetics studies in the wild or in controlled conditions tend to show that

✉ Samuel Ginot
samuel.ginot@umontpellier.fr

1 Institut des Sciences de l'Evolution, Université de Montpellier, Montpellier, France

2 Dept of Cell Biology & Anatomy, Cumming School of Medicine Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Canada

3 Institut für Evolutionsbiologie und Ökologie, Universität Bonn, Bonn, Germany

4 Faculty of Science, Chulalongkorn University, 254 Phaya Thai Rd, Wang Mai, Pathum Wan, Bangkok 10330, Thailand

morphological traits, which can influence fitness *via* their impact on other traits (Arnold, 1983), are more heritable than traits with a direct impact on fitness (e.g. life-history, behavioural, performance traits, often gathered under the umbrella term "fitness-related traits"; Mousseau & Roff 1987, Houle, 1992, Hansen et al., 2011, Hoffmann et al. 2016), and more heritable than fitness itself (Shaw & Shaw, 2014). The low heritability of fitness-related traits is often explained through Fisher's (1958) theorem of natural selection, which states that fitness and fitness-related traits will have lower additive genetic variance because they are under stronger stabilizing selection than other traits (Mousseau & Roff, 1987), reducing genetic variation, and possibly increasing canalization, to ensure sufficient performance for survival. However, Houle (1992) also proposed that low heritabilities in fitness-related traits compared to morphological traits might be due to larger amounts of non-additive genetic and residual variation, including environmental variation, but also noise, which is generally larger in fitness-related traits (for bite force it has been shown that temperature can strongly impact in vivo measures, but on the other hand that they are also highly repeatable within individuals; Anderson et al., 2008). These two non-exclusive views have different evolutionary implications because a trait with low additive genetic variance (even with low non-additive and environmental variance) will be less easily evolvable than one with high additive genetic variance (Houle, 1992, Hoffmann et al. 2016). Therefore, Houle (1992) proposed that quantitative genetics studies should always report the partitioning of variance of a trait between the additive genetic and other effects rather than to report only the heritability, and Hansen et al., (2011) argued that heritability should not be seen as a measure of evolutionary potential, as the implied total-variance standardization may hide the actual amount of additive genetic variance.

Numerous studies have documented links between morphological variation and performance (endurance, speed, bite force) with the aim of better understanding the functional relationship between phenotype and fitness (e.g. Herrel et al., 2005, Van Daele et al., 2008, Becerra et al., 2011, Ginot et al., 2017, Aerts et al., 2000, Vanhooydonck & Van Damme, 2001). However, these studies rarely include quantitative genetic analyses because it requires phenotyping both morphological traits and performance within a controlled pedigree context. These studies are practically non-existent for wild or wild derived populations of mammals, with the recent exception of a study on skull morphology and bite force in mouse lemurs (Zablocki et al., 2021; see also Garland 1988, Tsuji et al., 1989, Noble et al. 2014 for studies of morphology and running performance heritability in lizards and snakes). Selection should act on performance, driving morphological change (Arnold, 1983). Therefore, heritable variation and covariation between both is expected, a result supported by Zablocki-Thomas et al., (2021). Since morphology, function and performance are related, using quantitative genetic approaches may help reconcile their differential heritabilities, and better understand their co-evolution at the inter-specific scale.

This study therefore has two objectives: (i) identifying the morphological characters that relate to bite force in our population of lab mice; (ii) quantifying the heritability and importance of the additive genetic, dominance, and environmental variation in in vivo bite force and skull morphology (size, shape and morpho-functional traits). Based on previous studies and theory, we expect that (i) skull size and cranio-mandibular morphology should be correlated with bite force, (ii) bite force should be less heritable than morphological characters.

Materials and Methods

Specimens

All mice (*Mus musculus*) used in this study are from a colony of mice bred in the lab from wild ancestors captured on Mainland, the biggest of the Orkney Islands (Scotland). Mice in the Orkney archipelago are known to represent a specific haplogroup, and within Mainland have been shown to represent geographically isolated populations with neutral genetic divergence (Chevret et al., 2021), The individuals used in this study are all from the first to fifth generation after the colony was founded, therefore it is expected that despite being raised in the lab, they should be more representative of a natural population than laboratory strains which have undergone strong artificial selection. A half-sib design pedigree in which each father was bred with three different and unrelated females was produced. It was ensured that offspring were outbred by crossing individuals from geographically distant descent (i.e. different populations). In total, we used 18 fathers ("sires") that reproduced with 54 mothers ("dams"), and gave birth to 336 offspring. Litter sizes varied among families from 3 to 10 pups, with a mean of 6.2 pups. The number of specimens was limited by the wild origin of the colony, the need to cross genetically unrelated individuals, and the ethical necessities of raising vertebrate animals in refined conditions, and to reduce the number of specimens killed. Animals were treated in accordance with the guidelines of the American Society of Mammalogists, and within the European Union legislation guidelines (Directive 86/609/EEC and 2010/63/UE). All lab procedures were carried out under approval no. A34-172-042 (DDPP Hérault Prefecture).

