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Of "mice" and mammals: utilizing classical inbred mice to study the genetic architecture of function and performance in mammals

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Synopsis The house mouse is one of the most successful mammals and the premier research animal in mammalian biology. The classical inbred strains of house mice have been artificially modified to facilitate identification of the genetic factors underlying phenotypic variation among these strains. Despite their widespread use in basic and biomedical research, functional and evolutionary morphologists have not taken full advantage of inbred mice as a model for studying the genetic architecture of form, function, and performance in mammals. We illustrate the potential of inbred mice as a model for mammalian functional morphology by examining the genetic architecture of maximum jaw-opening performance, or maximum gape, across 21 classical inbred strains. We find that variation in maximum gape among these strains is heritable, providing the first evidence of a genetic contribution to maximum jaw-opening performance in mammals. Maximum gape exhibits a significant genetic correlation with body size across strains, raising the possibility that evolutionary increases in size frequently resulted in correlated increases in maximum gape (within the constraints of existing craniofacial form) during mammalian evolution. Several craniofacial features that influence maximum gape share significant phenotypic and genetic correlations with jaw-opening ability across these inbred strains. The significant genetic correlations indicate the potential for coordinated evolution of craniofacial form and jaw-opening performance, as hypothesized in several comparative analyses of mammals linking skull form to variation in jaw-opening ability. Functional studies of mammalian locomotion and feeding have only rarely examined the genetic basis of functional and performance traits. The classical inbred strains of house mice offer a powerful tool for exploring this genetic architecture and furthering our understanding of how form, function, and performance have evolved in mammals.

Introduction

Mammalian functional morphology maintains a long-standing interest in the evolutionary relationships among organismal form, function, and performance (Hildebrand et al. 1985; Ashley-Ross and Gillis 2002). Comparative morphologists studying the functional traits of mammals have effectively integrated with multiple biological disciplines ranging from physiology to developmental biology, evolutionary ecology and paleontology (Futuyma 1998). These interdisciplinary ties have significantly advanced efforts to describe and understand the evolution of organismal function and performance in mammals. This integrative approach also has helped solidify the role of functional morphology in evolutionary biology (Wake 1982; Liem and Wake 1985; Futuyma 1998).

Despite these multiple interdisciplinary inroads, it is apparent that we still lack a fundamental understanding of the underlying genetic architecture of most organismal-level functional traits, such as those related to locomotion and feeding (Schwenk 2001). The disconnect between functional morphology and genetic studies is perceivable from both the lack of discussion in reviews of research on functional morphology (Wake 1992; Biewener 2002) and the variance in predictions among those studies that speculate on the evolvability of functional and performance traits (Hiiemae and Kay 1973; Hiiemae 1978; Lauder and Shaffer 1988; Liem 1990; Smith 1994; Weijs 1994; Langenbach and van Eijden 2001; Wainwright 2002; Missitzi et al. 2004; Vinyard et al. 2007). Moreover, our current inability to link organismal performance to its genetic basis stands in contrast to the acknowledgment that evolution of performance will generally involve heritable changes in the morphological underpinnings of these traits

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(Bock and von Wahlert 1965; Arnold 1983). We argue that this shortcoming in understanding the genetic architecture of functional and performance traits will become a significant impediment to advancing research into mammalian evolutionary morphology. Given this concern, our goal here is to make a case for harnessing the prodigious biomedical research efforts focused on classical inbred-mouse strains to begin deciphering the genetic basis of the relationships among organismal form, function, and performance in mammals.

Inbred mice as models in mammalian functional and evolutionary morphology

Evolutionary biologists study house mice extensively (Boursot et al. 1993; Sage et al. 1993; Berry and Scriven 2005). Research focused on house mice has provided insights into speciation (Hunt and Selander 1973; Forejt and Ivanyi 1974; Thaler et al. 1981; Tucker et al. 1992; Forejt 1996; Capanna and Castiglia 2004; Payseur et al. 2004; Storchova et al. 2004; Britton-Davidian et al. 2005; Oka et al. 2007), adaptation (Lynch 1992), insular and mainland biogeography (Berry et al. 1978, 1991; Berry 1996; Orth et al. 2002; Pocock et al. 2005; Michaux et al. 2007), population genetics (Selander et al. 1969; Nachman 1997; Laurie et al. 2007), the evolution of morphological covariance structure (Wallace 1968; Leamy 1977a, 1977b; 1982; Atchley et al. 1981; Cheverud et al. 1983; Shea et al. 1990; Cheverud et al. 1997), experimental evolution (Falconer et al. 1978; Lynch 1980; Dohm et al. 1996; Atchley et al. 1997; Keightley 1998; Swallow et al. 1998; Garland et al. 2002), and the evolutionary developmental biology of complex mammalian phenotypes (Kangas et al. 2004; Willmore et al. 2006; Cretekos et al. 2008). A subset of this work documents the physiology as well as functional and evolutionary morphology of feeding and locomotion in house mice (Kimes et al. 1981; Byron et al. 2004; Kelly et al. 2006; Carlson and Judex 2007). Indeed, the establishment of the classical inbred strains was fostered in part by the interests of natural historians as well as the utility of inbred mice for cancer and ultimately genetic research (Morse 1978).

