HERITABILITY AND GENETIC CORRELATIONS IN THE DENTAL DIMENSIONS OF *SAGUINUS FUSCICOLLIS* AND *MACACA MULATTA*

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Abstract

The genetic inheritance of dental traits in primates is of interest to biological anthropologists due to the high-quality preservation of dental remains in the primate fossil record and, as a result, the frequent use of dental morphology in the study of primate evolution. Adaptive hypotheses for morphological evolution in the primate dentition often discuss individual teeth as independent characters, yet the dentition may be best described as an organ composed of serially homologous parts. Previous studies have shown that dental dimensions are both highly heritable and frequently genetically correlated with other dental features in human and baboon populations, yet it remains to be seen whether tooth size heritabilities and patterns of genetic correlation differ in primate populations with different living conditions or evolutionary histories. This dissertation uses quantitative genetic parameters estimated in the dental dimensions of brown-mantled tamarins (*Saguinus fuscicollis*) and rhesus macaques (*Macaca mulatta*) to address these blank spaces in our understanding of the genetic inheritance and integration of primate tooth size. The findings of this research further our knowledge of the genetic inheritance of tooth size in primates and generate new hypotheses about the impact of genetic integration on the evolution of the canine-premolar honing complex and the dentition more broadly.

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1 Introduction

Dental morphology is widely used to describe and differentiate fossil taxa in paleoanthropology due to the excellent preservation of dental remains in the primate fossil record. Much of our understanding of the evolutionary history of primates therefore relies upon our interpretations of morphological similarities and differences in the dentition. Although combined evolutionary and developmental approaches to the study of phenotypic patterning in primate dental characters have produced useful theoretical frameworks, these methods tend to describe morphological patterns observed on a large evolutionary scale. Additional analytical methods may be necessary to explain the slight variation in tooth morphology within populations upon which selection can act. Through quantitative genetic analyses, it is possible to evaluate the genetic structures underlying variation in dental morphology at the population level. Deeper knowledge of these genetic structures will help in the generation of more accurate hypotheses of primate phylogeny and adaptation that account for the manner in which genetic variability and correlation constrain and accelerate the evolution of dental morphology.

Adaptation in complex traits, including dental morphology, in natural settings occurs through multivariate selection acting upon multiple phenotypes simultaneously. The impact of selection on complex morphology is therefore multivariate in several respects: multiple selection pressures act simultaneously; multiple traits are under selection simultaneously; selection on polygenic traits impacts variation in many genes; selection on genetically correlated traits impacts genetic variation in many traits. The

interactions between selection pressures and traits, as modeled by Lande (1979), are expected to impact the evolution of correlated traits and produce different phenotypic responses to selection than would be predicted by univariate models. Deeper knowledge of the genetic inheritance of and genetic correlations between dental dimensions in primates will empower researchers to better account for genetic constraint and correlated response to selection in discussions of primate phylogeny and evolution.

Previous quantitative genetic studies of primate dental traits have estimated high heritabilities in tooth dimensions (Townsend and Brown, 1978; Townsend, 1980; Hughes et al., 2000; Dempsey and Townsend, 2001; Hlusko et al., 2002; Townsend et al., 2009b; Koh et al., 2010; Stojanowski et al., 2017), and have demonstrated significant positive genetic correlations between dental dimensions (Hlusko and Mahaney, 2009; Hlusko et al., 2011; Stojanowski et al., 2017). Although the interpretation of heritability and genetic correlation estimates is often complex due to estimate uncertainty and the impacts of population structure on estimates, a high heritability estimate generally demonstrates that variation in a trait is genetically inherited while a positive genetic correlation estimate suggests that the covariation between two traits is influenced by the same loci through pleiotropy or by loci that are inherited together through linkage disequilibrium. The genetic correlations estimated in primate dental traits may also indicate that correlated response to selection and multivariate selection pressures could impact the evolution of the primate dentition. The presence of complex genetic relationships between teeth in some primate populations demonstrates the need to investigate further how variable these genetic patterns are in primates broadly. Greater knowledge of genetic correlations in the

dental traits of a variety of primate populations will help anthropologists in the investigation of the evolution of genetically correlated morphological features.

This dissertation research estimates heritabilities of and genetic correlations between dental dimensions in two primate populations in which these parameters have not been previously estimated. The brown-mantled tamarin population (*Saguinus fuscicollis illigeri*) used in this research is the first platyrrhine population to be included in quantitative genetic analyses of dental dimensions. The Cayo Santiago rhesus macaque population (*Macaca mulatta*) included in this research is the first free-ranging non-human primate population in which quantitative genetic parameters of tooth size have been estimated. Results from this macaque population are also useful in comparison to results of previous studies of the the Southwest National Primate Research Center (SNPRC) hamadryas baboon population (*Papio hamadryas*) (Hlusko et al., 2002, 2011; Hlusko and Mahaney, 2009; Koh et al., 2010), since both are sexually dimorphic papionins. Through analyses of these two populations, the studies presented in this dissertation demonstrate that variation in dental dimensions tends to be highly heritable across a variety of primate populations. These studies also indicate that genetic integration in the primate toothrow is variable across populations, and that this variation may reflect the diverse evolutionary and environmental forces acting upon the dentition of different primate taxa. This chapter describes the models of dental patterning that are discussed throughout this dissertation and reviews quantitative genetic theory and its applications in the study of primate dental traits.

1.1 Dental Patterning and Morphology in Primates

1.1.1 Dental patterning

The mammalian dentition consists of serially homologous teeth that, while similar in overall structure, bear morphological differences governed by complex patterns. Odontogenesis occurs through epithelial-mesenchymal interaction, in which signaling between the oral ectoderm and neural crest cells result in the initiation of tooth development (Sharpe, 2001). Research into the genetic and developmental regulation of individual tooth morphology indicates that the same genes are, for the most part, involved in cusp development in mammals, and that differences in cusp placement between teeth may result from differences in timing rather than genetic activity (Jernvall and Thesleff; Keränen et al., 1998; Weiss et al., 1998). More recently, research has focused on the broader patterning of the mammalian dentition.

The developmental differentiation of tooth types within the maxilla and mandible has been classically explained using two distinct models. Butler's morphogenetic field model used the concept of morphogenetic gradients to explain morphological differences based on tooth position (Butler, 1939). The clone model ascribed these morphological differences not to the location of tooth development, but to the tissue of the dental lamina which buds off of earlier developing teeth to initiate development of the next tooth in the sequence (Osborn, 1978). These two models therefore disagree over whether the source of the patterning signal is the environment of tooth development or the tissue of the tooth. The identification of homeobox and other regulatory genes involved in odontogenesis led

to the formulation of an updated version of the clone model, the odontogenic homeobox code, which accounts for differential expression of some regulatory genes in incisors and molars (reviewed in Thesleff and Sharpe, 1997). It is now recognized that differences in gene expression in tooth tissues and the location of tooth development within the jaw likely both impact tooth differentiation and morphology, leading to a synthesis of the field, clone, and odontogenic homeobox code models (Mitsiadis and Smith, 2006; Townsend et al., 2009a). Assessments of these models of dental patterning have relied primarily on experimental manipulations of rodent teeth and observed differences in humans in clinical settings, yet quantitative genetic analyses of tooth size and morphology could also indicate how shared genetic contributions across the toothrow impact dental patterning.