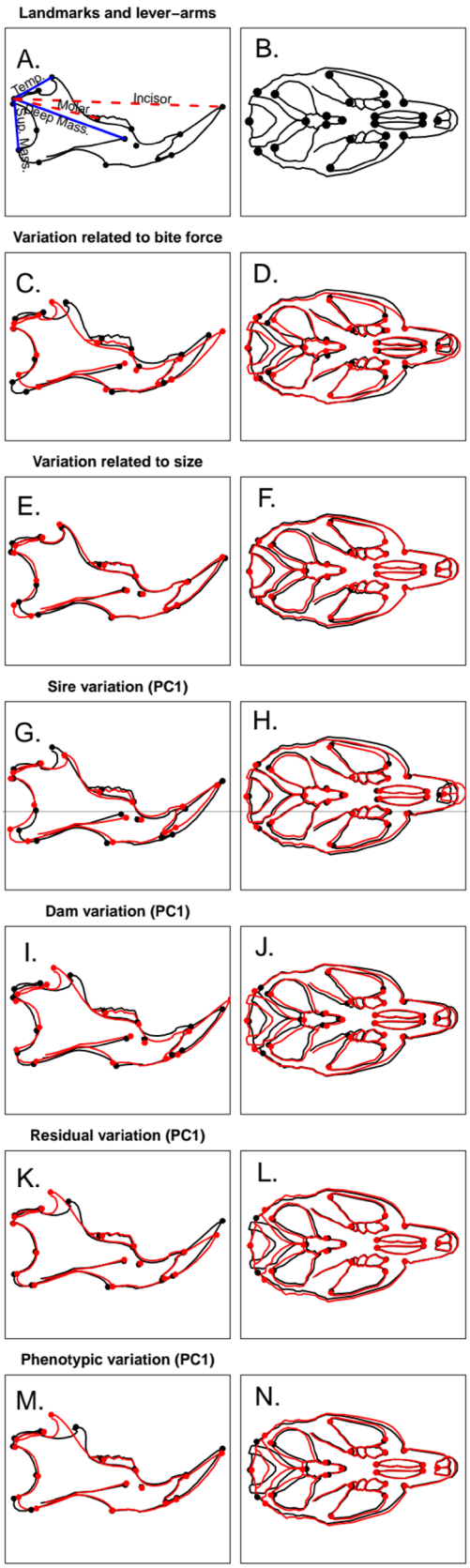


Fig. 1 **A** Mouse mandible outline in lateral view showing homologous landmarks and linear measurements corresponding to the lever arms studied here. Solid blue lines represent in-levers for the temporal (Temp.), deep masseter (Deep Mass.), and superficial masseter (Sup. Mass.); dashed red lines represent out-levers at the incisor or at the molar. **B** Mouse cranium outline in palatal view showing homologous landmarks used in this study. **C–D** Patterns of cranial and mandibular shape variation related to bite force obtained by projecting measured bite forces on a multivariate linear regression of shape on bite force. Black and red shapes respectively represent maximal and minimal deformations, amplified five times for better visualization. **E–F** Allometric (i.e. size-related) shape variation. **G–N** Patterns of cranial and mandibular shape variation. Black and red shapes respectively represent maximal and minimal deformations for the first principal component of variation, but note that the orientation of the axes is arbitrary and therefore not necessarily the same across components. Sire variation (**G–H**) corresponds to the heritable component of phenotypic variation. Dam variation (**I–J**) corresponds to the maternal (i.e. dominance and common nest) and heritable component of variation. Residual variation (**K–L**) corresponds to the residual individual variation including environmental variation. Phenotypic variation (**M–N**) corresponds to the total shape variation

Bite Force Measurements

Bite force measurements were performed when the offspring were strictly 68 days old, at which stage adult performance and morphology are acquired (Ginot et al., 2020). This allowed us to restrict bite force variation due to age, size, and allometric differences. All in vivo bite force data were recorded in Newtons (N) at the incisors using a Kistler force transducer linked to a charge amplifier, similar to the set-up presented in Herrel et al., (1999) and Aguirre et al., (2002). We performed three consecutive trials for each animal. The maximal bite force recorded across the three trials was retained and used in subsequent analyses. The mice were then euthanized by CO_2 inhalation. We also measured the parents' bite force in the same fashion, although their age varied.

Morphometric data

Using the software TPSDig2.0 (Rohlf, 2010), 24 landmarks were digitized on the crania of the parents and offspring in palatal view, and 16 landmarks on the mandibles in lateral jugal view (Fig. 1A–B). All coordinate data were imported into the R programming language (R Core Team 2015) and the shapes were centered and Procrustes superimposed using functions from Claude (2008). We also computed centroid sizes for the mandibles and crania.

In addition to these geometric morphometric data, we also used our landmarks to calculate univariate functional distances on the mandible (Fig. 1A). These traits represent in-lever lengths for three of the adductor muscles (temporal, deep masseter, and superficial masseter), and out-lever lengths at the molar and incisor. Using these lengths, we calculated the mechanical advantage (MA) for the various

levers for each individual as MA = In-lever length/Out-lever length (Radinsky, 1981). Phenotypic correlation matrices were computed for these functional traits, weight, and bite force using Pearson's product-moment correlation.

Bite force-related global shape variation was modelled using a multivariate regression of shape on bite force. Using the 'predict' function, modelled shapes were reconstructed, and individuals with the maximum and minimum bite force recorded were used to represent extreme cranium or mandible shape variation related to bite force. The differences being fairly small, they were amplified to be visible graphically.

Quantitative Genetics Analyses

Using in vivo bite force and selected univariate morphometric measurements (centroid sizes, in-lever and out-lever lengths, mechanical advantages), we calculated one parent-offspring regressions for the mother (dam) and father (sire) separately. We also tested for differences between male and female offsprings using Welch's t tests, and within the linear regression models by using sex of the offspring as an explanatory variable. Mother-offspring regressions tend to overestimate heritabilities because they include maternal effects, which is not the case with father-offspring regressions. This allowed us to get a first estimate of narrow-sense heritability ($h^2 = 2$*slope; Falconer 1989), with associated 95% confidence intervals computed from the standard error and degrees of freedom for the slope. Parent-offspring regressions suffer from several biases, notably because the parents are of variable ages, which can produce morphological, body condition and performance differences (however, previous results in the same mice colony suggest these changes are limited; Ginot et al., 2020), as well as individual condition differences. Furthermore, parent-offspring regressions do not allow to easily partition the variance between additive genetic (V_A) *versus* other effects. To achieve this, we used a mixed effect model, with the 'mmer' function from package sommer in R (Covarrubias-Pazaran, 2016). For each trait (centered but not scaled) we computed mixed models of the trait with sire and dam as random effects. This allowed us to partition the phenotypic variance (V_P) of our traits into a sire component ($\sigma^2_{sires} = 1/4*V_A$), a dam component ($\sigma^2_{dams} = 1/4*V_A + 1/4*V_D + V_{EC}$), and residual component ($\sigma^2_{residual} = 1/2*V_A + 3/4*V_D + V_{EW}$). V_A is the additive genetic variance, V_D the dominance variance, V_{EC} being the common environmental variance of full sibs and V_{EW} the environmental variance within a litter. We then calculated heritability as follows: $h^2 = \frac{V_A}{V_P} = \frac{4\times\sigma^2_{sires}}{\sigma^2_{sires}+\sigma^2_{dams}+\sigma^2_{residual}}$ (Falconer, 1989). For additive genetic variance estimates (mmer mixed models), we computed confidence intervals by jackknifing sires of our sample and taking the 0.975 and 0.025 quantiles of the computed pseudo-values. These quantile values were then passed into the heritability formula to obtain confidence intervals for mixed model heritability. This allowed us to assess whether the number of sires used in the study was large enough to actually obtain heritability estimates with some degree of confidence. If confidence intervals for heritabilities all included 0, then our sample clearly would not allow us to detect any heritable variation. We also calculated the evolvability of the same traits as: $I_A = \frac{V_A}{\bar{X}^2}$(Houle, 1992), where X bar is the mean of the trait studied.