Classical inbred strains of mice, which are descended from wild natives of Japan, China, and Europe (Silver 1995), serve as the principal animal model in research into human diseases (Bedell et al. 1997a, 1997b; Waterston et al. 2002; Davisson and Linder 2004; Peters et al. 2007). While this focus on public health continues to predominate, there is a growing interest in the evolutionary history of inbred mice among members of the biomedical community (Wade et al. 2002; Graber et al. 2006; Yang et al. 2007) as well as numerous examples where biologists have studied these inbred strains to address evolutionary questions. For the mammalian functional morphologist, one of the most relevant examples of evolutionary research using inbred mice involves the development of the mandible as a model for studying the genetic architecture and evolution of complex phenotypes (Atchley et al. 1985a, 1985b; Atchley and Hall 1991; Cheverud et al. 1997). This work by Atchley, Cheverud, and colleagues has yielded significant evolutionary insights into the quantitative genetics of complex phenotypes by exploring patterns of morphological integration and modularity (Atchley et al. 1990; Mezey et al. 2000; Ehrich et al. 2003; Klingenberg et al. 2003, 2004), the nature and genomic distribution of underlying quantitative trait loci (QTL) (Cheverud et al. 1997, 2004; Leamy et al. 1997; Klingenberg et al. 2001; Workman et al. 2002), as well as quantitative genetics of development in this complex morphological structure (Atchley et al. 1985a, 1985b; Atchley and Hall 1991; Atchley 1993).

The success and impact of this research clearly demonstrates the benefits of using inbred strains to study evolutionary questions relating to the genetics of mammalian form. We argue that it is useful to build on this morphological work by incorporating studies on function and performance in these strains. By exploring the genetic basis of function and performance among strains, functional morphology can develop a more complete understanding of how these complex functional systems and their underlying morphological components evolve.

Benefits of inbred strains

There are key benefits to utilizing the classical inbred strains of mice as models for studying the genetic architecture of functional traits:

(i) Inbred mice are a model system for basic and biomedical science. Consequently, detailed biological information that has yet to be collected for most mammals is already publically available for inbred mice. For example, efforts are underway to measure large numbers of phenotypes and obtain dense genotypes from dozens of inbred strains (Blake et al. 2006; Bogue et al. 2007; Frazer et al. 2007), and more ambitious projects have been proposed (Churchill et al. 2004). The widespread study of inbred mice provides functional morphologists the opportunity to immediately place their results in a broader biological context.

Additionally, functional studies can take advantage of technological and methodological advances largely driven by the biomedical community.

(ii) Inbred mice offer tremendous genetic power. Mice within an inbred strain are genetically homogeneous and their phenotypes can be treated as replicate samples. This important characteristic enables better estimates of genetic effects when mice from different strains are raised in a common environment as well as improved characterization of nongenetic effects when mice from the same strain are raised in different environments (Festing 1979). Genetic differences identified through surveys of strains can be mapped to specific genomic regions by crossing inbred strains (Abiola et al. 2003). Candidate regions and genes can be nominated and tested using available mutants and more advanced breeding designs, including the construction of congenic and transgenic strains (Silver 1995). The ability to genetically characterize phenotypic variation among inbred strains of mice exceeds that in any other mammal.

Limitations of inbred strains

While we contend that the positives outweigh the negatives, there are limitations and concerns when using inbred mice as a model for mammalian functional morphology.

(i) Patterns of variation among inbred strains are the result of both artificial and evolutionary processes. The artificial manipulation of preexisting variation across house mice (i.e., variation due to evolutionary processes) limits our ability to make evolutionary interpretations of variation in strains. We cannot reliably extrapolate patterns of variation observed in these strains to natural populations (Festing 1979). Differences in morphology and performance among inbred mice may be the result of artificial processes rather than neutral variation or selection for relevant behaviors in ecologically appropriate environments (Guénet and Bonhomme 2003). Furthermore, many of the behaviors that might be studied in inbred mice lack explicit biological roles (*sensu* Bock and van Wahlert 1965) in wild house mice. For example, we consider the genetic architecture of maximum jaw-opening performance without explicit behavioral evidence from field studies describing jaw-opening behaviors in house mice. In sum, functional studies of inbred mice will provide insights into the structural, and in some cases preexisting, associations among genotype, phenotype, and performance in a model system rather than provide opportunities to explore the mammalian adaptive pathway in naturalistic case studies.

(ii) Many experimental designs, such as those employing crosses to identify the genetic loci underlying morphological variation, require phenotypic measurement in large numbers of individuals. Because some functional variables are costly and time-consuming to quantify, it is likely that only a subset of functional measurements will be amenable to the demands of high-throughput phenotyping (Lussler and Liu 2006; Solberg et al. 2006).

(iii) Like all extant mammals, house mice are derived. Consequently, the mouse morphotype may not be an appropriate model for many interesting behaviors exhibited by other mammals. While this limitation would exist for any species put forth as a mammalian model, it is worth indicating that some functional traits will not be usefully studied in a mouse model.

(iv) The small size of mice may pose significant technological challenges for taking accurate and precise measurements of function and performance.

Existing resources

We do not take on the task of providing a detailed roadmap for navigating mouse phenotypic and genomic databases. Numerous publications have already described these vast resources and interested readers are referred to the most recent publications describing this rapidly expanding tool kit (Hedrich and Bullock 2004; Bogue et al. 2007; Hancock et al. 2007; Mayusa et al. 2007; Peters et al. 2007; Bult et al. 2008).