Recent research on dental patterning in mammals has identified inhibitory interactions between developing teeth. The impacts of these interactions are described by the inhibitory cascade model (Kavanagh et al., 2007), which states that the development of one tooth is variably inhibited by neighboring teeth that precede and succeed them in the developmental sequence. This model indicates that the size relationships between molars in any mammalian species would be predictable based on the strength of activation and inhibition during tooth development. The primary dentition also plays an important role in the inhibitory cascade (Evans et al., 2016). Assessment of the inhibitory cascade model through quantitative genetic analyses would require genetic correlation estimates with lower uncertainty than those included in this dissertation, and the results would be difficult to interpret as relating specifically to the inhibitory cascade since they

would also reflect other pleiotropic effects between dental dimensions. For these reasons, the inhibitory cascade model is not assessed here, but should be addressed in future quantitative genetic analyses of primate dental dimensions.

1.1.2 Teeth of Saguinus fuscicollis

While the general development and patterning of the primate dentition is consistent across the Primate order, there is considerable variation in the dental formula and dental morphology of extant primates. The differences between primate species and the evolutionary histories of these differences provide useful information about the patterning of dental dimensions. This dissertation describes the inheritance of tooth dimensions in brown-mantled tamarins and rhesus macaques, so the dental morphology of these two species is described here.

Brown-mantled tamarins (*Saguinus fuscicollis*) are small-bodied platyrrhine primates in the subfamily Callitrichinae with body weights ranging from 350 to 410 grams in wild populations (Garber and Teaford, 1986). The third molars (M3s) have been lost in callitrichines, so all callitrichines, with the exception of the likely secondarily derived *Callimico goeldi*, share the 2:1:3:2/2:1:3:2 dental formula (Scott, 2015). M3 loss in callitrichines accompanies a suite of derived features including small body size and claw-like nails, indicating that callitrichines are well-adapted to the use of vertical clinging postures during foraging (Garber, 1992). Callitrichines are the only extant primates without M3s, although M3 agenesis is not rare in some modern human

populations (reviewed by Carter and Worthington, 2015). Members of the genus *Saguinus* are not specialized gummivores, unlike many marmoset species (Ferrari and Martins, 1992), and *Saguinus fuscicollis* eats primarily insects, in combination with fruits and gums (Garber, 1988, 1992). The dental morphology of *Saguinus* is characterized by tall maxillary canines and tusk-like mandibular canines. The maxillary molars generally have three cusps, and the maxillary second molar (M^2) is often profoundly reduced relative to the maxillary first molar (M^1). The mandibular premolars demonstrate a strong morphological gradient from the second premolar (P_2), which is caniniform, to the mandibular fourth premolar (P_4), which is somewhat molariform (Swindler, 2002: 96-103). A lateral view of the teeth of the closely related species *Saguinus nigricollis* is shown in Figure 1.1.

Figure 1.1. Lateral view of the dentition of a male tamarin (*Saguinus nigricollis*)

1.1.3 Teeth of Macaca mulatta

Rhesus macaques (*Macaca mulatta*) are medium-sized catarrhine primates in the tribe Papionini. Body size is moderately sexually dimorphic in rhesus macaques; at Cayo Santiago, the average male weight is 11.9 kg while the average female weight is 9.6 kg

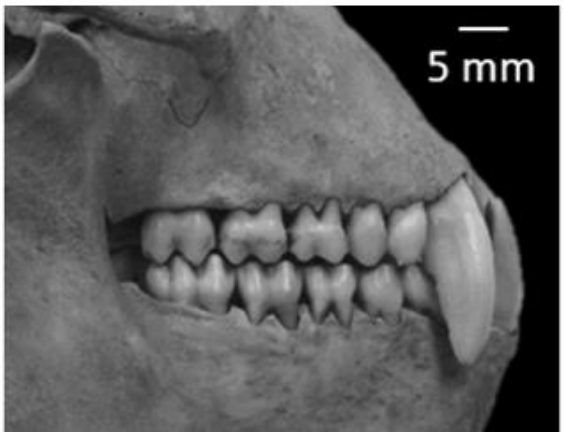

Figure 1.2. Lateral view of the dentition of a male rhesus macaque (*Macaca mulatta*)

(Turnquist and Kessler, 1989). *Macaca mulatta* is geographically widespread and many aspects of the species' diet and ecology differ by region and setting (Jaman and Huffman, 2013), although they rely heavily on fruit and herbaceous vegetation (Goldstein and Richard, 1989). As in other catarrhine primates, the dental formula for rhesus macaques is 2:1:2:3/2:1:2:3. The molars of *Macaca mulatta* and other cercopithecoid primates are bilophodont, meaning the mesial and distal cusps on each molar are arranged into parallel transverse crests called lophs. The canine-premolar honing complex of rhesus macaques consists of a mesio-distally expanded mandibular third premolar (P_3), which leaves a space or diastema between the mandibular canine (C_1) and P_3. The maxillary canine (C^1) occupies this diastema during occlusion and maintains sharp mesial and distal crests by shearing against the distal crest of the C_1 and the buccal surface of the P_3 as the mouth opens and closes. The canines and canine-premolar honing complex of *Macaca mulatta* is sexually dimorphic; based on data collected for this research, the average male C^1

crown height is 21.47 mm in the Cayo Santiago macaques, over twice the female average C^1 crown height of 10.47 mm.

1.2 Quantitative genetics

The study of evolutionary change in biological anthropology relies upon two largely separate approaches. Studies of phenotypic change over evolutionary timescales compare the anatomy of multiple extant and fossil species to understand how lineages have changed over time. Meanwhile, studies of genetic change focus on using gene sequences to understand how species differ on a molecular scale. The disconnect between the phenotypic approach and the genetic approach is due, at least in part, to the intricacies of genetic contributions to the complex morphological traits that are most frequently used to differentiate between primate taxa. Quantitative genetic theory directly addresses the genetic inheritance of complex traits and therefore provides one path towards bridging study of genetics and phenotypes in biological anthropology (Hlusko et al., 2016).

Modern quantitative genetic theory, established in the early 20th century by R.A. Fisher (Fisher, 1930), employs mathematical concepts from population genetics to describe genetic and environmental variation in quantitative traits. Technological advances in computing and gene sequencing over the last century have made it possible to study the molecular genetics of quantitative traits through analyses of quantitative trait loci and genome-wide association studies, yet traditional quantitative genetic theory and methods continue to play an important role in the study of genetics. Genomic analyses

demonstrate that many genes are each contributing very little to most quantitative traits, and these findings are consistent with traditional quantitative genetic models of complex, polygenic traits. This empirical support for traditional quantitative genetic theory demonstrates that traditional quantitative genetic methods can supplement molecular genetic research in valuable ways.

Several key assumptions are foundational to quantitative genetic theory. First, it is assumed that the inheritance of every locus contributing to a trait is Mendelian so that the locus contributes to the phenotype based on two alleles and the dominance interaction between them. The second assumption states that as the phenotypic variation in a trait approaches a completely continuous, normal distribution, the number of loci contributing to the trait approaches infinity. It is also assumed that these loci each have a very small impact on the phenotype. Additionally, traditional quantitative genetic theory assumes that the proportion of genetic information shared between related individuals reflects the degree to which those individuals share loci that contribute to a given quantitative trait.