Variance-covariance and Correlation Matrices Between Traits

Still using the 'mmer' function, we computed sire, dam and residual covariance estimates between pairs of traits, with two traits as the dependent variables and again sire and dam as random factors. We combined these with the variances previously computed to obtain variance-covariance matrices for the chosen linear traits and for cranium and mandible shape. Total phenotypic, additive genetic (sire), dam and residual components of mandible shape, cranium shape and morpho-functional traits were thereby obtained. When possible (i.e. when trait additive genetic variance were significantly different from 0), correlation matrices were computed from the variance-covariance matrices. For the sire variance-covariance matrix, many correlations between pairs of traits were outside the [−1, 1] range, due to error in variance of covariance estimates which sometimes produced covariance larger than standard deviation products. Based on the variance-covariance matrices for shape, we computed a multivariate heritability estimate, following Monteiro et al., (2002). This index consists in dividing the sum of the diagonal values of the additive genetic variance-covariance matrix by the sum of the diagonal of the total phenotypic variance-covariance matrix, and dividing by 0.25 for half-sib designs. This index is given for providing a general idea of shape heritability but we are aware of potential biases as Klingenberg & Monteiro (2005) have raised issues with this estimate when matrices are not isotropic; something that was likely the case here due to unsolvability of some of our variance-covariance matrices. In consequence, results for multivariate heritability and correlations between matrices are reported as Supplementary Information for disclosure, but should be taken cautiously. Finally, we graphically represented the first principal components of shape variation by projecting the original superimposed coordinates on the variance-covariance matrices (sire, dam,

residual, size-related and global phenotypic) to identify whether major axes of additive genetic (sire) and other variation might relate with bite force-related morphological variation.

Results

Phenotypic Correlations Between bite Force and Morphology

Bite force is correlated with centroid size as well as shape of both the mandible and the cranium (Fig. 1C–D, SI Fig. 1). Higher bite force is related to more anteriorly positioned coronoid process (temporal muscular insertion), more posteriorly developed angular process (superficial masseter and pterygoid muscular insertion), shorter and higher mandible (i.e. more 'robust' morphologies) (Fig. 1C). In the cranium, variation related to bite force was less conspicuous, with higher bite force related to slightly shorter and wider crania with larger zygomatic arches and fossa (Fig. 1D). It appears that only some of the shape changes related to bite force are also related to size-related shape changes (i.e. allometric variation): the allometric shape changes in the mandible affect the angular and condylar processes, but not the coronoid and incisor region (Fig. 1E); while allometric shape changes in the cranium notably affect the width of the zygomatic region (Fig. 1F). Some lever arms and mechanical advantages of the mandible are also correlated with bite force (SI Fig. 1). These are the in-lever of the superficial masseter (related to posteriorly and ventrally positioned angular process), the mechanical advantages for the superficial masseter/incisor, the temporal/incisor (related to the position of coronoid process), and the temporal/molar levers, and negatively related to the incisor out-lever (e.g. length of the mandible from the condylar process to the tip of incisors, Fig. 1A, SI Fig. 1).

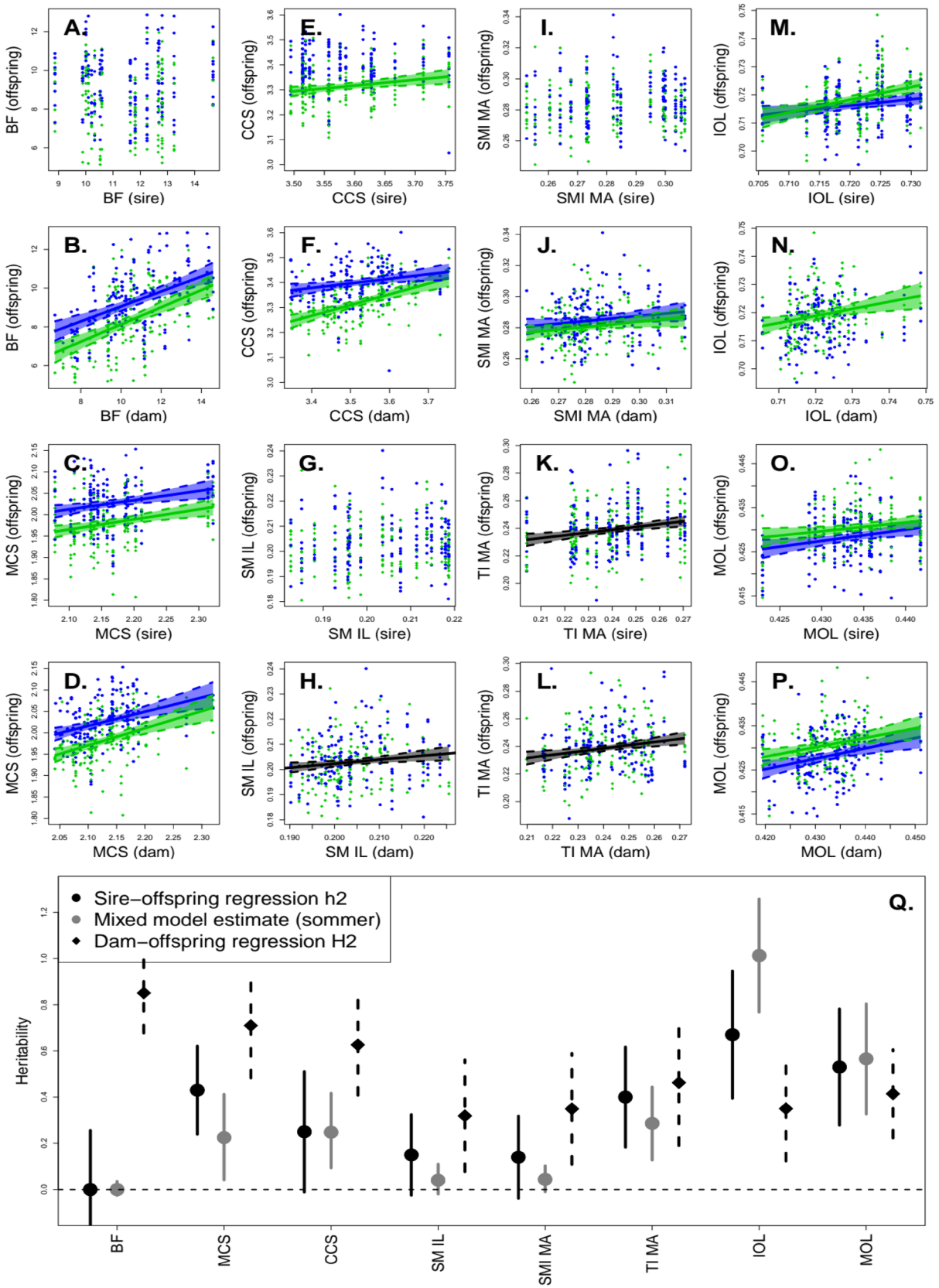
From these results, a subset of univariate traits was chosen for which we obtained additive genetic variance, heritability estimates and genetic correlation when it was possible: bite force, centroid size (cranium and mandible), superficial masseter in-lever length, superficial masseter/incisor mechanical advantage, temporal/incisor mechanical advantage, and out-lever lengths.