Case study: maximum jaw-opening performance among inbred strains of mice

We explore the potential for using inbred mice as a tool for the quantitative genetics of mammalian functional morphology in a single case study. We purposely consider the masticatory apparatus as it represents, along with the locomotor system, one of the primary concentrations in comparative mammalian functional morphology. Mammals use their

masticatory apparatus in numerous behaviors ranging from displays and aggressive encounters to multiple activities related to feeding (Nowak, 1991; Vaughn et al. 1999). For many of these behaviors, the ability to open the jaw widely is an important performance (Wolf-Exalto 1951; Herring 1972, 1975; Greaves 1974, 1995; Herring and Herring 1974; Hylander 1979; Emerson and Radinsky 1980; Lucas 1981, 1982; Smith 1984; Joeckel 1990; Jablonski 1993; Jablonski and Crompton 1994; Dumont and Herrel 2003; Vinyard et al. 2003, 2008) (Fig. 1). Given its functional significance in multiple behaviors, it is reasonable to speculate that variation among mammals in maximum jaw-opening ability, or maximum gape, may be in part the result of natural selection acting on this performance.

Despite the potential evolutionary significance of maximum jaw-opening ability, we know relatively little about the underlying morphological and genetic architecture of this performance. While the rodent jaw has become a model for studying the genetic architecture of complex morphology (see above citations) and functional studies have identified several morphological features that theoretically affect maximum gape (Herring and Herring 1974; Vinyard et al. 2003), these two areas of research remain separate. Here, we attempt to link these two threads by developing the inbred mouse as a model for examining the genetic architecture of the maximum jaw-opening phenotype. We specifically address two questions: (1) Is there heritable genetic variation in maximum jaw-opening performance across inbred-mouse strains, and (2) what are the phenotypic and genetic correlations among maximum gapes and morphological variables that influence maximum jaw-opening performance?

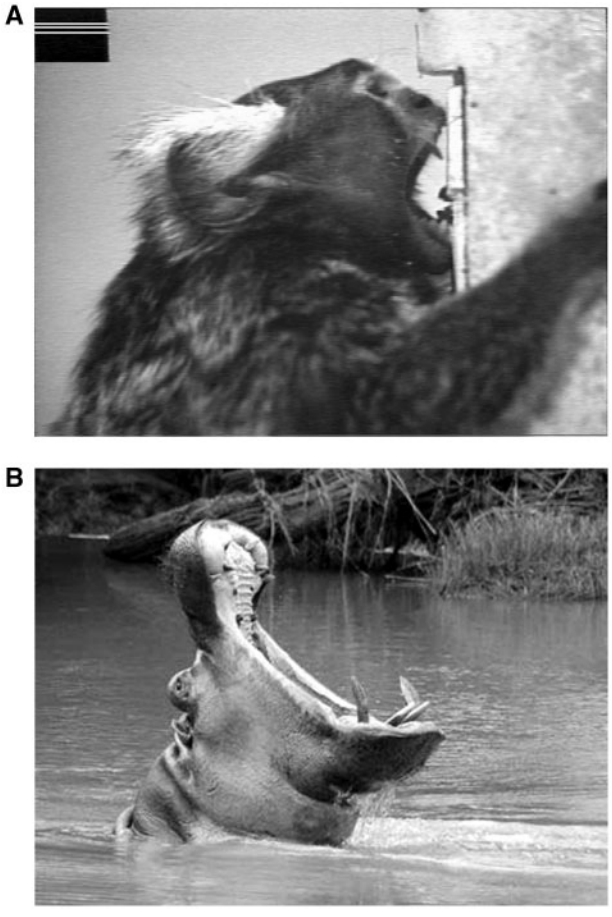

Fig. 1 Wide jaw-opening behaviors in a common marmoset (*Callithrix jacchus*) (**A**) during simulated tree gouging in the laboratory and a hippopotamus (*Hippopotamus amphibius*) (**B**) during an aggressive display (photograph credit and copyright to Karen Paollilo of the Turgwe Hippo Trust, http://www.savethehippos.com/turgwehippos.html).

Samples

We measured 413 mice from 21 inbred strains listed as current or former priority strains by the Mouse Phenome Database (http://phenome.jax.org) (Table 1). All individuals were raised at Jackson Laboratory until 9–12 weeks of age under their

Table 1 Strains of mice that were examined

Strain	Sample Size (♀/♂)[a]	Age (Weeks)
129S1/SvImJ	10/10	9/10
A/J	10/10	9/11
AKR/J	10/10	9/10
BALB/cByJ	10/10	9/10
BTBR T(+)tf/J	10/10	9/10
C3H/HeJ	10/10	10/10
C57BL/10J	10/10	10/10
C57BL/6J	10/9	9/9–10
C57BLKS/J	10/10	10/10
C57L/J	10/10	9–10/9
C58/J	8/8	9/9
CAST/EiJ	9/10	9/9
CBA/J	10/10	9 and 12/11
DBA/2J	10/10	10/9
FVB/NJ	10/10	9/9
NOD/LtJ	10/10	9/9
NON/LtJ	11/10	9/9
NZB/B1NJ	10/10	9/10
PL/J	10/9	9/9
RIIIS/J	9/10	9/9
SJL/J	10/10	10/10
Total	207/206	–

[a]Sample sizes (*n*) and ages (in weeks) are listed for females followed by males for each strain.

standardized laboratory conditions. Immediately upon arrival, mice were euthanized. Whenever possible, we sampled 10 females and 10 males per strain. The NEOUCOM Institutional Animal Care and Use Committee approved all protocols used in this study.

Phenotypic measurements

We measured maximum jaw gape immediately after euthanizing and prior to the onset of postmortem rigidity in the jaw muscles. We manually opened the jaws to their maximum passive motion and measured maximum jaw gape as the linear distance between the upper and lower incisors (Wall 1999) (Fig. 2A). This measure estimates the maximum structural capacity for jaw opening rather than a performance captured during a specific behavior (e.g., an activity with an explicit biological role).