Assuming all of this, it is mathematically possible to determine how genes and the environment contribute to phenotypic variation in a population using individuals of known pedigree. The phenotype is modeled as the combination of genetic effects and environmental effects. In this context, environmental effects include any non-genetic factors influencing the phenotype including diet, disease, and behavior. The phenotypic variance (σ^2_P) is then modeled as the sum of the variance from genetic effects (σ^2_G) and the variance from environmental effects (σ^2_E) in addition to an error estimate (e), so that:

$$\sigma^2_P = \sigma^2_G + \sigma^2_E + e$$

σ^2_G can be further decomposed into its constituent parts, such that σ^2_G is the sum of the additive genetic variance (σ^2_A), variance from dominance interactions between alleles (σ^2_D), and variance from epistatic interactions between genes (σ^2_I). σ^2_E is also the sum of variance components associated with many different aspects of the environment. σ^2_P can be calculated using phenotypic data from a population, estimation of σ^2_G and σ^2_E requires decomposition of σ^2_P using the pedigree structure of the population. When populations have been bred purposefully for quantitative genetic study, often in a manner that maximizes the number of full- or half-siblings in the population depending on the research question, σ^2_G estimation can be performed through ANOVA. The statistical tools necessary to estimate σ^2_G in natural populations are more recent and are still being developed. Maximum likelihood estimation (ML) is one such tool that uses the matrix of coefficients of relatedness for individuals in a population with the phenotypic variance-covariance matrix for the same individuals to estimate the genetic variance components that best fit the data. The parameters estimated by the ML model are those values that maximize the likelihood of the existing data. These methods are also used to estimate genetic and environmental covariance parameters in multivariate quantitative genetic analyses. While ML estimation makes possible the quantitative genetic analysis of natural populations, its use in natural populations can be biased when environmental covariance between individuals cannot be distinguished from genetic covariance (Shaw, 1987). Additionally, natural populations often lack the large numbers of full- and half-sibling

relationships necessary to estimate σ^2_D, and most quantitative genetic analyses of natural populations estimate only σ^2_A in place of σ^2_G.

Once genetic and environmental variance and covariance components are estimated, they must be interpreted. The genetic variance describes a specific aspect of a trait that is most easily interpreted relative to the total phenotypic variance in the population. This ratio, also called the broad-sense heritability ($H^2 = \sigma^2_G/ \sigma^2_P$), represents the proportion of total phenotypic variance in a trait that can be attributed to the genetic variance. Because studies of natural populations generally cannot estimate σ^2_D and therefore estimate σ^2_A rather than σ^2_G, the narrow-sense heritability ($h^2 = \sigma^2_A/ \sigma^2_P$) is often analyzed in place of H^2. Based on the breeder's equation (Lush, 1937), a trait's response to selection is proportional to the heritability of the trait making H^2 and h^2 particularly useful in animal and plant breeding. Heritability estimates are, however, limited to populations because h^2 reflects differences in environment, through the impact of σ^2_E, in addition to differences in additive genetic variability. For those interested in changes in σ^2_A over evolutionary timescales during which σ^2_E may fluctuate from generation to generation, scaling σ^2_A by the trait mean may provide a more useful measure of σ^2_A between populations. The mean-scaled genetic variance, also called the evolvability (I_A), describes the genetic variability in a trait relative to the mean trait value and is expected to reflect degree to which the trait overall can evolve (Houle, 1992). Comparisons of I_A between traits and between populations are, however, limited because environmental effects are expected to impact trait values and differences of scale may impact the relationship between σ^2_A and the trait mean.

Genetic covariation between traits, estimated through multivariate ML estimation, is most often interpreted as the genetic correlation (ρ_G) between traits where the genetic covariance estimate is scaled by the genetic variance estimates for the two traits being analyzed. Because σ^2_E is not used in the estimation of ρ_G, cross-population comparisons of ρ_G present less risk of conflating differences in σ^2_E with differences in the additive genetic variability. Homogeneity in the genetic variance-covariance matrix, and genetic correlation matrix, across species can indicate long-term stability in the genetic architecture (Lynch and Walsh, 1998: 650-653).

1.2.1 Quantitative genetics of primate dental traits

The population-specificity of many quantitative genetic parameters is one motivation for this research, and it is necessary to conduct quantitative genetic analyses across species and populations to elucidate broader principles in the evolution of complex phenotypes. Heritabilities of and genetic correlations between dental measurements have thus far been estimated in several human samples and a single non-human primate population. The impact of different environmental conditions on the heritability of primate dimensions is therefore broadly unclear, and it has not been possible to discuss patterns of genetic covariance in the dental traits of primates broadly. The papers presented in this dissertation discuss h^2 and ρ_G estimates in linear dental dimensions of two primate species, and compare the results to those of similar studies of humans and baboons.

Studies of tooth size heritability in human populations demonstrate consistently high heritability of linear dental dimensions in multiple populations using a variety of analytical methods. Early analyses of full siblings from Finland (Alvesalo and Tigerstedt, 1974) and twins from an Aboriginal Australian population (Townsend and Brown, 1978) demonstrated the generally large and significant heritability estimates associated with human permanent tooth dimensions; deciduous tooth dimensions in the same Australian population are also highly heritable, although the results indicate greater common environmental effects than on permanent tooth dimensions (Townsend, 1980). Early ML-based approaches also estimated significant and large heritabilities of dimensions in some parts of the toothrow (Kolakowski and Bailit, 1981). The combination of modern statistical methods with long-term data collection from human populations have allowed for more powerful quantitative genetic parameter estimation also demonstrating significant additive genetic contributions to phenotypic variation in human dental dimensions (e.g. Hughes et al., 2000; Dempsey and Townsend, 2001; Stojanowski et al., 2017).

Quantitative genetic parameters have been estimated previously in one non-human primate population, the Southwest National Primate Research Center (SNPRC) baboons (*Papio* spp.). Research on the genetic inheritance of molar crown size (Hlusko, 2000; Hlusko et al., 2002), tooth crown morphology (Hlusko and Mahaney, 2003; Koh et al., 2010), and enamel thickness (Hlusko et al., 2004) indicate significant additive genetic contributions to these traits in the SNPRC baboons. Estimates of genetic correlations within the dentition (Hlusko and Mahaney, 2009; Hlusko et al., 2011) and between tooth

size and body size (Hlusko et al., 2006) demonstrate that the teeth are not genetically independent from each other or from the rest of the skeleton. These findings suggest that the SNPRC baboon dentition cannot evolve independently from body size, and that certain teeth within the SNPRC baboon dentition cannot evolve independently from other teeth.

Quantitative genetic parameter estimation in the SNPRC baboon population yields valuable information about the genetic architecture of dental traits, but there are no comparable studies of the dental dimensions of smaller-bodied, or monomorphic, or non-captive primate populations. Because sexually dimorphic traits pose additional challenges in the estimation of quantitative genetic parameters (Wolak et al., 2015), genetic correlations from a sexually dimorphic population should not be assumed to describe the genetic patterning of tooth size in other populations. The papers presented in this dissertation provide heritability and genetic correlation estimates from a captive population of the small-bodied, monomorphic platyrrhine *Saguinus fuscicollis* and a free-ranging population of the medium-bodied, dimorphic catarrhine *Macaca mulatta* to assess hypotheses on the inheritance, integration, and modularity of tooth size in a diverse set of primate taxa.