Parent-offspring Regressions

Parent-offspring regressions for the selected characters (Fig. 2) revealed differences between father (sire) and mother (dam) regressions (Table 1). Father-offspring regressions suggested significant ($p < 0.05$) heritable variation for cranium and mandible centroid size ($h^2 = 0.25$ and $h^2 = 0.43$ respectively, Fig. 2C, E and Q). The heritability of the temporal/incisor mechanical advantage is 0.4, 0.67 for the incisor out-lever length and 0.51 for the molar out-lever length (Fig. 2K, M, O and Q, Table 1). However, the slopes were not significant for bite force and for the superficial masseter in-lever and mechanical advantage and heritabilities were therefore low and not quantifiable with significance for these variables (Table 1). Mother-offspring regressions were significant for all characters, as their slopes include not only additive genetic effects. When slopes were significant, the differences between the slopes for male and female offspring were generally not significant (all $p > 0.1$, except cranium centroid size for the mother-offspring regression, Fig. 2F, Table 1) despite the intercept being generally significantly different ($p < 0.01$, i.e. significant sexual dimorphism, see SI Fig. 2; Table 1). The incisor out-lever length visually appeared to show different slopes for males and females (Fig. 2M), but even in this case, the difference was not significant (Estimate = − 0.225, S.E. = 0.139, t = − 1.625, df = 330, $p > 0.1$). This showed that, although characters were sexually dimorphic (i.e. regressions had different intercepts for males and females, Fig. 2; Table 1, SI Fig. 2), the patterns of transmission of variability were not different between sexes (i.e. the slopes were not different). Therefore, we pooled males and females in the following mixed model analyses, and added sex as a fixed effect in the cases where univariate variables were sexually dimorphic (Fig. 2, SI Fig. 2).

Mixed Effect Model Analyses

The mixed effect linear model analyses run on the selected traits allowed us to partition the phenotypic variation between sire variance (related to additive genetic variance: $\sigma^2_{sires} = 1/4 * V_A$), and dam variance and residual variance (involving additive genetic, dominance, environmental and error variance; SI Table 1). Looking at the sire, dam and residual components of variance, it appears that bite force has the lowest sire variance, while having the highest dam and residual components (and generally highest variance overall). In comparison, all other variables have much lower total variance (therefore much lower dam and residual components). Among these traits, centroid sizes had both high sire and high dam and residual variances, followed by mechanical advantages (except for the superficial masseter, which had much lower sire variance than the temporal mechanical advantages). Although the in-levers and out-levers had rather low sire variance, they also had much lower dam and residual components than mechanical advantages or centroid sizes. In particular, the incisor and molar


A.
BF (offspring)
BF (sire)
E.
CCS (offspring)
CCS (sire)
I.
SMI MA (offspring)
SMI MA (sire)
M.
IOL (offspring)
IOL (sire)
B.
BF (offspring)
BF (dam)
F.
CCS (offspring)
CCS (dam)
J.
SMI MA (offspring)
SMI MA (dam)
N.
IOL (offspring)
IOL (dam)
C.
MCS (offspring)
MCS (sire)
G.
SM IL (offspring)
SM IL (sire)
K.
TI MA (offspring)
TI MA (sire)
O.
MOL (offspring)
MOL (sire)
D.
MCS (offspring)
MCS (dam)
H.
SM IL (offspring)
SM IL (dam)
L.
TI MA (offspring)
TI MA (dam)
P.
MOL (offspring)
MOL (dam)
Q.
Sire–offspring regression h2
Mixed model estimate (sommer)
Dam–offspring regression H2
Heritability
BF
MCS
CCS
SM IL
SMI MA
TI MA
IOL
MOL

◂**Fig. 2** **A–P** Parent-offspring regressions for chosen univariate morphometric traits and bite force. Blue circles are male offspring, green diamonds are female offspring. Significant regression lines were plotted separately in green and blue when a significant sex effect (intercept) and / or interaction effect (slopes) was detected, or in black when no significant difference between males and females was found. Dashed lines and transparent areas represent 95% confidence intervals on the regression line. **Q** Heritability estimates for univariate morphometric traits and bite force, obtained from the slope of parent-offspring regression or mixed models. Note that dam-offspring regressions do not represent true narrow-sense heritabilities, as they include non-additive genetic effects, mother and common environment effects. Whiskers represent 95% confidence intervals for the heritability estimates. *BF* Bite force, *CCS* Cranium centroid size, *IOL* Incisor out-lever, *MCS* Mandible centroid size, *MOL* Molar out-lever, *SM IL* Superficial masseter in-lever, *SMI MA* Superficial masseter-Incisor mechanical advantage, *TI MA* Temporal-Incisor mechanical advantage

out-levers had much lower dam and residual components than all other variables.

Accordingly with the levels of additive genetic variance versus total phenotypic variance, heritability (Fig. 2Q) for bite force is not detected (not significantly different from zero), but it is high for the out-lever lengths especially the incisor out-lever length (molar out-lever $h^2 = 0.55$, incisor out-lever $h^2 = 0.94$). Centroid sizes and the temporal/incisor mechanical advantage have intermediate heritabilities (cranium centroid size $h^2 = 0.17$, mandible centroid size $h^2 = 0.16$, mechanical advantage $h^2 = 0.29$) with confidence intervals not including 0, while the superficial masseter in-lever and mechanical advantage have low heritabilities ($h^2 = 0.04$ for both) which are not different from 0 according to confidence intervals. These results are similar to the estimates obtained from the father-offspring regressions although errors are larger for parent-offspring estimates (Fig. 2Q).

Evolvability of the traits shows divergent results from heritability (SI Table 1). However, since bite force V_A is the lowest, bite force evolvability is also the lowest. Contrary to heritability, the out-levers have fairly low evolvability (especially the molar out-lever), as do centroid sizes and in-lever for the superficial masseter. Only the temporal mechanical advantage has a notably larger evolvability.

Sire, maternal and residual correlation matrices were computed from their corresponding variance-covariance matrices (SI Fig. 1). However, the sire component correlations between traits cannot be computed for all pairs of traits (notably for bite force which had no detectable additive genetic variance). We decided to remove these values because for these traits, variance was either 0, or so small that covariances could not be estimated precisely (due to algorithm tolerance limits), leading to a correlation coefficient larger than 1 or smaller than − 1. These problems did not arise for the other components of variance-covariance and correlation. The variance-covariance patterns of shape change are illustrated in Fig. 1. It appears clearly that for the mandible, the sire (additive genetic) pattern of variation differs from the dam pattern and phenotypic pattern. Notably, the degree of anterior/posterior variation of the coronoid process (smaller for additive genetic effects), and anterior/posterior projection of the angular process (larger for the additive genetic effects). Dam and phenotypic patterns are similar, notably for the coronoid and angular process. Finally, the residual variation pattern is very similar to the dam and phenotypic pattern for the coronoid process, but displays a unique pattern of variation in the incisor, probably reflecting its growth. For the cranium, the main additive genetic variation was in the shorter snout and wider zygomatic arches, a pattern not observed in the dominance, environmental and phenotypic variation. Dam, residual and phenotypic patterns varied mostly in the posterior (occipital) region.