We measured several dimensions of the jaw muscles and mandible that theoretically influence maximum gapes. Jaw-muscle stretch is one factor that may limit maximum gape in mammals (Herring and Herring 1974). To quantify the position of the masseter on the jaw, and hence estimate certain aspects of relative masseter stretch, we dissected away superficial tissue and photographed the head with attached jaw muscles using a stereomicroscope (Leica MZ7.5) (Fig. 2B). We digitized the anterosuperior and anteroinferior attachments of the superficial masseter and the location of the condyle using SigmaScan Pro 4.01 (Table 2; Fig. 2B).

Shape of the jaw is also predicted to influence maximum gape (Herring and Herring 1974; Dumont 1997; Wall 1999; Fukui et al 2002; Vinyard et al. 2003; Hirsch et al. 2006). We took medial-view photographs of skeletionized mandibles under a stereomicroscope and digitized six points in SigmaScan (Fig. 2C). Four scalar dimensions and one angle, each predicted to correlate with maximum gape, were computed from these digitized points (Table 2).

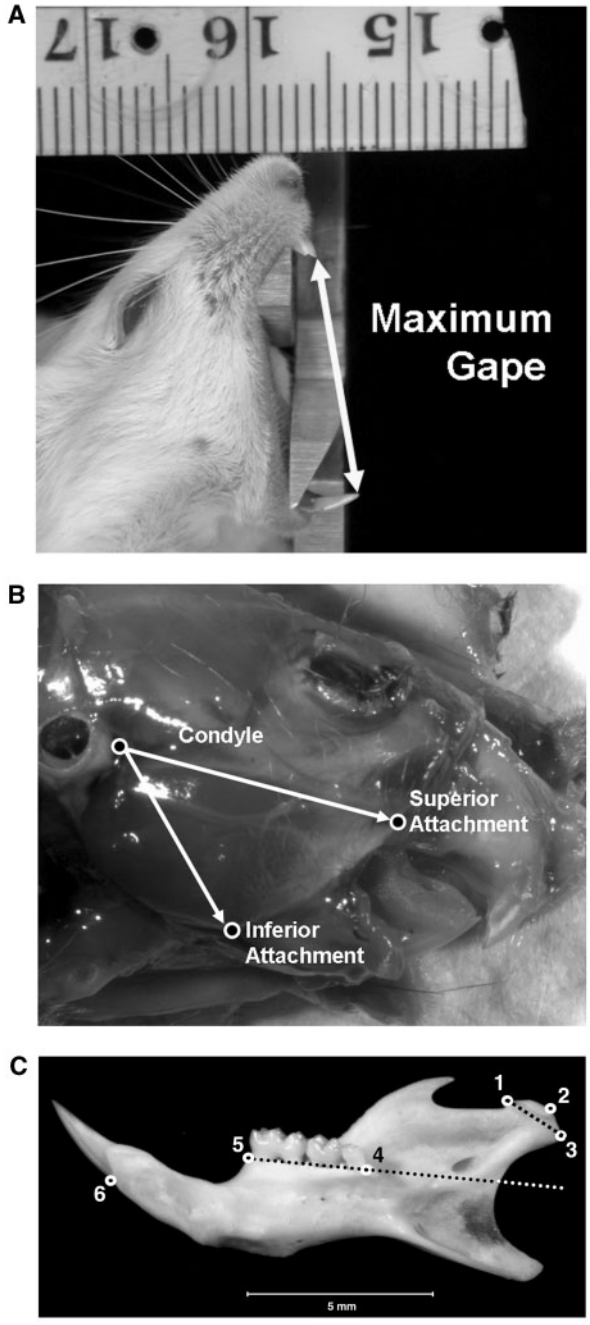

Fig. 2 Measurements and digitized landmarks used in estimating maximum jaw gape (**A**), the masseter attachment ratio (**B**), and several mandibular measurements that theoretically influence maximum jaw gape (**C**). Measurements are defined in Table 2. Landmarks in (C) are: Pt 1—anterosuperior extent of condylar articular surface; Pt 2—highest point on condyle taken perpendicular to line passing through points 1 and 3; Pt 3—posteroinferior extent of condylar articular surface; Pt 4—posterosuperior extent of M_3 alveolus; Pt 5—anterosuperior extent of M_1 alveolus; Pt 6—anteroinferior tip of incisor alveolus.

Analyses

An initial two-way analysis of variance (ANOVA) for gape identified significant effects of strain ($F = 61.9$, $P < 0.001$) and sex ($F = 46.6$, $P < 0.001$) and sex by strain interaction ($F = 7.34$, $P < 0.001$). Thus, we analyzed gapes in females and males separately. [Females and males differ in age within several of the strains. Examination of Table 1 and Fig. 3 shows some tendency for the older sex to have a larger gape within a particular strain. Because we lack variation in age within a sex for a strain, we cannot fully account for this factor in an ANOVA design. (This same problem exists for among-strain comparisons per sex, despite the lack of a significant age effect in the ANOVA comparisons.). We avoid this age-related sex-effect within strains by analyzing the two

Table 2 Performance, morphological measurements, and predicted morphological influences on maximum gape