1.3 Why study the inheritance of primate dental morphology?

In summary, information about the inheritance of dental traits in diverse primate populations, ideally inhabiting a variety of environments and exhibiting a range of body sizes, sex differences, and dental formulae, is necessary to understand the genetic

patterning underlying the development and evolution of primate teeth. In addition, integration of genetic and morphological research in biological anthropology requires examination of the genetic structures underlying dental phenotypes that are frequently used in paleoanthropological research (e.g. Suwa et al., 1994, 1996; Haile-Selassie et al., 2004; Pan et al., 2004; McNulty et al., 2015). This work contributes to both of these goals through quantitative genetic analyses of dental measurements in two primate populations.

This dissertation expands upon previous quantitative genetic studies of primate dental traits to answer questions that could not be addressed in other populations or with fewer comparative samples. In the first paper, heritabilities and evolvabilities of dental dimensions are estimated in tamarins and macaques to assess whether tooth size is highly heritable across diverse primate taxa living in captive and free-ranging settings. These are the first published estimates of the heritability of tooth size in a platyrrhine primate and a free-ranging non-human primate. The second paper uses genetic correlation estimates in the dental dimensions of brown-mantled tamarins to assess genetic integration in the toothrow. The results are used to test multiple hypotheses over the genetic patterning of primate teeth, in particular whether the pattern of genetic modularity observed in the rodent and baboon dentition (Hlusko et al., 2011) is the ancestral condition, or whether the dentition is variably integrated and modular in extant primate populations. Research on the genetic patterning of primate teeth may also help us to identify the evolutionary forces that cause evolutionary change outside of the expected pattern. The third paper addresses questions of modularity and integration in the canine-premolar honing complex. Phenotypic variation in the honing complex across primate species indicate that

the canines are somewhat independent from other tooth types in Old World monkeys (Grieco et al., 2013) and in anthropoid primates more broadly (Delezene, 2015), although there is considerable variation in the degree to which the dentition as a whole, and the canines more specifically, are phenotypically modular. Quantitative genetic studies of tooth size in non-human primates have not been able to include canine dimensions in their analyses, so the extent to which variation in these patterns of covariance can be attributed to environmental or genetic sources is not clear. Through analyses of dimensions of the canine-premolar honing complex, this research assesses the degree of genetic modularity and integration in the honing complex of the Cayo Santiago rhesus macaque population. Understanding the genetic relationships within and between regions of the dentition will generate new evolutionary hypotheses regarding canine sexual dimorphism and canine reduction in the human lineage. Together these papers contribute to a broader understanding of the genetic inheritance of primate dental traits, demonstrating that genetic patterning of tooth size may be more variable in extant primates than was previously indicated and challenging the assumption of genetic modularity in the primate dentition.

2 Genetic contributions to variation in tooth size of non-human primates

2.1 Introduction

Variation in dental morphology provides a powerful toolset that anthropologists can use to clarify the often-obscured picture of primate evolution. Teeth preserve well in the fossil record and are recovered in large numbers relative to other skeletal elements at paleontological sites, and the use of tooth size and morphology in the reconstruction of fossil primate relationships is widespread (e.g. Wood and Abbott, 1983; Hunt and Vitzthum, 1986; White et al., 1994; Ross and Kay, 1998; Quam et al., 2009; Gómez-Robles et al., 2011, 2012). These reconstructions rely on several assumptions regarding variation and change in dental morphology, including the assumption that variation in dental morphology has been produced primarily by genetic differences. Morphological similarities in the teeth of closely related primate species demonstrate that aspects of tooth size and shape are genetically inherited, and the high degree to which extant primate teeth are adapted to the observed diets of these taxa (Winchester et al., 2014; Allen et al., 2015) indicates that dental morphology can evolve rapidly via natural selection. While dental morphology is already very useful for both phylogenetic and dietary reconstruction, improved understanding of genetic variability and evolvability of primate dental traits will allow us to generate more precise, testable hypotheses to explain patterns of dental evolution in primates.

Theoretically, the rate at which traits respond to natural selection depends on the intensity of the selection pressure and the degree to which the trait is genetically variable in the population under selection (Lush, 1937; Lynch and Walsh, 1998). Adaptive hypotheses, therefore, assume that traits of interest were reproductively advantageous and heritable at the same time. The assumption of heritability can be assessed in the teeth of present-day primate populations through the estimation of quantitative genetic parameters, although this does not necessarily indicate the degree to which dental traits were heritable in the distant past. Nevertheless, estimates of trait heritability from diverse extant primate populations may demonstrate patterns that are shared by fossil primates. Quantitative genetic research can therefore provide valuable information about the genetic variability of traits used to understand primate evolution and adaptation.

Traditional quantitative genetic theory estimates trait heritability using mathematical models of genetic inheritance in which continuous phenotypic variation (σ^2_P) results from environmental and genetic variation within the population. The environmental variance (σ^2_E) represents the population-level variation in the phenotype produced by non-genetic factors, including differences in diet, disease, or behavior that could impact individuals' phenotypes. The genetic variance of a population (σ^2_G) can be broken into constituent parts including the additive genetic variance (σ^2_A) and the impacts of dominance and epistasis. The estimation of variance components produced through dominance (σ^2_D) or epistasis (σ^2_I) requires the modeling of complex interactions among alleles and genes, and therefore tends to require experimentally designed pedigrees. When factors that contribute to σ^2_G, such as σ^2_D and σ^2_I, cannot be estimated, but σ^2_A can

be estimated, the ratio of additive genetic variance to phenotypic variance (σ^2_A/ σ^2_P) is the narrow-sense heritability (h^2) (Falconer and Mackay, 1996). Because primates tend to reproduce and develop slowly, and require considerable investment to house and breed, quantitative genetic studies of primate populations tend to estimate h^2, rather than the broad-sense heritability ($\sigma^2_G/ \sigma^2_P = H^2$). Although these constraints have also limited the use of quantitative genetic methods in anthropological research, heritabilities of cranial and dental variables have been estimated previously in humans and non-human primates.

At present, much of our understanding of the inheritance of dental morphology has emerged from studies of human twins (Biggerstaff, 1973, 2005; Townsend and Brown, 1978; Sharma et al., 1985; Corruccini et al., 1986; Boraas et al., 1988; Townsend and Martin, 1992; Liu et al., 1998; Dempsey and Townsend, 2001; Townsend et al., 2009a, 2006). The quantitative genetic parameters of human and non-human populations with complex pedigrees can also be analyzed using maximum likelihood (ML) estimation (Shaw, 1987), as performed previously on human and non-human primate dental features (Hlusko et al., 2002, 2004, 2006, 2011; Hlusko and Mahaney, 2009; Koh et al., 2010; Stojanowski et al., 2017). Thus far, dental trait heritabilities have been estimated from a single non-human primate population, the Southwest National Primate Research Center baboons (*Papio* spp.). These studies show that molar size (Hlusko et al., 2002), molar cusp size (Koh et al., 2010), molar crown features (Hlusko and Mahaney, 2003), and tooth dimensions (Hlusko and Mahaney, 2009; Hlusko et al., 2016) are significantly heritable in this captive baboon population; similar dental trait heritabilities have not been estimated in other non-human primate species. The variation in tooth size, morphology

and development observed in primates gives reason to suspect that the genetic variability of tooth size differs across living primate populations. Heritability estimates may also vary due to environmental effects related to living conditions (Weigensberg and Roff, 1996; Pemberton, 2010); the inclusion of free-ranging or wild populations in quantitative genetic studies will help to assess the impact of living conditions on the heritability of tooth size. Hence, the inclusion of multiple species and populations living in different settings in studies of quantitative genetic parameters will allow for better assessment of the genetic and environmental contribution to variation in tooth size, and will bring greater attention to the complexity of interpreting the quantitative genetic parameters across populations.