Discussion

Phenotypic Bite Force-Morphology Correlation

As expected, we determined that morphology and performance are linked at the intra-specific level. The strongest predictor of bite force is size, with a correlation coefficient of about 0.4 (SI Fig. 1), which could be explained by larger mandibles having larger and stronger muscles (Ginot et al., 2018), but also in part by allometric changes in some of the mandible lever arms (Fig. 1E–F). However, while morphology does correlate significantly with bite force (Fig. 1C–D, SI Fig. 1), the correlation is relatively low suggesting that a large part of realized (i.e. measured) bite force performance variation is due to other factors, which may include other non-measured morphological traits such as muscle characteristics, but also behavioral or environmental factors which are generally known to increase the global variance of performance traits (Anderson et al., 2008; Ginot et al., 2017, 2020). Note, however, that residual variance in bite force is equivalent to dam variance (SI Table 1), suggesting significant but not extreme environmental or noisy variation.

Heritability of Bite Force and Morphology and Sources of Variation in Mice

Parent-offspring regressions clearly show that realized in vivo bite force is not significantly heritable in our study (Fig. 2A, Q), while elements of skull morphology that relate to jaw mechanics are (Fig. 2C–F, H, J–Q). The globally higher slopes observed in dam-offspring regressions compared to sire-offspring regressions can be explained by the added variance they include (part of the maternal effects, and part of the residual effects), in

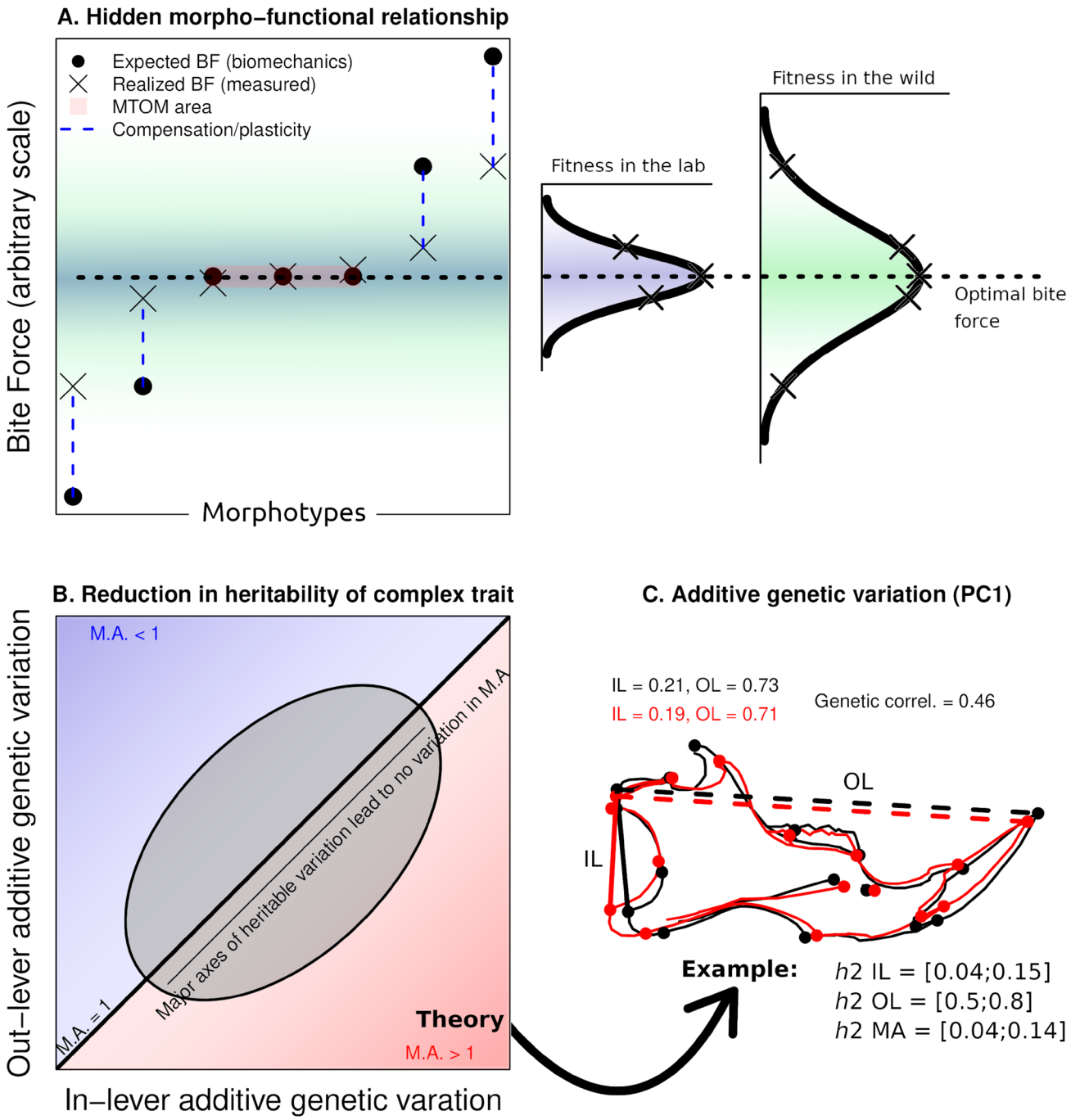
Table 1 Results of the parent-offspring regressions for bite force, size and morphometric traits in our pedigree of wild-derived *Mus musculus*. Models with non-significant interaction terms between the trait and sex (all but one) were reduced by removing the interaction term and running a new model

	Estimate	Std.Error	tvalue	Pr(>|t|)
Bite force (offspring) ~ Bite force (sire) + Sex (offspring)				
(Intercept)	8.308286	0.727856	11.415	< 2e-16
Bite force (dam)	0.004622	0.062634	0.074	0.941
Sex	0.971035	0.180306	5.385	1.38e-07
Adjusted R-squared: 0.07611				
Bite force (offspring) ~ Bite force (dam) + Sex (offspring)				
(Intercept)	4.00009	0.45838	8.727	< 2e-16
Bite force (dam)	0.41387	0.04232	9.780	< 2e-16
Sex	0.89684	0.16076	5.579	5.15e-08
Adjusted R-squared: 0.2875				
Mandible centroid size (offspring) ~ Mandible centroid size (sire) + Sex (offspring)				
(Intercept)	1.490156	0.096708	15.409	< 2e-16
Mandible centroid size (sire)	0.226627	0.044473	5.096	5.85e-07
Sex	0.045516	0.005707	7.975	2.50e-14
Adjusted R-squared: 0.2039				
Mandible centroid size (offspring) ~ Mandible centroid size (dam) + Sex (offspring)				
(Intercept)	1.200953	0.113352	10.595	< 2e-16
Mandible centroid size (dam)	0.366990	0.053152	6.905	2.76e-11
Sex	0.043367	0.005638	7.692	1.85e-13
Adjusted R-squared: 0.2418				
Cranium centroid size (offspring) ~ Cranium centroid size (sire) + Sex (offspring)				
(Intercept)	2.800939	0.208887	13.41	< 2e-16
Cranium centroid size (sire)	0.143148	0.058187	2.46	0.0144
Sex	0.086215	0.008594	10.03	< 2e-16
Adjusted R-squared: 0.2391				
Cranium centroid size (offspring) ~ Cranium centroid size (dam) + Sex (offspring)				
(Intercept)	1.80706	0.24950	7.243	3.70e-12
Cranium centroid size (dam)	0.42939	0.07094	6.053	4.22e-09
Sex	0.94513	0.34201	2.763	0.00607
Size:Sex interaction	− 0.24522	0.09716	− 2.524	0.01212
Adjusted R-squared: 0.3095				
Superficial masseter In-lever (offspring) ~ Superficial masseter In-lever (sire) + Sex (offspring)				
(Intercept)	0.189424	0.009026	20.986	< 2e-16
Superficial masseter In-lever (sire)	0.061326	0.044486	1.379	0.1690
Sex	0.002241	0.001039	2.156	0.0318
Adjusted R-squared: 0.01593				
Superficial masseter In-lever (offspring) ~ Superficial masseter In-lever (dam) + Sex (offspring)				
(Intercept)	0.170508	0.012528	13.610	< 2e-16
Superficial masseter In-lever (dam)	0.154233	0.061394	2.512	0.0125
Sex	0.001988	0.001059	1.877	0.0615
Adjusted R-squared: 0.02531				
Superficial masseter-Incisor M.A. (offspring) ~ Superficial masseter-Incisor M.A. (sire) + Sex (offspring)				
(Intercept)	0.262919	0.012746	20.627	< 2e-16
Superficial masseter-Incisor Mechanical advantage (sire)	0.063700	0.045292	1.406	0.16053
Sex	0.004112	0.001570	2.619	0.00922
Adjusted R-squared: 0.02302				