Performance and morphological vriables	Measurement definition[a]	Predicted change for increased gape[b]
Maximum jaw gape	Distance between upper and lower incisor tips at maximum passive jaw opening (Fig. 2A)[d]	–
Masseter attachment ratio[c]	Ratio of condyle-superior masseter attachment distance to condyle—inferior masseter attachment distance (Fig. 2B)	Gape increases as ratio deviates from 1.0 because muscle stretch is reduced.[e]
Jaw length	Distance from the incisor alveolus to the posterior surface of the mandibular condyle (Fig. 2C: Pts 3–6)	Gape increases with increased jaw length.
Condyle length	Anteroposterior length of condylar articular surface (fig 2c: Pts 1–3)	Gape increases with elongated condyles as rotation is facilitated (at a given condylar curvature).[f]
Condyle articular height	Height of condylar articular surface (Fig. 2C: ⊥ from Pt. 2 to line created by Pts 1–3)	Gape increases with height as height relates to curvature. Increased curvature provides increased rotation.[g]
Condyle curvature	Angle of condylar curvature (Fig. 2C: angle created by Pts 1–2–3)	Gape increases with increased curvature as rotation is increased.[g]
Condyle height	Height of the condyle above the molar tooth row (Fig. 2C: ⊥ from Pt. 2 to line created by Pts 4–5).	Gape increases with lower condyle heights as muscle stretch is reduced.[e]
Body weight$^{0.33}$	Cube root of body weight	–

[a]Measurements or digitized points are depicted in Figure 2A–C. "Pt" or "Pts" refer to numbered digitized points defined in Fig. 2C. "⊥" symbolizes perpendicular from the indicated line.
[b]Predictions represent changes in morphology that would increase maximum gape, while holding all other factors constant. Linear relationships are assumed between morphologies and gape in statistical tests.
[c]The points of attachment of the superior and inferior masseter were identified on lateral-view photographs as the anterosuperior and anteroinferior extent of attachment for the superficial masseter on the skull, respectively.
[d]Wall (1999).
[e]Herring and Herring (1974).
[f]Ruff (1988), Hamrick (1996), and Vinyard et al. (2003).
[g]Herring (1972), Bouvier (1986), Jablonski (1993), and Wall (1999). Condyle curvature and condyle articular height both estimate curvature of the mandibular condyle and hence have similar predicted influences on gape. Condyle curvature and condyle articular height share significant phenotypic (females: $r = -0.78$, $P < 0.001$; males: $r = -0.75$, $P < 0.001$) and genetic (females: $r = -0.67$, $P = 0.001$; males: $r = -0.61$, $P = 0.003$) correlations across strains.

sexes separately.] We also observed that gape is significantly correlated with body weight$^{0.33}$ in both females ($r = 0.5$, $P < 0.001$) and males ($r = 0.6$, $P < 0.001$). We created shape ratios (Mosimann and James 1979) by dividing linear dimensions by body weight$^{0.33}$ and analyzed both absolute and relative measures of gape. Age was not a significant covariate in subsequent one-way ANOVAs for gape and relative gape in either females (gape: $F = 3.61$, $P = 0.06$; relative gape: $F = 1.53$, $P = 0.22$) or males (gape: $F = 0.78$, $P = 0.38$; relative gape: $F = 1.06$, $P = 0.31$). We subsequently ignored the effects due to age. [Age (in weeks) did not have a significant effect on gape in a one-way ANOVA across all individuals ($F = 0.49$, $P = 0.69$).]

Following these initial analyses, we performed one-way ANOVAs for absolute and relative gape by strains in females and males. We estimated broad-sense heritabilities using the coefficient of genetic determination (g^2) (Festing 1979; Falconer and Mackay 1997):

$$g^2 = \frac{\mathrm{MS}_{\mathrm{among}} - \mathrm{MS}_{\mathrm{within}}}{\mathrm{MS}_{\mathrm{among}} + (2n - 1) \times \mathrm{MS}_{\mathrm{within}}}$$

$\mathrm{MS}_{\mathrm{among}}$ and $\mathrm{MS}_{\mathrm{within}}$ were estimated mean squares from a fixed-effects ANOVA with strain as an independent variable and "n" = average sample size per strain (Festing 1979). We estimated the 95% confidence interval (CI) for g^2 from 1000 bootstrap replicates.

We examined phenotypic, genetic, and environmental correlations between gape and musculoskeletal dimensions theoretically related to maximum jaw-opening performance in both sexes. Using GLM in SPSS 13.0, we estimated phenotypic correlations from the total sum-of-squares and cross-products (SSCP) matrix (i.e., observable variation), genetic correlations from the among-strain SSCP matrix (i.e., among strains), and environmental correlations from the within SSCP matrix (i.e., within strains) (Mhyre et al. 2005). Significance for individual correlations were calculated using Fisher's r-to-Z transformation and $\alpha = 0.05$. We calculated correlations for both absolute and relative dimensions. When absolute or relative gape was significantly correlated with a musculoskeletal/size dimension in males and/or females, we compared male and female correlations

using an analysis of covariance (ANCOVA) for gape that included sex and the musculoskeletal dimension. A significant interaction effect between sex and the musculoskeletal measure was taken as initial evidence that male and female correlations differed between gape and the musculoskeletal dimension.

Results

Phenotypic variation and heritability of maximum gape

The inbred strains exhibit significant phenotypic variation in gape and relative gape (i.e., gape/body weight$^{0.33}$) both in females and males (Table 3; Fig. 3). Females differ from males within several of the strains, although within-strain variation in age between males and females likely plays some role in these differences. Coefficients of g^2 indicate a significant genetic component to this phenotypic variation (Table 3). This genetic component reflects additive and/or epistatic (i.e., additive × additive) variation. Because the strains are inbred, dominance does not contribute. This result represents the first evidence that variation in maximum-gape performance is heritable in a group of mammals.