Comparisons of heritability estimates across populations may, however, prove problematic, since h^2 estimates are specific to one population and can change over generations (Falconer and Mackay, 1996). Due to these limitations, it is difficult, and often unwise, to interpret inter-population differences in h^2. The additive genetic coefficient of variation, sometimes called the evolvability (I_A), was designed to allow for comparisons of σ^2_A between populations by scaling σ^2_A by the trait mean rather than σ^2_P (Houle, 1992). Because the trait mean is likely influenced by population-specific features of the environment, interpretation of differences in I_A can also be challenging. Given the complexities inherent in interpreting h^2 and I_A, it is useful to estimate both h^2 and I_A to better understand the inheritance of complex traits.

Estimating the heritabilities and evolvabilities of dental traits in multiple primate populations is crucial to understanding how dental traits are genetically inherited in

primates broadly, and how genetic variability is maintained in primate dental traits. This study estimates h^2 and I_A in the linear dental measurements of a captive brown-mantled tamarin population and a free-ranging rhesus macaque population and compares these findings to estimates previously acquired from human and baboon populations.

2.2 Materials and Methods

2.2.1 Populations and pedigrees

The Oak Ridge brown-mantled tamarin (*Saguinus fuscicollis illigeri*) population was bred in captivity for biomedical research over several decades (Clapp and Tardif, 1985; Cheverud, 1995, 1996). The associated skeletal collection, now housed at the Osteometric Variation Analysis Laboratory (OVAL) at the University of Tennessee, includes hundreds of brown-mantled tamarin specimens that are part of an extended pedigree. A pedigree of 386 individuals, spanning four generations, was used in this study. Dams and sires are known for 190 individuals; the other 196 individuals are founders.

The Cayo Santiago rhesus macaques were introduced to the island near Puerto Rico in 1938 as a free-ranging population maintained for biomedical and behavioral research (Dunbar, 2012). Records of maternal parentage have been collected since the early 1950s and skeletal remains have been collected and maintained since the 1970s (Rawlins and Kessler, 1986). The skeletal collection, housed at the Caribbean Primate Research Center Laboratory of Primate Morphology and Genetics at the University of

Puerto Rico, now contains hundreds of *Macaca mulatta* specimens from the Cayo Santiago population.

Although many paternity identities in the Cayo Santiago macaque population have been determined through genetic testing (Widdig et al., 2016; Ruiz, personal communication), paternities are not known for most individuals in the skeletal collection. To maximize the use of the known maternities from this population, individuals with known mothers, based on behavioral observation, were assigned a "dummy sire". In previous studies, these dummy sires were related to only one offspring in the pedigree (Konigsberg and Cheverud, 1992; Joganic et al., 2012), so that all individuals with the same dam were half siblings. The use of this half-sib dummy sire model is likely to produce coefficients of relatedness that are smaller than the degree to which individuals are truly related across the population; this method may therefore inflate heritability estimates. To assess the impact of dummy sires on the estimation of heritabilities in the Cayo Santiago macaque population, all heritabilities were estimated twice in this population: once for all traits with a half-sib dummy sire model, and once with a set of dummy sires assigned so that all individuals with the same dam were assigned the same dummy sire (as in Myers et al., 2006; Adams, 2011). Estimates of additive genetic variance in this population are likely overestimated for the half-sib model and under-estimated in the full-sib model, so that the actual heritability falls between these estimates. A pedigree containing 400 individuals was used for the macaque population. 66 of these individuals are founders with no known dam, and dams are known for the

remaining 334 individuals. 334 dummy sires were added to the pedigree for the half-sibling model and 152 dummy sires were added to the pedigree for the full-sibling model.

2.2.2 Measurements

Linear dental measurements were collected from 302 brown-mantled tamarin skeletons and 364 rhesus macaque skeletons. All measurements were taken using Mitutoyo nib-style digital calipers with a digital input tool to minimize human error during data entry.

Mesiodistal lengths and buccolingual breadths were measured from all teeth on half of the toothrow, excluding any teeth with wear or damage that could impact the dimensions of the tooth crown. Mesiodistal length for incisors, premolars, and molars was measured as the maximum length parallel to the lingual margin of the tooth crown and buccolingual breadth was measured as the maximum breadth perpendicular to the lingual edge of the tooth crown. For canines, mesiodistal length was measured as the maximum mesiodistal length, and the buccolingual breadth was the maximum breadth perpendicular to the mesiodistal length measurement. The left and right sides of the toothrow were considered interchangeable based on the evidence of complete pleiotropy between antimeres shown by previous studies (Hlusko et al., 2011; Stojanowski et al., 2017), so the half with the least damage and fewest missing teeth was measured for each individual.

Intra-observer measurement reliability was assessed by measuring ten individuals from each population three times. Calculation of measurement reliabilities was performed in Excel, where:

$$\text{Reliability} = 1 - (\text{repeated measure variance} / \text{population variance})$$

Additional analyses are performed on all traits, even those with low reliability, but any measurements with reliability below 80% (meaning that 80% of the population variance is not related to measurement variance) are marked and discussed separately throughout this paper. Previous quantitative genetic studies of tooth dimensions have not reported measurement reliabilities for linear dental measurements (Hlusko et al., 2002; Stojanowski et al., 2017), although standard error of measurement estimates are provided for the same data elsewhere (Hlusko, 2000). Measurements of the tamarin teeth are especially prone to poor reliability since they are very small, and so it was deemed important to account for reliability in this study. Standard errors of measurements were also estimated as percentages and were less than 4% for measurements analyzed here. Incisor labio-lingual breadth was not measured due to the noticeable impact of wear on this trait in both samples.

2.2.3 Analyses

Following traditional quantitative genetic theory, the total phenotypic variance in a trait, $\sigma^2_{P,}$ can be decomposed into genetic and environmental variance, σ^2_G and σ^2_E respectively, so that:

$$\sigma^2_P = \sigma^2_G + \sigma^2_E$$

Variance related to dominance could not be estimated in the study populations because many full sibling relationships would be necessary for the estimation of σ^2_D and are rare in the tamarin and macaque pedigrees. For this reason, the additive genetic variance (σ^2_A) was estimated in place of σ^2_G and the resulting heritability estimates reflect the narrow-sense heritability ($h^2 = \sigma^2_A / \sigma^2_P$), rather than the broad-sense heritability ($h^2 = \sigma^2_G / \sigma^2_P$). The phenotype of interest was then modeled as

$$y = \mu I_n + (X - 1_n s') \beta + a + e$$

where y is the n x 1 vector of phenotypes, μ is the mean phenotype of the population, X is the n x k matrix of k covariates, 1_n is a vector of n ones, s is the vector of baseline covariates (equal to 0 for discontinuous covariates such as sex and birthplace, and equal to the mean value of each covariate for continuous covariates such as age), β is the k x 1 vector of regression coefficients, a is the vector of additive genetic values and e is the vector of random environmental effects (following Wang et al., 1997). The variance-covariance matrix for y is used to calculate σ^2_A and σ^2_E as

$$Var(y) = 2\Phi\sigma^2_A + I_n\sigma^2_E$$

where Φ is the n x n matrix of kinship coefficients and I_n is an n x n identity matrix. A general model, in which σ^2_A and σ^2_E are estimated, is compared to restricted models, in which parameters σ^2_A or σ^2_E are constrained to zero, using likelihood-ratio tests. The likelihood-ratio test statistic is calculated as

$$\Lambda = -2(\text{log-likelihood}_{\text{general}} - \text{log-likelihood}_{\text{restricted}})$$

The likelihood-ratio test statistic (Λ) follows a chi-squared distribution, providing the probability that the restricted model, in which h^2 is equal to zero, fits the data as well as the general model, in which h^2 is estimated without restriction. Heritability estimates are considered significantly different from zero when $p<0.05$.

