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Development of the mouse mandible: a model system for complex morphological structures

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Introduction

Our understanding of evolutionary processes has changed tremendously in the last few decades, most notably by advances in genetics and developmental biology that have transformed the approaches of evolutionary biologists (Amundson, 2005; Klingenberg, 2010). Among other changes, the use of model systems has become more widespread in evolutionary biology. One of those models is the mandible of the house mouse, which is now widely used as a model for complex morphological structures in general (Atchley and Hall, 1991; Atchley, 1993).

The mandible is a complex structure with respect to its composition, developmental origin, and function. It is composed of several anatomical units: the ramus, the coronoid, condylar and angular processes, and the alveolar components where the teeth insert (Moore, 1981; Atchley and Hall, 1991). It is made up of bone, cartilage, and the mineralized tissues of the teeth, as well as other types of connective tissues, bone marrow, nerves, and vascular tissues. The mandible develops from cells of the neural crest and paraxial mesoderm under the influence of various signalling interactions (Depew *et al.*, 2002; Hall, 2005; Chai and Maxson, 2006). Mandibular structure reflects various functional demands for gnawing and chewing, which in turn feed back to development and growth through bone remodelling (Renaud *et al.*, 2010). A key property of the anatomical, developmental, and functional complexity of the mouse mandible, like other morphological structures, is that it is shaped by various interactions and feedbacks among the processes involved, which leads to integration and possible modular organization of its component parts (Klingenberg, 2008).

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Despite this complexity, the mandible is sufficiently simple so that the effects of the various processes contributing to its development and variation can be identified and studied. Because it is a single bone, the mandible of the mouse and other rodents is suitable for morphometric studies and has been used widely to study intraspecific variation (Klingenberg *et al.*, 2003) as well as evolutionary change (Monteiro *et al.*, 2005; Zelditch *et al.*, 2008). Because the mouse has long been a model organism in genetics, many resources are available for studying the genetic basis of shape variation in the mandible (Klingenberg and Leamy, 2001; Klingenberg *et al.*, 2001). The dentition provides the opportunity for studying a somewhat different kind of complexity (Workman *et al.*, 2002; Macholán, 2006; Laffont *et al.*, 2009).

This chapter provides a review of the development of the mouse mandible, including embryonic patterning and morphogenesis, as well as postembryonic growth and remodelling. We also summarize genetic studies of mandible shape, using either quantitative trait locus (QTL) approaches or classical quantitative genetics. Based on this developmental and genetic perspective, we discuss findings on the evolution of mandible shape in mice and other rodents. Finally, we evaluate what can be learned from the mouse mandible as a model of a complex morphological structure that can be applied to other structures.

Development of the mandible

The mouse mandible consists of several anatomically and functionally differentiated parts, which are also developmentally distinct (Fig. 6.1; Atchley and Hall, 1991). The posterior part of the mandible, the ascending ramus, consists of several parts that serve for the attachment of the mandible to the cranium and for insertion of the jaw musculature. The condylar process articulates with the cranium to form the temporomandibular joint. The most powerful of the jaw muscles is the masseter, which attaches to a large area on the outside of the mandible extending to the angular process, whereas the temporalis muscle, attaching to the coronoid process, is weaker. The anterior part of the mandible supports the teeth and serves for transmission of the forces generated by the jaw muscles to the food or other substrate. This part contains the teeth, which are embedded in alveolar bone that is partly derived from cells of the tooth bud mesenchyme (Diep *et al.*, 2009). The alveolus of the incisor tooth extends far back through the ramus of the mandible, whereas the three molar teeth are grouped together in a region posterior to a wide diastema, a toothless region between the incisor and first molar.