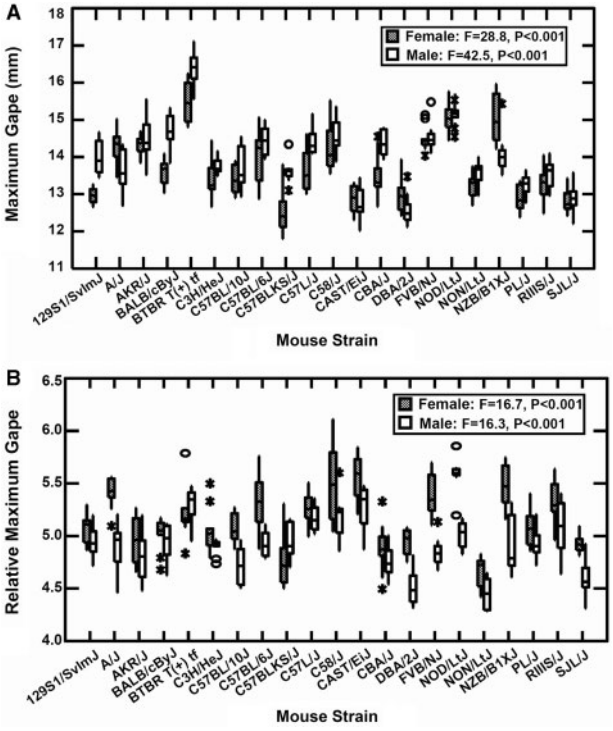

Fig. 3 Box plot of absolute (**A**) and relative (**B**) maximum gape for females and males across the 21 inbred-mouse strains. The inset provides values of *F* and *P* for the one-way ANOVAs comparing gapes among the strains as reported in Table 3. Each box indicates the interquartile range with the central line at the median. Vertical lines extending from a box indicate the range of observed values within 1.5 interquartile distances. Asterisks indicate values between 1.5 and 3.0 interquartile distances, while circles indicate values >3.0 interquartiles.

Correlations among gape and musculoskeletal dimensions

A second important question regarding the genetic architecture of gape focuses on the associations among maximum gape and the morphological variables that influence this jaw-opening performance. Absolute and relative maximum gapes are significantly correlated with body weight$^{0.33}$ both in males and females (Table 4; Fig. 4). As might be expected, larger mice tend to have larger gapes regardless of sex. The genetic correlations between absolute maximum gape and body weight are also highly significant (Table 4), suggesting a genetic contribution to the phenotypic pattern seen in Fig. 4. The significant negative phenotypic correlations between relative maximum gape and body weight (Table 4) suggest a decrease in relative gape with size across these strains. This observation is supported by the negatively allometric slope for regression of *ln* maximum gape on *ln* body weight$^{0.33}$ in females [least-squares regression slope (LSR slope) = 0.58 ± 0.14] and males (LSR slope = 0.66 ± 0.14). [In this comparison, isometry equals a slope of 1.0. Additionally, it is worth mentioning that the reduced-major axis regression estimates include both a potential isometric and positively allometric scaling pattern for these same data.]

Environmental correlations between relative gape and body weight are highly significant, suggesting that environmental factors might also contribute to

Table 3 Heritability estimates and one-way ANOVAs comparing maximum jaw gape and relative gape (gape/body weight$^{0.33}$) among strains for females and males

	Females			Males		
Variable	*F*	*P*-value[a]	g^2 (95% CI)[b]	*F*	*P*-value	g^2 (95% CI)
Gape	28.82	<0.001	0.57 (0.53–0.69)	42.50	<0.001	0.67 (0.61–0.77)
Relative Gape	16.67	<0.001	0.43 (0.38–0.57)	16.30	<0.001	0.42 (0.35–0.55)

[a]"*F*" and "*P*-value" indicate the *F*-statistic and associated *P*-value for one-way ANOVA comparing estimates of gape among strains.
[b]"g^2" indicates the coefficient of genetic determination (Festing 1979) as an estimate of the broad-sense heritabilities for gape measures. The 95% CI is given in parentheses.

Table 4 Phenotypic, genetic, and environmental correlations between gape or relative gape (gape/body weight$^{0.33}$) and musculoskeletal dimensions.

Musculoskeletal or size dimension[a]	Females			Males		
	Phenotypic[b]	Genetic	Environmental	Phenotypic	Genetic	Environmental
Body weight$^{0.33}$	**0.50**/**−0.37**	**0.58**/−0.33	**0.20**/**−0.49***	**0.60**/**−0.37**	**0.69**/−0.31	**0.15**/**−0.56**
Masseter attachment ratio	−0.07/−0.13	−0.07/−0.24	−0.09/−0.10	−0.11/−0.01	−0.34/−0.20	0.07/0.10
Jaw length	**0.38***/**0.20**	**0.45**/0.16	0.13/**0.32**	**0.58**/**0.42**	**0.68**/**0.45**	0.13/**0.37**
Condyle length	**0.36**/**0.21**	**0.52**/0.29	0.07/0.13	**0.42**/**0.26**	**0.62**/0.42	−0.04/0.04
Condyle articular height	0.04*/**0.18**	0.02/0.22	0.06/**0.17**	**0.27**/**0.23**	**0.63**/**0.57**	−0.10/0.01
Condyle curvature	**0.24***/−0.04	**0.46**/0.03	−0.03/−0.11	0.01/−0.06	−0.03/−0.13	0.06/0.02
Condyle height	−0.08/−0.10	−0.11/−0.18	−0.04/0.01	0.06/0.06	0.06/−0.01	0.07/**0.17**