Univariate quantitative genetic analyses were performed for each measurement in both populations using maximum likelihood-based variance decomposition performed in the open-source software package SOLAR (Almasy and Blangero, 1998). The effects of covariates were estimated simultaneously using the screening function, which uses likelihood-ratio tests to compare models in which covariates are included to those without covariates. When the model with the covariate was significantly more likely than the model without the covariate ($p<0.1$), the covariate was included in the final model. For the macaque population, the effects of sex, age, and age-by-sex were estimated, whereas the effects of sex and birthplace (wild or captive birth, hereafter WC) were screened in the tamarin population.

Although h^2 is a useful expression of the proportion of phenotypic variance that is genetically inherited, an estimate of h^2 is specific to one population and one environment (Falconer and Mackay, 1996). It may therefore be inappropriate to use h^2 to compare the genetic variability of multiple populations if the comparison indicates differences in σ^2_E, and not σ^2_A. Direct comparisons of σ^2_A are also flawed, since σ^2_A is proportional to the trait mean. The mean-scaled σ^2_A or evolvability (I_A), which describes the genetic variability of the trait relative to its size and is not influenced by σ^2_E, may therefore be more appropriate for comparisons across populations (Houle, 1992; Hansen et al., 2011).

Estimates of σ^2_A were calculated manually as the product of the h^2 and σ^2_P, with σ^2_P corrected to account for variance associated with significant covariates. I_A is estimated as this σ^2_A calculation, divided by the population trait mean without sex correction to capture the overall mean across males and females.

2.3 Results

2.3.1 Measurement reliability

Measurement reliabilities are provided in Table 2.1. Sixteen of twenty-eight measurements from the brown-saddled tamarin population and twenty-six of twenty-eight measurements from the rhesus macaque population were found to be reliable. Extremely low reliability of I^2 length and I_1 length in the tamarin sample merit their exclusion from additional analyses.

Table 2.1. Measurement reliability for dental dimensions, grey-shaded cells indicate measurements with reliability below 80%, darker grey cells indicate measurements excluded from further analyses.

	Saguinus fuscicollis				*Macaca mulatta*			
	Maxillary		Mandibular		Maxillary		Mandibular	
	MD	BL	MD	BL	MD	BL	MD	BL
I1	0.55		0.32		0.96		0.69	
I2	0.17		0.65		0.99		0.99	
C	0.81	0.86	0.69	0.77	0.97	0.99	0.97	0.99
P2	0.91	0.76	0.88	0.75				
P3	0.81	0.88	0.87	0.77	0.83	0.97	0.93	0.95
P4	0.80	0.91	0.82	0.88	0.85	0.95	0.69	0.91
M1	0.90	0.72	0.93	0.78	0.93	0.88	0.95	0.93
M2	0.91	0.98	0.88	0.61	0.95	0.91	0.96	0.91
M3					0.97	0.97	0.98	0.94

2.3.2 Tamarins

Results of univariate analyses of dental dimensions in the Oak Ridge tamarins are provided in Table 2.2. Covariate effects were incorporated into the final models for all but eight of the twenty-six dental measurements that were analyzed. Captive birth (WC) had a statistically significant negative effect relative to wild birth on fifteen measurements. Sex was a statistically significant covariate for four traits. Covariates account for up to 7.8% of the total variance in a trait (σ^2_C).

The distributions for four traits (P^4 breadth, C_1 breadth, P_2 breadth, M_1 breadth) have high measures of kurtosis, so an inverse normal transformation was applied to these traits to account for skew in the data (following Hlusko et al., 2002).

Quantitative genetic analyses of tooth size in the Oak Ridge tamarin population yielded statistically significant, non-zero heritability estimates for twenty-five out of the twenty-six analyzed measurements. Only the heritability of P_4 length was not significantly more likely than an estimate of zero. Heritability estimates ranged from 0.185 (P_4 length) to 0.985 (M_1 breadth), meaning that the additive genetic variance accounted for between 18.5% and 98.5% of the phenotypic variance in dental dimensions in this population. The standard error calculated for these h^2 estimates allows for comparison of the confidence interval within which the heritability lies, provided in Figure 2.1. For most traits, these margins of error overlapped, although some traits showed markedly greater heritability estimates. Buccolingual breadth measurements produced notably larger heritability estimates than did mesiodistal length measurements, with eight of the ten highest heritability estimates belonging to breadth dimensions and

nine of the ten lowest heritability estimates belonging to length dimensions. Within each tooth, the buccolingual dimension produced a greater heritability estimate than the mesiodistal dimension for all teeth except C^1 and M^1. There were no obvious and consistent trends in heritability estimates among tooth types.

Table 2.2. Heritability estimates from tamarin dental traits. Mean trait value does not include covariate correction. C: significant covariates, σ2C: variance accounted for by covariates. Bold h2 values are statistically significantly different from zero. Traits with low measurement reliability (<0.80) are shaded in gray.

Tooth	Trait	N	Mean	σ^2_P	h^2	p	SE	C	σ^2_C	I_A
I^1	MD	263	2.17	0.024	**0.642**	<0.001	0.111	WC	2.97	0.0069
C^1	MD	273	2.34	0.052	**0.697**	<0.001	0.110			0.016
	BL	271	1.95	0.030	**0.647**	<0.001	0.127	WC	0.93	0.0099
P^2	MD	271	1.80	0.026	**0.454**	<0.001	0.125	WC	7.63	0.0061
	BL	274	2.14	0.026	**0.562**	<0.001	0.108	Sex	0.73	0.0068
P^3	MD	256	1.57	0.016	**0.285**	0.008	0.132			0.0029
	BL	280	2.44	0.037	**0.609**	<0.001	0.115	Sex, WC	2.45	0.0090
P^4	MD	255	1.59	0.016	**0.315**	0.011	0.157			0.0032
	BL^K	276	2.64	0.037	**0.678**	<0.001	0.110	WC	5.83	0.0089
M^1	MD	282	2.19	0.028	**0.876**	<0.001	0.089			0.011
	BL	282	2.74	0.029	**0.748**	<0.001	0.093	WC	2.59	0.0077
M^2	MD	250	1.43	0.027	**0.305**	0.003	0.132	Sex	1.35	0.0057
	BL	270	2.27	0.051	**0.879**	<0.001	0.070			0.020
I_2	MD	266	1.34	0.015	**0.482**	<0.001	0.137	WC	7.77	0.0050
C_1	MD	270	2.16	0.041	**0.569**	<0.001	0.111	WC	3.50	0.010
	BL^K	270	2.46	0.050	**0.824**	<0.001	0.096	WC	1.04	0.017
P_2	MD	274	2.11	0.042	**0.385**	<0.001	0.127	Sex	2.04	0.0075
	BL^K	279	1.95	0.026	**0.419**	<0.001	0.111	WC	0.92	0.0055
P_3	MD	245	1.71	0.019	**0.286**	0.008	0.138			0.0032
	BL	272	1.78	0.021	**0.815**	<0.001	0.099	WC	0.97	0.0095