These anatomically distinct components of the mandible also have separate developmental origins, but are integrated into mandible in a highly controlled

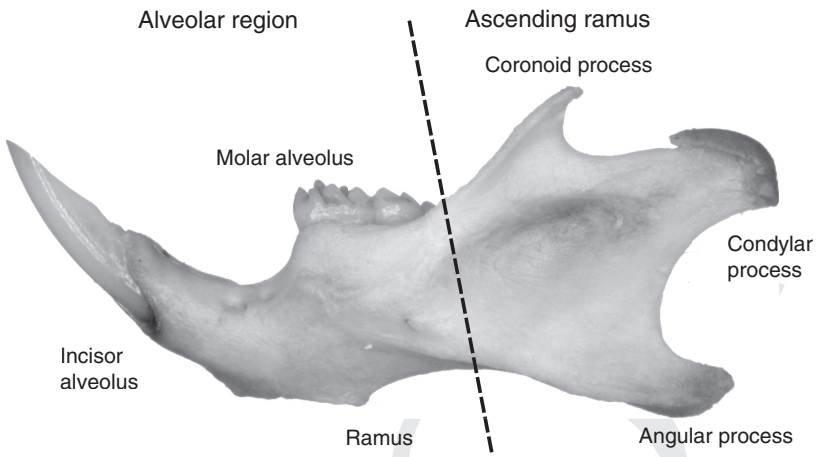

Figure 6.1 The main anatomical parts of the mouse mandible in lateral view. The dashed line is a rough indication of the boundary between the alveolar region and ascending ramus.

manner. While more and more information on the developmental processes involved in the patterning and growth of the mandible is available (Depew *et al.*, 2002; Hall, 2005; Chai and Maxson, 2006; Depew and Simpson, 2006), many questions remain unanswered. In particular, developmental genetic approaches, while powerful for identifying pathways involved in mandible development, are less well suited to investigating how those pathways are integrated and fine-tuned to produce a functional structure and respond to outside stimuli in a coordinated way. Quantitative approaches are more useful for addressing those issues (Klingenberg, 2010). In the end, however, both approaches need to be combined if we are to reach a full understanding of mandible development.

Embryonic development and patterning

Much of the mandible is formed by cells that originate from the cranial neural crest and migrate into the branchial arch region, but cells from the paraxial mesoderm also contribute substantially to the mandible (Chai *et al.*, 2000; Depew *et al.*, 2002; Aggarval *et al.*, 2010). The mandible forms in close association to Meckel's cartilage, which is also substantially derived from neural crest and acts as a sort of scaffold for the mandible (Moore, 1981; Tomo *et al.*, 1997; Depew *et al.*, 2002; Ramaesh and Bard, 2003). Meckel's cartilage originates as a pair of straight rods that grow anteriorly and posteriorly from the molar region of the prospective mandible and fuse together anteriorly. The body of the mandible

forms as a mesenchymal cell concentration lateral to Meckel's cartilage and expands to surround it as well as the developing teeth (Ramaesh and Bard, 2003). The body of the mandible undergoes intramembranous ossification, whereas the angular, condylar, and coronoid processes originate from cartilages that derive from separate mesenchymal condensations (Tomo *et al.*, 1997; Ramaesh and Bard, 2003). The anterior part of Meckel's cartilage eventually disappears, partly by resorption and partly by being incorporated in the rostral-most part of the mandible (Ramaesh and Bard, 2003).

The formation of the mandible is accompanied by a variety of signalling and regulatory events that induce and coordinate patterning and morphogenesis and achieve its spatial patterning. Signalling interactions that are critical for mandible formation take place between the mesenchyme and both the oral ectoderm and pharyngeal endoderm (Depew *et al.*, 2002; Chai and Maxson, 2006). These events establish the identity of branchial arches and set up a molecular 'coordinate system' within each branchial arch, which provides the basis for the elaboration of prospective mandibular structures (Depew *et al.*, 2002; Chai and Maxson, 2006). For instance, the *Dlx* genes are important in conveying positional information in the jaws through a '*Dlx* code' (Depew *et al.*, 2005). Signalling interactions and positional specification enable the development of the mandible in a coordinated manner.