Table 1 (continued)

	Estimate	Std.Error	tvalue	Pr(>|t|)
Superficial masseter-Incisor M.A. (offspring) ~ Superficial masseter-Incisor M.A. (dam) + Sex (offspring)				
(Intercept)	0.233448	0.017194	13.577	< 2e-16
Superficial masseter-Incisor Mechanical advantage (dam)	0.167766	0.060765	2.761	0.0061
Sex	0.003815	0.001600	2.384	0.0177
Adjusted R-squared: 0.03613				
Temporal-Incisor M.A. (offspring) ~ Temporal-Incisor M.A. (sire) + Sex (offspring)				
(Intercept)	0.190082	0.013303	14.288	< 2e-16
Temporal-Incisor Mechanical advantage (sire)	0.200433	0.055228	3.629	0.000329
Sex	0.001613	0.001887	0.855	0.393160
Adjusted R-squared: 0.0351				
Temporal-Incisor M.A. (offspring) ~ Temporal-Incisor M.A. (dam) + Sex (offspring)				
(Intercept)	0.1828427	0.0167533	10.914	< 2e-16
Temporal-Incisor Mechanical advantage (dam)	0.2302745	0.0694419	3.316	0.00102
Sex	0.0009344	0.0019256	0.485	0.62785
Adjusted R-squared: 0.02845				
Incisor out-lever (offspring) ~ Incisor out-lever (sire) + Sex (offspring)				
(Intercept)	0.4788798	0.0500927	9.560	< 2e-16
Incisor out-lever (sire)	0.3327586	0.0694225	4.793	2.48e-06
Sex	− 0.0023986	0.0008739	− 2.745	0.00639
Adjusted R-squared: 0.08052				
Incisor out-lever (offspring) ~ Incisor out-lever (dam) + Sex (offspring)				
(Intercept)	0.5954753	0.0411622	14.467	< 2e-16
Incisor out-lever (dam)	0.1714992	0.0570373	3.007	0.00285
Sex	− 0.0026457	0.0009197	− 2.877	0.00429
Adjusted R-squared: 0.04689				
Molar out-lever (offspring) ~ Molar out-lever (sire) + Sex (offspring)				
(Intercept)	0.3318164	0.0276198	12.014	< 2e-16
Molar out-lever (sire)	0.2272859	0.0635957	3.574	0.000404
Sex	− 0.0019856	0.0005769	− 3.442	0.000652
Adjusted R-squared: 0.07294				
Molar out-lever (offspring) ~ Molar out-lever (dam) + Sex (offspring)				
(Intercept)	0.3330972	0.0205731	16.191	< 2e-16
Molar out-lever (dam)	0.2256426	0.0476273	4.738	3.27e-06
Sex	− 0.0025580	0.0005868	− 4.360	1.76e-05
Adjusted R-squared: 0.1015				

which maternal condition may have played a role, since all mothers did not give birth at the same age. The mixed effect model analyses show that the absence of significant bite force heritability is not only due to high residual variance (Houle, 1992), but also to the fact that additive genetic effects cannot be detected in the variance partitioning of this trait (SI Table 2). On the other hand, morphological characters display various levels of additive genetic variance. As expected, heritability and evolvability of the characters studied show divergent results (Houle, 1992; Hansen et al., 2011). Out-levers (related to mandible length), centroid sizes and temporal mechanical advantage have high heritabilities, while only temporal mechanical advantage is highly evolvable. However, both heritability and evolvability indices suggest that realized bite force may be unresponsive to selection, while morphological traits will show varying levels of response. It should be kept in mind, however, that the sample size of sires involved in this study may not be sufficient to detect low additive genetic variance and therefore heritability, as may be the case for bite force. Therefore, we obviously cannot affirm that bite force has absolutely no additive genetic component (proving an absence is logically impossible), but it is comparatively much lower than for



morphological traits, for which we do detect additive genetic variance. Low signal to noise ratio is in any case expected in quantitative genetics studies (Falconer, 1989). Our results appear more extreme, but similar to those reported by Zablocki et al., (2021), who found low heritability for bite force compared to associated morphological traits. This study had the advantage of a larger sample size, building upon a colony of wild mouse lemurs which has been started from wild individuals over 50 years ago. Our study could not equal this sample size, but still had enough power to detect intermediate and high additive genetic variances, and may suffer less from biases due to evolution in captivity. It should also be noted that despite a larger sample size, Zablocki et al., (2021) also reported non-significant weak heritability for another performance trait: pull strength, which demonstrates that, even within the same population, different performance traits may or may not be detectably heritable.