P_4	MD	222	1.74	0.020	0.185	0.103	0.159	WC	4.13	0.0020
	BL	242	1.84	0.028	**0.492**	<0.001	0.127	WC	6.17	0.0070
M_1	MD	235	2.11	0.027	**0.465**	0.0011	0.151	WC	6.39	0.0056
	BL^K	241	1.91	0.018	**0.985**	<0.001	0.100	WC	2.64	0.0090
M_2	MD	218	1.97	0.024	**0.446**	0.0048	0.184			0.0054
	BL	241	1.63	0.013	**0.915**	<0.001	0.095			0.0073

^{K} indicates inverse normalization was used to correct for skew

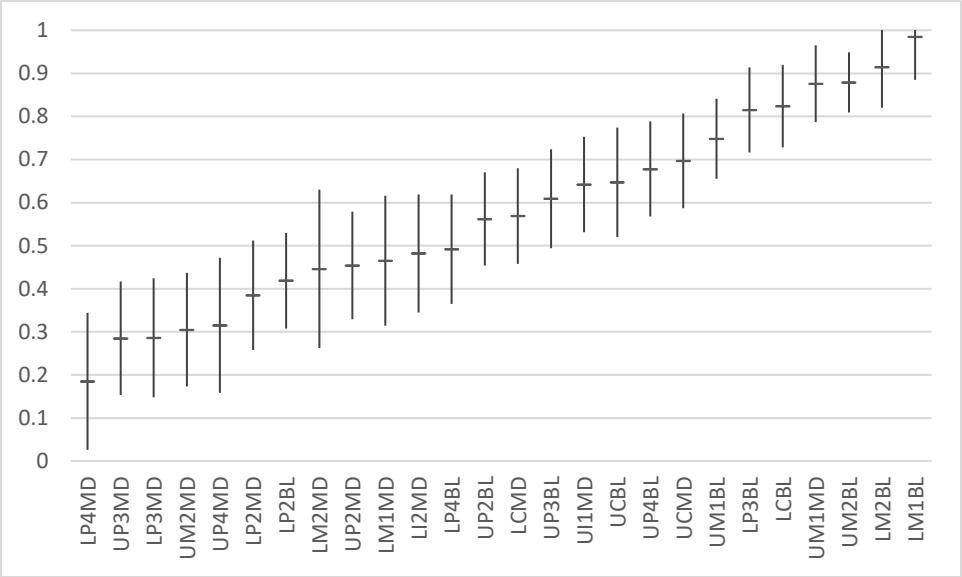

Figure 2.1. Heritability estimates from tamarin dental traits sorted from smallest h^2 value (P_4 length) to largest (M_1 breadth) with one standard error on either side of the estimate.

2.3.3 Macaques

Results of univariate analyses of half-sibling and full-sibling pedigree models for the Cayo Santiago rhesus macaques are provided in Table 2.3. Covariate effects were incorporated into the analyses for all 28 macaque dental measurements; sex was a statistically significant covariate for all traits across both pedigree models, age had a statistically significant effect on 13 traits across both pedigree models, and sex by age

interaction had a statistically significant effect on 6 half-sibling pedigree traits and 9 full-sibling pedigree traits. P^4 breadth, M_1 length, and M_3 breadth had statistically significant sex by age interactions in the full-sibling but not half-sibling models. Covariates accounted for between 5.9% and 86.2% of the total phenotypic variance in a trait.

The distributions for twelve half-sibling traits (C^1 length, P^3 length, P^4 length, M^1 breadth, M^3 breadth, C_1 length and breadth, P_4 breadth, M_1 length, M_2 length and breadth, M_3 length) and eleven full-sibling traits (C^1 length, P^3 length, P^4 length, M^1 breadth, M^3 breadth, C_1 length and breadth, P_4 breadth, M_1 length, M_2 length and breadth) had high measures of kurtosis, so an inverse normal transformation was applied to these analyses to account for skew in the data.

Quantitative genetic analyses of tooth size in the Cayo Santiago macaque population yielded significant non-zero heritabilities for the same 25 traits ($p<0.05$) in the half-sibling and full-sibling pedigree models. For M^1 breadth, P_3 length, and M_1 breadth, h^2 estimates were not significantly different from zero. Heritability estimates were consistently smaller for full-sibling models than for half-sibling models of the same trait, the only exception being M_3 breadth (half-sibling $h^2 = 0.591$, full-sibling $h^2 = 0.636$). Half-sibling h^2 estimates ranged from 0.214 (P_3 length) to 1.0 (M_3 length), while full-sibling h^2 estimates ranged from 0.080 (M_1 breadth) to 0.675 (M_3 length). As in the tamarin sample, the standard error calculated for these h^2 estimates allows for comparison of h^2 across traits within the macaque population; h^2 and standard error values are shown in Figure 2.2 and Figure 2.3. The margins of error for most traits overlapped, although

Table 2.3. Heritability estimates from macaque dental traits. Mean trait value does not include covariate correction. C: statistically significant covariates, $\sigma 2_C$: variance accounted for by covariates. Bold h^2 values are statistically significantly different from zero. Traits with low measurement reliability (<0.80) are shaded in gray.

Tooth	Trait	N	Mean	σ^2_P	Half-sib σ^2_A	Full-sib σ^2_A	Half-sib h^2	Full-sib h^2	Half-sib SE	Full-sib SE	C	σ^2_C	Half-sib I_A	Full-sib I_A
I^1	MD	258	6.24	0.121	0.092	0.041	**0.889**	**0.407**	0.235	0.154	sex	14.3-16.6	0.015	0.0066
I^2	MD	266	4.88	0.123	0.031	0.010	**0.404**	**0.263**	0.218	0.154	sex	37.8-38.0	0.0063	0.0041
C^1	MD^K	246	7.27	2.811	0.779	0.665	**0.737**	**0.616**	0.183	0.198	sex	61.6-62.4	0.11	0.091
	BL	251	6.19	1.459	0.183	0.087	**0.890**	**0.433**	0.190	0.175	sex, age, sex*age	85.9-86.2	0.030	0.014
P^3	MD^K	332	5.23	0.114	0.044	0.035	**0.524**	**0.424**	0.150	0.13	sex, sex*age	26.5-26.6	0.0084	0.0068
	BL	337	6.40	0.116	0.070	0.046	**0.714**	**0.474**	0.150	0.154	sex	15.9-16.6	0.011	0.0072
P^4	MD^K	337	5.31	0.089	0.028	0.025	**0.345**	**0.299**	0.139	0.123	sex	7.6	0.0053	0.0046
	BL	332	6.90	0.126	0.057	0.045	**0.571**	**0.445**	0.141	0.142	sex, age, $sex*age^{FS}$	20.5-20.6	0.0083	0.0065
M^1	MD	335	7.63	0.133	0.077	0.049	**0.696**	**0.452**	0.193	0.169	sex, age	16.4-17.9	0.010	0.0065
	BL^K	263	7.21	0.119	0.024	0.020	0.255	0.213	0.196	0.159	sex	19.4	0.0034	0.0028
M^2	MD	342	8.80	0.181	0.069	0.068	**0.464**	**0.460**	0.149	0.143	sex	18.3-18.4	0.0078	0.0077
	BL	306	8.46	0.201	0.099	0.065	**0.718**	**0.475**	0.162	0.147	sex, age	31.2-32.1	0.012	0.0077
M^3	MD	259	8.86	0.210	0.049	0.043	**0.406**	**0.354**	0.172	0.157	sex, age, sex*age	42.3-42.4	0.0055	0.0048
	BL^K	252	8.40	0.311	0.122	0.100	**0.642**	**0.524**	0.156	0.145	sex, age, sex*age	38.4-38.8	0.015	0.012
I_1	MD	254	4.19	0.059	0.028	0.018	**0.535**	**0.339**	0.200	0.162	sex	10.0-10.1	0.0068	0.0043
I_2	MD	241	4.01	0.293	0.118	0.094	**0.450**	**0.360**	0.172	0.141	sex	10.6-10.7	0.029	0.024
C_1	MD^K	235	4.61	0.878	0.159	0.099	**0.521**	**0.325**	0.258	0.219	sex, age	65.2-65.3	0.035	0.022
	BL^K	213	7.37	3.418	0.487	0.361	**0.423**	**0.312**	0.234	0.175	sex, age	66.3	0.066	0.049
P_3	MD	310	8.79	4.401	0.175	0.096	0.214	0.117	0.176	0.109	sex, age,	81.4	0.020	0.011