The development of teeth has been a focus of particular attention (e.g. Catón and Tucker, 2009; Cobourne and Sharpe, 2010). Teeth are particularly interesting because of their wide range of morphologies in any one species (chisel-shaped incisors and multi-cusped molars in mice) and because of the marked evolution of their number and appearance (Kavanagh *et al.*, 2007; Cobourne and Sharpe, 2010). Tooth development is initiated by signalling interactions between oral epithelium and the underlying mesenchyme, and both epithelium and mesenchyme contribute cells to the developing tooth (Chai *et al.*, 2000; Catón and Tucker, 2009). The mouse dentition is highly reduced by comparison to other mammals: each quadrant of the mouth has only a single incisor and three molars, which are separated by the diastema, an extensive gap without teeth. During embryonic development of mice, tooth primordia that may correspond to the 'missing' premolar teeth form in the region of the prospective diastema, but these primordia are either resorbed or incorporated into the first molar tooth (Prochazka *et al.*, 2010). Signalling between teeth developing in adjacent positions is important for the control of molar number and size, and may have important implications for the potential for evolutionary change (Kangas *et al.*, 2004; Kavanagh *et al.*, 2007).

Overall, the available evidence indicates that mandible development is a highly interactive process that involves many molecular cellular mechanisms. Accordingly, it is no surprise that knock-out experiments for a large number of genes produce craniofacial abnormalities as part of their phenotypic effects

(e.g. review by Depew *et al.*, 2002). In addition, it is to be expected that many additional genes are involved in these processes, even if elimination of their activity does not produce an obvious morphological effect.

Molecular approaches to the study of craniofacial development have mostly focused on the consequences of experimental intervention on patterns of gene expression or on gross phenotypes that were assessed qualitatively. Embryonic development is also increasingly investigated with morphometric methods to capture subtle morphological changes (Young *et al.*, 2007; Boughner *et al.*, 2008; Parsons *et al.*, 2008; Schmidt *et al.*, 2010). These studies used computed tomography to produce scans of embryos, from which landmark positions were recorded for geometric morphometric analyses. This method is promising for the direct study of embryonic development of craniofacial shape, but it also faces considerable methodological challenges, such as substantial artefacts from changes of size and shape during fixation (Schmidt *et al.*, 2010).

Postembryonic growth and remodelling

Development is not terminated at birth; rather, the mouse mandible undergoes considerable change in size and shape during postembryonic growth. There are pronounced changes in the shape of the mandible during postnatal growth, particularly a strong development of the coronoid and angular processes, which leads to an increase in the relative height of the mandible. This is an example of the nearly ubiquitous phenomenon of ontogenetic allometry, the systematic association of changes of size and shape during growth (Cock, 1966; Gould, 1966; Klingenberg, 1996). Even among adult mice, there is clear static allometry, and relation between size and shape within samples of mice of the same age and from the same population. This has been shown by associations of mandible measurements with measures of body size in mice (Atchley *et al.*, 1985b; Bailey, 1985), as well as by the current methods of geometric morphometrics, which show that size and shape of the mandible itself are clearly associated (Fig. 6.2).

Because variation in the extent of growth is an important possible source of variation at a given stage, the connection between static and ontogenetic allometry is potentially important for understanding the origin of phenotypic variation in populations (Cheverud, 1982; Klingenberg and Zimmermann, 1992; Klingenberg, 1998). The pattern of static allometry in the mouse mandible (Fig. 6.2) is qualitatively similar to the main shape changes in postembryonic growth. For other measurements in mice, relationships between static and ontogenetic allometry have also been reported (Leamy and Bradley, 1982), and there are also clear relations to the patterns of evolutionary allometry concerning the divergence among related species (Atchley, 1993). Using the current methods