An important feature in our study is that the mice were reared in laboratory conditions, but were only recently

◂**Fig. 3** **A** Theoretical graph illustrating several factors that can blur the relationship between morphology and performance, and reduce heritability. Each black dot represents an individual's expected bite force based on its unique morphology (e.g. based on biomechanical model). The crosses represent the realized bite force, which can differ from the expected bite force due to plastic changes such as muscular compensation or behavioural differences (blue vertical dashed lines). In the example we consider that this plasticity tends to bring the realized bite force closer to the optimal bite force (dashed horizontal line), but also that this plasticity is limited for every individual. This plasticity will therefore reduce heritable variation in realized bite force, while at the same time blurring the morpho-functional relaptionship, so heritable morphological variation will be less visible in the realized bite force than it would in expected bite force. The three individuals in the middle represent the effect of many-to-one mapping: despite having different morphologies, their bite force performance will be the same, which again will blur the morpho-functional relationship. Finally, the fitness gradients related to bite force show that these effects may be even stronger in laboratory conditions: keeping animals in standard conditions with only one type of food, we may have selected out the extreme individuals, that could not compensate in terms of bite force, and less extreme individuals would tend to plastically respond to these lab conditions. In the wild, extreme individuals may have maintained thanks to more variable food sources, and other individuals could plastically reach higher fitness, or have more similar realized and expected bite forces. **B** Additionally, we propose that complex traits, such as mechanical advantage (MA), which depend on two or more unidimensional traits, here the corresponding in-lever (IL) and out-lever (OL), may present reduced heritability. Indeed, these complex traits generally do not depend on additive relationships between their components, and frequently show many-to-one mapping. Here, MA is a ratio of IL over OL. The figure shows that, in the case where the IL and OL are both heritable and genetically positively correlated, the major axis of heritable covariation between them corresponds to no heritable variation in MA (MA ~ 1, as shown by the ellipse and lighter gradient colors). **C** This example illustrates that the mechanism suggested in B. does happen in real-life data. Here we show the superficial masseter IL (solid lines) and OL at the incisor (dashed lines). It appears that both are genetically correlated, as can be seen on the outline (black shape has longer IL and longer OL compared to red shape). Heritability of the superficial masseter MA is about 0, despite the OL being the most heritable trait found in this study. It should be noted that this effect not only reduces heritability, but more precisely reduces additive genetic variation, and could be extended in more complex traits such as performance or fitness

extracted from their natural environment (five generations maximum). Mice from the Orkney archipelago as a whole, and of the Mainland island itself were shown to display amounts of phenotypic variation similar to continental populations, despite a more homogeneous climate across the Orkneys, and despite changes in mean mandible and molar shape (Souquet et al., 2019, Chevret et al., 2021). These studies also showed that rates of morphological evolution were much higher in the Orkney archipelago than in neighbouring mainland Scotland or than across continental populations. Some evidence also suggests, at least for mandibular measurements, that morphological diversity was not reduced between Mainland mice captured in the field and their lab descendants (see Souquet et al., 2019 and Fig. 6 therein, which relies on the same colony as our study). In terms of genetic variation, Orkney mice form a well-supported clade (Chevret et al., 2021 and references therein), which is split into mostly endemic haplotypes representative of the different islands, and even of specific localities within islands, with congruent results between microsatellite and mitochondrial data. This is interpreted by Chevret et al. (2021) as "a first invading population being resilient to subsequent invasions", followed by geographical spread and neutral diversification, with differences between populations maintained by the limited dispersal ability of mice outside of human transport. The matching patterns found for genetic and tooth morphological population differentiation suggest that the evolution of Orkney mice is mostly due to neutral processes, possibly allowed by relaxed selective pressures in this island environment (Souquet et al., 2019; Chevret et al., 2021). These elements do not support the idea that the mice studied here were under strong stabilizing selection, and therefore suggest that they should not have "depleted" additive genetic variance, either for the morphological or performance traits studied here.

The founding of the lab colony, and the choice of limited number of parents for this study, may have acted as a genetic and phenotypic bottleneck. However, this effect should be limited by our outbreeding approach, crossing individuals from distant populations of Mainland, which, as mentioned previously have a phenotypic diversity comparable to continental populations. Similarly, genetic diversity in that particular lab population may in fact be higher than that of individual natural populations in Mainland.

In the lab, mice were not subjected to any active human selection, nor to extreme or varied diets. Laboratory conditions likely involve reduced environmental/residual variance (reduced variation of food hardness and energetic content, stable climate, identical measurement conditions) compared to natural conditions, and were argued by some authors to entail increased additive genetic variation (e.g. Charmantier & Garant 2005, and references therein). While reduction in environmental variance would, in principle, increase heritability (by reducing the denominator of the heritability equation), it is possible that the opposite would actually occur for bite force: the reduced range of food hardness can limit the genetic expression of developmental variation related to food hardness variability. In other terms, genetic-environment (GxE) interactions are probably modified. More stressful environmental conditions might reveal genetic variation in bite force because individual animals use a larger range of their available bite force to process food of varying physical properties (Fig. 3A). A recent paper on wild-derived strains of *Peromyscus leucopus* (Lacy et al., 2018) confirms that heritability and additive genetic variance change through generations of captivity. The changes however were not consistent (both increases and decreases were found)

across generations and across traits. Similarly, we do not know what would happen under conditions of directional selection created by a change in diet requiring an increase in bite force under natural conditions. Interestingly, based on simulations, Shaw & Shaw (2014) noted that when conditions changed, and with them the selection regime, additive genetic variance of fitness increased, which would increase heritability, yet this remains to be tested empirically on fitness-related traits. Charmantier & Garant (2005) however showed, through a meta-analysis of empirical comparative studies, that heritabilities of morphological characters were higher in more "favorable" conditions in wild populations, but that this was not the case for fitness-related traits. Further studies, if possible in the wild or semi-captivity, are therefore needed to investigate how changing environmental conditions could alter the genetic variance-covariance among characters, especially performance characters which are determined by morphological factors.

Non-exclusive from the phenomena explained in the previous paragraph, the reduced additive genetic variance for bite force may "simply" be due to strong stabilizing selection on this fitness-related character (i.e. Fisher's theorem). Indeed, because mechanically expected bite force performance is related to the optimal ability to feed (Fig. 3A), its margin for variation is expected to be low (Cheverud, 1996). Our study would be an extreme case but is consistent with both theoretical expectations and empirical studies (Fisher, 1958; Mousseau & Roff, 1987, Hoffman 2016). However, as noted above, the genetic and morphological patterns observed in the ancestral wild population do not suggest past or ongoing strong selection (Souquet et al., 2019, Chevret 2021). Due to its reduced additive genetic variance, bite force is genetically uncorrelated with morphology, despite covarying phenotypically. It would therefore appear that the phenotypic morphology-performance correlation emerges from sources other than the genetic correlation such as environmental variance or maternal factors. However, if bite force additive genetic variance had been detected, it may have been genetically correlated to morphological traits, as was found by Zablocki et al., (2021).