[a]See Table 2 for measurement definitions.
[b]Product–moment correlations (r) between gape and musculoskeletal/size dimensions are listed first followed by correlations between relative gape and relative musculoskeletal dimensions. Linear dimensions were size-adjusted by dividing by body weight$^{0.33}$. The masseter attachment ratio and condyle curvature were not adjusted by body weight$^{0.33}$ as they are already dimensionless. Finally, body weight$^{0.33}$ was not altered in comparison with relative gape. Here, a significant correlation between relative gape and body weight$^{0.33}$ suggests an allometric relationship between gape and body weight. Values in **boldface** are significantly different from $r = 0$.
Asterisks indicate that correlations differ in males versus females. This determination is based on a significant interaction between sex and the musculoskeletal/size dimension in an ANCOVA for gape including sex and the musculoskeletal/size measure.

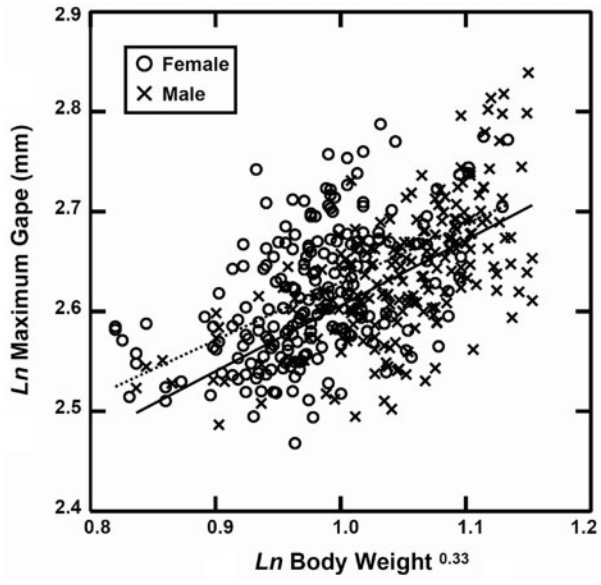

Fig. 4 Plot of *ln* maximum gape versus *ln* body weight$^{0.33}$ for female ($n = 207$) and male ($n = 206$) mice from the 21 inbred strains. The lines shown in the plot represent LSR slopes for females (LSR slope $= 0.58 \pm 0.14$, dashed line) and males (LSR slope $= 0.66 \pm 0.14$, solid line). Product–moment correlations between these variables are 0.50 for females and 0.60 for males. In all cases, estimates of slope and correlation are significantly different from zero ($P < 0.05$).

this phenotypic association (Table 4). We hypothesize that this environmental influence may reflect an overall negatively allometric pattern of growth for gapes and variation among individuals in their relative stages of somatic development (despite the constrained age of the samples).

We observe a mixed pattern of associations among gape and craniofacial measures that influence this performance (Table 4). Both the masseter attachment ratio and condyle height above the toothrow show little association with absolute or relative maximum gape across these strains (Table 4). Alternatively, both lengths of the jaw and of the condyle exhibit significant phenotypic correlations with absolute and relative maximum gape (Table 4). Significant genetic correlations are observed for these two lengths and absolute gape, but only relative jaw length in males shows a significant genetic correlation with relative maximum gape. The two shape measures of the mandibular condyle show sex-specific patterns. In males, condylar articular height exhibits significant phenotypic and genetic correlations both with absolute and relative maximum gapes (Table 4). While male and females differ significantly for phenotypic correlations between gape and condylar articular height (Table 4), a sex-specific difference in the genetic correlation only approaches significance (sex by condyle articular height; $F = 3.8$, $P = 0.059$). Alternatively, females exhibit significant phenotypic correlations with condylar curvature, while males do not (Table 4). These sex-related differences in correlation patterns may reflect size-related changes in condylar shape that are differentially captured by these two measures. In sum, the complex pattern of results hinders a simple, straightforward interpretation of the genetic architecture underlying jaw-opening performance in these strains.

Discussion

The inbred-mouse model in mammalian perspective

We have argued that inbred mice can be an informative model for mammalian morphologists by providing insight into the genetic architecture of function and performance. After noting that jaw opening is an important performance in several mammalian behaviors, we demonstrated the feasibility of this model by exploring the genetic architecture of maximum gape across several strains of inbred mice. In order to illustrate new insights gained through this inbred-mouse model, it is equally important to consider how these results relate to previous studies exploring the functional morphology of gape in mammals.

Numerous researchers studying form and function of the skull have suggested, either explicitly or implicitly, that maximum jaw-opening ability is an evolutionary adaptation related to feeding or to display behaviors in several mammalian clades (Herring 1972, 1975; Emerson and Radinsky 1980; Lucas 1981, 1982; Reduker 1983; Smith 1984; Jablonski 1993; Jablonski and Crompton 1994; Dumont and Herrel 2003; Vinyard et al. 2003; Viguier 2004; Hylander and Vinyard 2006). These studies typically use comparative metric analyses to link craniofacial morphologies to the behavioral observation of large gapes. One complication for interpreting the results from inbred strains in this broader evolutionary context is that variation in jaw morphology and gape performance has been influenced both by artificial processes, such as inbreeding, artificial selection, and manipulation of environments in which animals are reared, and evolutionary processes that established preexisting variation among progenitors of strains. The combination of artificial and natural sources of variation restricts our ability to confidently assert that differences among strains resulted from selection in a natural environment. The variation among strains, however, may represent a random sample of genes affecting these traits in the progenitor populations (assuming no selection on these traits in the strains). Furthermore, selective events throughout the evolution of house mice have likely influenced the observed associations among traits in these strains. Despite these interpretive challenges, we can confidently explore patterns of variation among strains as model pathways for changes in form and function during the evolution of gape-related behaviors in other mammals.