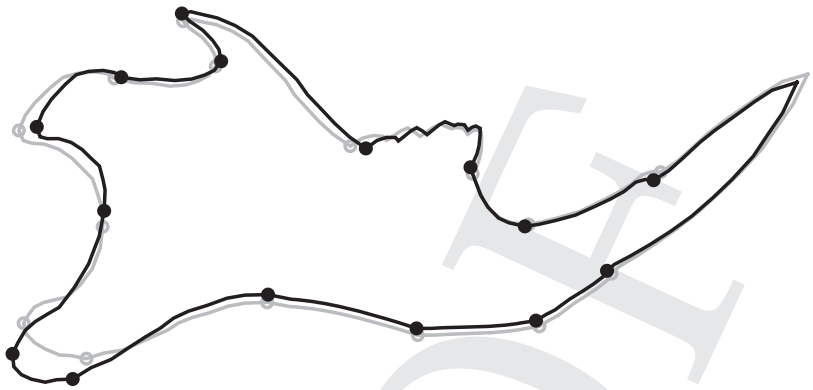

Figure 6.2 Static allometry in the mouse mandible. The diagram shows the change from the average shape (grey outline) to the shape expected for a mandible with a centroid size 5 mm greater than average (an approximately 30% increase). Mandible shape in a heterogeneous stock of mice (Valdar *et al.*, 2006) is characterized by 15 morphological landmarks whose coordinates were subjected to Procrustes analysis (Dryden and Mardia, 1998; Klingenberg, 2010). The allometric change is estimated by multivariate regression of shape on centroid size (Monteiro, 1999; Drake and Klingenberg, 2008).

of geometric morphometrics, such a relationship between static allometry and evolutionary diversification of mandible shape was recently established in a study of mainland and island forms of the house mouse (Renaud and Auffray, 2010). Overall, these studies of allometry highlight the potential for growth processes to provide biases or constraints for evolutionary diversification of mandibular morphology (Arthur, 2001; Klingenberg, 2010).

Bone growth is a dynamic process in which resorption and new deposition of the intercellular matrix in bone tissue create a turnover of material (Enlow and Hans, 1996; Hall, 2005). This remodelling of bone is able to respond to mechanical forces experienced (Herring, 1993), and is therefore a means for developmental processes to respond to environmental stimuli.

A number of studies have documented the effects of the mechanical stimuli on craniofacial morphology in mice with several experimental approaches. Lightfoot and German (1998) used two strains of mice carrying mutations that cause muscular dystrophy and compared the course of growth with a healthy control strain. Mice with the more severe mutation showed considerably reduced growth of various measurements, including the mandible, whereas the more weakly dystrophic strain showed less clear differences. In a different strain of mice with muscular dystrophy, males had larger mandibles than the controls (Renaud *et al.*, 2010). In a strain of mice with overdeveloped musculature due to myostatin deficiency, mandibles were

smaller in newborn mice than in controls, but grew larger by the age of 180 days (Vecchione *et al.*, 2010). Mandible shape also responded to these differences in mechanical loading by genetic manipulations of muscle activity (Renaud *et al.*, 2010; Vecchione *et al.*, 2010). Similarly, experimental manipulation of the forces that the mandible experienced by feeding mice either hard or soft food also produced a clear effect on mandible shape (Renaud and Auffray, 2010; Renaud *et al.*, 2010). Another study manipulated the mechanical loading of the mandible by trimming the tip of the mandibular incisor teeth and found a clear response by a lengthening of the condyle (Tagliaro *et al.*, 2009). All these studies show that the mandible can respond by altered growth to various changes in the mechanical forces acting on it. This remodelling enables the mandible to adapt to changes in the environmental conditions and may have considerable evolutionary implications (West-Eberhard, 2003).

Developmental integration and modularity

Morphological structures are integrated so that variation in one part is associated with variation in other parts to maintain overall functionality of the structure as a whole. Development is an important cause of integration, because developmental interactions are the basis for an important component of observable covariation between traits (Klingenberg, 2010).

To investigate the developmental component of integration, it is therefore important to identify covariation of morphological traits that is caused by developmental interactions and to separate it from covariation from other possible origins. An effective way to achieve this is to focus on the covariation in the fluctuating asymmetry among different traits (Klingenberg, 2003, 2005). Because fluctuating asymmetry arises from random variation in developmental processes, correlations between the asymmetries of different traits only occur if there are direct developmental interactions between the developmental processes that produce the traits, so that variation can be transmitted between them. Likewise, the focus on asymmetry also automatically minimizes the effects of confounding factors such as genetic and environmental variation, which can generate covariation among traits without direct developmental interactions between them (for more detailed discussion, see Klingenberg, 2003, 2005).