Disconnection Between Heritabilities of a Complex Trait and its Components

The magnitude of additive genetic variance of a trait not only determines its heritability but also its evolvability (Fisher, 1958; Houle, 1992). Our results therefore suggest that selection on realized bite force in itself will resist more to evolutionary changes than morphology. The conundrum here is that bite force correlates with morphology, which is heritable, and yet bite force is not itself heritable (or much less heritable than morphology). This might occur because bite force is determined not only by bone but also by muscular structure. However, muscle size and morphology have well-known and strong relationships with bone morphology including the shape of the mandible and skull (Herring, 1993). Further, muscular morphology is also heritable, which should therefore "add up" into bite force additive genetic variance. An alternative explanation we propose is that bite force has a complex relationship to its morphological basis such that multiple and quite different anatomical arrangements generate similar bite forces (i.e. a many-to-one relationship). As shown in Fig. 3B–C, heritable variation in the in and out-levers of the mandible might translate to no heritable variation in bite force if additive genetic variances for these traits covary such as to produce a region over which the additive genetic variance for mechanical advantage is essentially invariant. Since both variables correlate imperfectly with bite force, this region is an ellipse rather than a line which also means that there is effectively a multivariate range of morphological variation that is compatible with genetically invariant bite force. Our data provides some support for this idea (Fig. 3C, SI Fig. 1). The in-lever (IL) and incisor out-lever (OL) length of the superficial masseter muscle both show some detectable additive genetic variance, and therefore both are heritable (SI Table 1), the out-lever being much more heritable than the in-lever. Both are also genetically positively correlated ($r = 0.46$, SI Fig. 1), and their ratio constitutes the mechanical advantage of the lever system for the superficial masseter (M.A. = IL/OL), which directly impacts the proportion of muscular force that can be transmitted to the incisors. Despite the out-lever being the most heritable trait in our study, it appears that the heritability and additive genetic variance of the mechanical advantage is actually restricted by the lower additive genetic variance of the in-lever, combined with the positive additive genetic correlation between the in-lever and out-lever (Fig. 3C, SI Fig. 1). Therefore, it may be that the additive genetic variance of complex traits such as bite force or mechanical advantage, which depend on numerous inter-correlated other traits, may actually not behave additively. Such an explanation for low heritability of performance or fitness-related traits is not exclusive of other effects, but would require formal testing in the future.

Akin to the model of Schluter (1996), the region of lever arm additive genetic covariation that is compatible with relatively invariant bite forces may form a line of least resistance along which craniofacial morphology may evolve even under stabilizing selection for bite force (Fig. 3). This selection on bite force should also produce pleiotropy and/or linkage disequilibrium between morphological traits mechanically related to bite force. That is because in stable conditions the additive genetic variance-covariance pattern will evolve

to match the stabilizing selection pattern (Cheverud, 1984, 1996). In the case of a many-to-one relationship, variable combinations of traits can be inherited together, as long as they imply performance close to the optimum (Cheverud, 1996). This could explain that some genetic covarition patterns of lever arms or shape do not relate to a major component of mechanical performance variation (Fig. 1C–D, 3B, SI Fig. 1).

Modularity and many-to-one mapping can serve to maintain standing genetic variance without impacting the selection process on the system in normal conditions. The system is therefore not doomed to the reduction of additive genetic variation, and evolution of performance would still be possible if changes occur in the pleiotropic/linkage relationships underlying genetic integration within modules or traits (such as lever arms). Causes of pleiotropic breakdown can be multiple, and genetic correlations have been shown experimentally to be modified under selection, sometimes in opposite directions to the original or expected genetic correlation (Sikkink et al., 2015). It is therefore likely that stabilizing selection would favor modularity and the many-to-one relationship in normal conditions, while directional selection may disrupt these patterns in changing environments.

Fisher's theorem and the non-expression of GxE interactions (see previous section) could explain the non-detectability of additive genetic variance in bite force in our study. In addition to these phenomena, we propose that non-additive mechanical relationships between components (or functional modules) of a complex performance trait (Fig. 3B–C), provide a non-exclusive and complementary explanation for the reduced heritability of fitness-related and performance traits under stable conditions.

Implications for the Evolution of Performance at the Inter-specific Scale

The most heritable morphological traits are size and the out-lever lengths of the mandible, both at the incisor and molar, while the most evolvable trait is the mechanical advantage of the temporal muscle. These traits broadly correspond to a general lengthening (incisor out-lever) or heightening (molar out-lever) of the mandible, and changes in the condyloid and coronoid process (temporal mechanical advantage). These changes are also seen when looking at the genetically heritable shape variation. They can have functional consequences, by modifying the mechanical advantage of the different masticatory muscles, and thereby impacting the amount of force produced and transmitted to food, and the speed of the jaw closure (e.g. Hiiemae 1971, Hiiemae & Houston, 1971, Satoh, 1997). Comparative morpho-functional studies at the inter-specific level in rodents have often noted changes in the length and height of the mandible, as well as in the coronoid and condyloid processes, associated with changes in muscular insertions and tooth morphology (e.g. Michaux et al., 2007, Hautier et al., 2012, Maestri et al., 2016). These trends were linked to ecological aspects at different scales, within (Ctenohystrica, Hautier et al., 2012; Sigmodontinae, Maestri et al., 2016) and between (Samuels, 2009) various groups of rodents. For example, herbivorous rodents were shown to have more "robust" or "massive" mandibles, while insectivorous have more "slender" mandibles (Michaux et al., 2007). Such morphological changes have been repeatedly selected during rodent evolution. Our data suggest that size, as well as the lengthening and heightening of the mandible, associated with lever arm changes in the masticatory apparatus, are evolvable characters in the strict definition of Houle (1992), which, because of their functional consequences, may constitute one of the adaptive pathways when rodents modify their diets or mode of life. It should however be kept in mind that additive genetic variance, heritability and evolvability are not constants, and it therefore remains debatable whether the most heritable and/or evolvable traits within a population can really be extrapolated to have more evolutionary potential than others at the macroevolutionary scale (Hansen et al., 2011).

Conclusion

Here, we report on the finding that bite force, a key measure of performance for craniofacial morphology, is not heritable. Our results, although expected from theory and previous empirical studies, show that the heritability and evolvability of performance traits such as bite force can be complex. Indeed, not only its heritability is low, which could be explained by high residual variance, but its additive genetic variance itself is too small to be detected. In theory, this would be expected from populations under stabilizing selection, which may not be true here (Souquet et al., 2019; Chevret et al., 2021). We present a hypothesis for the structure of additive genetic variation in the morphological determinants of bite force that is compatible with our data. This hypothesis reveals that an apparent lack of heritability for such a trait within a population does not necessarily mean that the performance trait is not evolvable (Fig. 3B–C). When there are multiple morphological determinants of performance that covary and have a many-to-one, rather than additive, relationship to the functional output, the result is latent genetic variation in performance. This latent variation may be revealed under conditions in which the performance optimum is altered due to environmental change (e.g. in a speciation context), which breaks down genetic correlations between morphological traits or modules involved in producing the performance output.

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Author Contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by Samuel Ginot, and Sylvie Agret. Data analysis was performed by Samuel Ginot, and Julien Claude. The first draft of the manuscript was written by Samuel Ginot and Julien Claude and Benedikt Hallgrímsson commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Animals were treated in accordance with the guidelines of the American Society of Mammalogists, and within the European Union legislation guidelines (Directive 86/609/EEC and 2010/63/UE). All lab procedures were carried out under approval no. A34-172-042 (DDPP Hérault Prefecture). More details are provided in the Material and Methods section.

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