We suggest that this analysis of inbred mice offers three significant insights into comparative work on mammalian gapes. First, this study provides the first evidence of heritable variation in maximum jaw-opening ability in a mammalian group and demonstrates the potential for a genetic contribution to maximum gape in other mammalian species. Second, this analysis is one of only a few studies in mammals to quantify the relationships between maximum gape and its underlying morphological contributors. Outside of work with humans (Muto and Kanazawa 1996; Fukui et al. 2002; Hirsch et al. 2006), there has been little quantitative assessment of how craniofacial form relates to maximum gape. In part, this deficiency reflects the difficulty of measuring gapes in large samples of mammals. In contrast, the ability to measure large numbers of individuals is an added benefit of working with inbred mice. Third, this study offers the first evidence of a genetic association between gape and several morphological variables including craniofacial measures and body size. These correlations highlight the possibility of genetic contributions to craniofacial form and overall size that influence jaw-opening ability in mammals. By demonstrating a potential genetic basis for correlated change, the inbred-mice model supports these previously hypothesized adaptive scenarios describing the evolution of mammalian gapes.

Building a better morphological model of jaw gapes

In the final two sections, we briefly explore potential improvements in our original analysis as well as novel additions to this initial survey of strains in order to highlight how future work could build on our current findings.

A number of morphological factors potentially influence maximum gape. We only considered those relating to position of the masseter muscle and shape of the mandible. Several other possible influences are associated with limits of stretch in soft tissues of the masticatory apparatus. The fiber architecture of a muscle affects its extensibility, indicating that jaw-muscle architecture may play a role in limiting maximum gape (Herring and Herring 1974; Herring 1975; Taylor and Vinyard 2004; Satoh and Iwaku 2006). Similarly, the location and constituent tissues (e.g., collagen orientation and properties) of the skin at the angle of the mouth (Herring 1975), the aponeuroses of the masticatory muscles (Anapol and Herring 1989; Herring et al. 2002), the temporomandibular as well as the accessory mandibular ligaments (Osborn 1989, 1993) may each limit maximum gape in different animals. Many of these soft-tissue components are difficult to quantify despite their possible role in limiting gape. Taylor et al. (2008) provided an initial

analysis of variation in masseter fiber architecture for the mice examined here. The preliminary results of this work suggest that strains with relatively longer masseter fibers have larger gapes, thereby furthering the potential role of muscle fiber architecture as a gape-limiting factor in mammalian evolution.

Developing the analysis of genetic architecture: new experiments and analyses

We did not observe a consistent pattern of correlations between maximum gape and the craniofacial variables that potentially influence this trait (with the exception of overall size). One explanation of this pattern combines the multiple morphological factors that can potentially influence maximum gape with the historical observation that maximum gape was likely altered several times, independently, during the development of these strains. Thus, in all likelihood these independent changes in gape resulted from different changes in craniofacial morphology. Given this potential for different morphologies underlying the independent changes in gape, we would not necessarily expect a strong pattern of correlations among strains in this structurally redundant system. [The nested relationships among inbred strains of mice (Petkov et al. 2004) likely contributes to the observed patterns of correlations as no account was made for it in this analysis.] One of the important implications from this observation for mammalian comparative analyses is that mice may not exhibit biases that limit modifications of gape to one or a few of these potential morphological pathways. This translates into an expectation of diverse patterns of morphological changes related to the independent evolution of large gapes in different mammalian clades (Vinyard et al. 2003).

The observed pattern of correlations is also partly related to our decision to survey gapes across a large number of inbred strains. We predict that a subsequent analysis of progeny from a cross of two strains differing in maximum gape would generate stronger correlations between gape and a specific set of these morphological variables. By effectively reducing the number of independent changes in gape, we would be better able to identify the morphological contribution to differences in maximum gape for those two strains. The choice of strains would require careful consideration as different crosses would likely result in different observed patterns of morphological influence on gape performance. This initial survey across strains both justifies this future cross(es) and provides the necessary preliminary data for identifying appropriate strains for this future analysis.

The feasibility of conducting crosses also opens the door to identifying specific genomic regions and genes that underlie the genetic variation in gape documented in this survey. The availability of very large numbers of informative molecular markers (Frazer et al. 2007) and the prolific breeding patterns of these strains facilitate the straightforward identification of QTL for differences in gape between any pair of strains using a standard F2 or backcross design. These genomic regions can be subsequently narrowed by constructing recombinant inbred lines and congenic strains. Furthermore, genomic regions contributing to variation in gape can be nominated even without performing crosses by testing for correlations between gape and marker genotypes across the inbred strain panel surveyed here.

Although the small number and unusual history of the classical inbred strains causes reductions in power and increases in the false-positive rate for such genome-wide association mapping (Payseur and Place 2007), the possibility of finding genes that underlie variation in performance traits, such as maximum gape, will motivate improvements in analytical methods. Collectively, the existing power and future promise of genetic analyses in inbred mice make it a highly attractive model system for exploring the genetic basis of function and performance in mammalian functional morphology.

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