Integration of asymmetry in the mouse mandible was first reported in a study using traditional morphometric methods (Leamy, 1993), and later confirmed with a geometric morphometric approach (Klingenberg *et al.*, 2003; Klingenberg, 2009). Because the patterns of covariation for fluctuating asymmetry and for the variation among individuals are broadly consistent, it appears likely that a substantial component of the observable phenotypic integration in the mandible originates

from direct developmental interactions. A similar study was also conducted for the mandible of deer mice (*Peromyscus maniculatus*) and produced comparable results (Zelditch *et al*., 2008).

Laffont *et al*. (2009) investigated developmental integration in the molar tooth row of voles (*Microtus arvalis*). They found significant covariation between different teeth for the variation among individuals, but not for fluctuating asymmetry. This contrast suggests that the different molar teeth are developmentally independent of each other to a considerable degree.

Inheritance of mandible shape

To investigate the genetic basis of mandible shape in mice, a range of approaches are available. Because the mouse is a classical model organism in genetics, the genetic tools are particularly well developed. First, the approach of developmental genetics focuses on particular genes of interest and uses loss-of-function mutations to eliminate their function. This approach tends to produce large phenotypic effects that are relatively easy to interpret, and therefore yields unambiguous evidence concerning the gene's involvement in particular processes. But this approach is artificial in a number of ways and therefore is unsuitable for answering many questions, particularly in an evolutionary context. An alternative is to use a QTL approach, to search for genomic regions or genes that are responsible for variation in phenotypic traits. This approach provides useful information about the genetic architecture of a trait, but there are also limitations due to statistical power with manageable sample sizes. Finally, there is the approach of classical quantitative genetics, where information about relatedness among the individuals in the study is used to estimate genetic components of variance and covariance for the traits of interest. This approach is very flexible in that it provides direct information on the total genetic variation and constraints in a population and can be applied in many contexts, as long as genealogical information is available. But this approach does not provide any information about the number, location, or identity of the genes responsible for the observed variation. All three approaches have been used for the study of mouse mandibles. Because the first approach, focusing on particular candidate genes, has mostly been used in developmental genetics, we will not discuss it further here (see discussion above and especially Depew *et al*., 2002).

Analysis of genetic architecture

Several studies have searched for quantitative trait loci (QTLs) affecting the morphology of the mandible in mice. The most widespread method is to use the F_2 generation from a cross between two inbred lines of mice, and to obtain

both the trait measurements and genotype information for genetic markers from a large number of individuals. The QTLs can then be found by correlations between markers and the traits (Lynch and Walsh, 1998).

Cheverud *et al.* (1997) conducted a search for QTLs affecting linear measurements of the mandible in a cross between the Large (LG/J) and Small (SM/J) inbred strains of mice. They found that multiple traits affected by the same QTLs tended to be concentrated either in the alveolar region or in the ascending ramus of the mandible, suggesting a degree of genetic modularity. This impression was reinforced by later analyses (Mezey *et al.*, 2000; Ehrich *et al.*, 2003). Similarly, a QTL analysis for a range of skull measurements in the same cross produced a similar distinction between QTLs affecting mostly measurements of skull parts that are initiated early or late in embryonic development (Leamy *et al.*, 1999).

The methods of geometric morphometrics were applied to analyse landmark data for the same cross of mice (Klingenberg *et al.*, 2001, 2004). The search yielded a substantial number of QTLs, but principal component analysis did not show a clear division between clusters of QTLs whose effects are mostly either in the anterior or posterior region of the mandible. A further analysis suggested that there was a very weak degree of modularity between the two parts of the mandible with respect to the QTL effects (Klingenberg *et al.*, 2004). Moreover, the analysis of QTLs for geometric shape revealed fairly substantial dominance effects. A similar search for QTLs affecting the shape of the molar tooth row produced comparable results (Workman *et al.*, 2002). The QTL study by Burgio *et al.* (2009) used a different design, recombinant congenic strains, to map QTLs affecting cranial shape.

Genetic integration and constraints

To examine the patterns of genetic integration and possible genetic constraints, it is possible to estimate genetic and environmental components of variance and covariance for the traits of interest. This is the approach of classical quantitative genetics, which has recently seen much renewed interest (Falconer and Mackay, 1996; Lynch and Walsh, 1998; Kruuk *et al.*, 2008). This approach has been used extensively for distance measurements of the mouse mandible (e.g. Atchley *et al.*, 1985a, b; Atchley, 1993).

More recently, the methods of geometric morphometrics have been applied in this context (Klingenberg and Leamy, 2001). This study was based on a parent–offspring breeding design and used the 'animal model' to estimate variance and covariance components for the shape variables (Lynch and Walsh, 1998; Wilson *et al.*, 2010). The results showed that different shape variables differed considerably in their heritabilities: there was a range from more than 0.7 to near-zero.

Using the multivariate breeder's equation, predictions were made for the response to several hypothetical selection regimes, which suggested that the genetic covariance structure of the mandible deflected the response away from the direction of selection by a considerable angle. Overall, therefore, there is clear evidence for relative constraints, but there is no clear evidence for absolute constraints (see also the discussion in Klingenberg *et al.*, 2010).

The patterns of integration for the genetic and phenotypic covariance matrices of the mouse mandible were similar (Klingenberg and Leamy, 2001) and were also similar to the main patterns of variation among the effects of QTLs obtained by separate studies (Klingenberg *et al.*, 2001, 2004). It therefore appears that there is a consistent pattern of variation at both the phenotypic and genetic levels.

Evolution of mandible shape in mice and other rodents

Studies of variation in the house mouse mandible can provide valuable information that can assist investigators to interpret results from field studies. House mice have diversified considerably, and there are studies that have analysed changes of mandible shape. Renaud and Auffray (2010) compared mandible shape of mice from continental and island populations and considered the possible roles of diet and allometry. Corti and Rohlf (2001) studied mandibles and skulls of different chromosome races of mice, and even found a correlation between mandible shape and aggressive behaviour.

Studies of house mice also provide a basis for analyses in other rodents. Various investigators have studied the evolution of mandible shape in groups such as marmots (Cardini, 2003; Caumul and Polly, 2005), squirrels (Velhagen and Roth, 1997; Swiderski and Zelditch, 2010), or spiny rats (Monteiro *et al.*, 2005; Monteiro and dos Reis, 2005). These studies cover a wide spectrum of approaches and a great diversity of species, but the information derived from studies of house mice provides a useful background for them.

The mouse mandible as a model system

The use of the mouse mandible as a general model system for 'complex morphological structures' (Atchley and Hall, 1991) has inspired many researchers. Accordingly, many of them investigated the mandible in other mammals, such as bats (Monteiro and Nogueira, 2010) and shrews (Young and Badyaev, 2006). This raises the question of how far one can extrapolate the insights gained in this one-model system. How simple or how complex can a system be? And how far can the insights be extended to phylogenetically remote taxa?

The mandible is intermediate in anatomical complexity between systems such as insect wings and the mammalian cranium. Insect wings are structurally simple (a single epithelium folded over once) and also presumably have a relatively simple development (although it is known in great detail only for *Drosopila*). In contrast, the cranium is substantially more complex than the mandible, because it contains more structural parts, which also imply many developmental processes that are all highly interactive. So the question is whether the findings from these simpler or more complex systems will be compatible with the intermediate level of the mandible. It is too early to answer this question conclusively. From our personal experience, however, we have the impression that many general patterns extend across these levels. Besides the generality across levels, there is also a good deal of diversity among closely similar systems, which makes any large-scale generalization difficult. But in any case, regardless of the ability to generalize results, the mouse mandible has been a most fruitful model system in that it has produced a large number of pioneering studies that provide inspiration for work in other systems.

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