											sex*age			
	BL	303	4.53	0.189	0.051	0.029	**0.542**	**0.306**	0.230	0.159	sex	49.9-50.5	0.011	0.0063
P_4	MD	322	5.83	0.120	0.068	0.059	**0.640**	**0.552**	0.139	0.133	sex, age, sex*age	11.3-11.4	0.012	0.010
	BL[K]	318	5.12	0.085	0.026	0.022	**0.330**	**0.283**	0.145	0.125	sex	8.9	0.0050	0.0043
M_1	MD[K]	299	7.46	0.104	0.046	0.037	**0.553**	**0.444**	0.235	0.182	sex, age, sex*age[FS]	19.8-20.9	0.0062	0.0049
	BL	236	5.87	0.074	0.030	0.005	0.498	0.080	0.429	0.182	sex	17.8-18.6	0.0051	0.00083
M_2	MD[K]	332	8.58	0.158	0.069	0.049	**0.511**	**0.361**	0.182	0.157	sex	14.0-14.2	0.0081	0.0057
	BL[K]	305	7.16	0.138	0.048	0.033	**0.442**	**0.306**	0.173	0.142	sex, age	21.6-21.7	0.0067	0.0046
M_3	MD	256	10.74	0.507	0.461	0.322	**1.000**	**0.675**	-	0.179	sex	5.9-9.1	0.043	0.030
	BL	253	7.49	0.161	0.068	0.074	**0.591**	**0.636**	0.153	0.155	sex, age, sex*age[FS]	27.7-28.1	0.0091	0.0099

[K] indicates inverse normalization was used to correct for skew

[FS] indicates that a covariate was statistically significant only in the full-sibling pedigree analysis

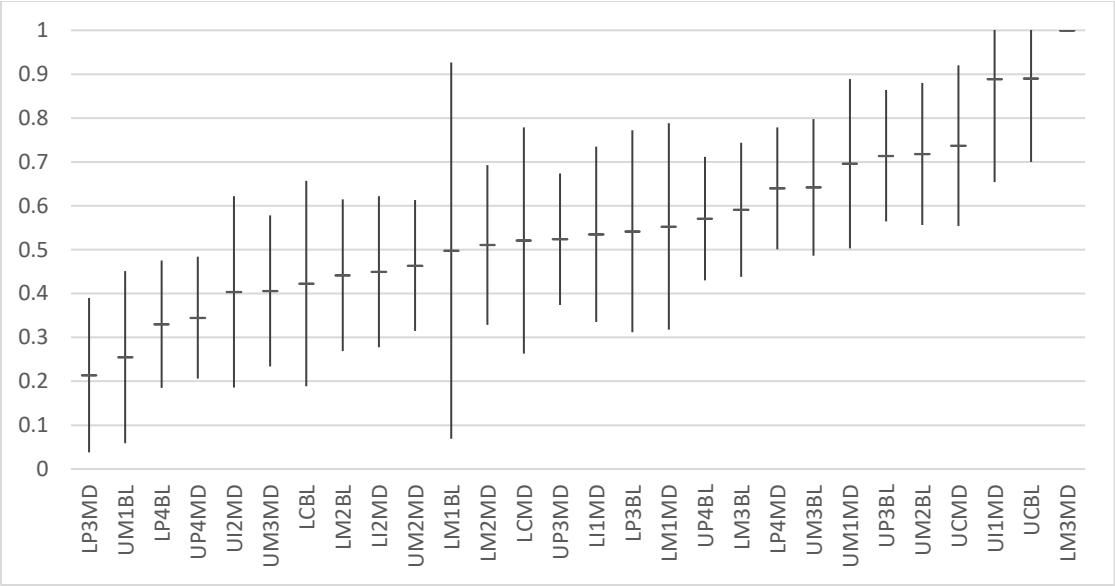

Figure 2.2. Heritability estimates from half-sib models of macaque dental traits sorted from smallest h^2 value (P_3 length) to largest (M_3 length) with one standard error on either side of the estimate.

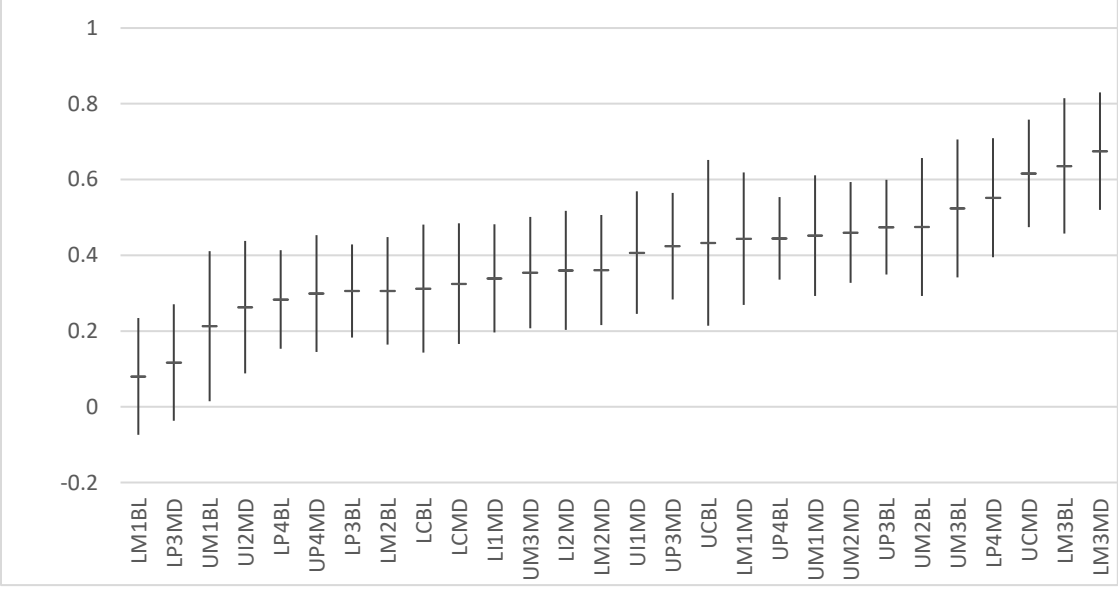

Figure 2.3. Heritability estimates from full-sib models of macaque dental traits sorted from smallest h^2 value (M_1 breadth) to largest (M_3 length) with one standard error on either side of the estimate.

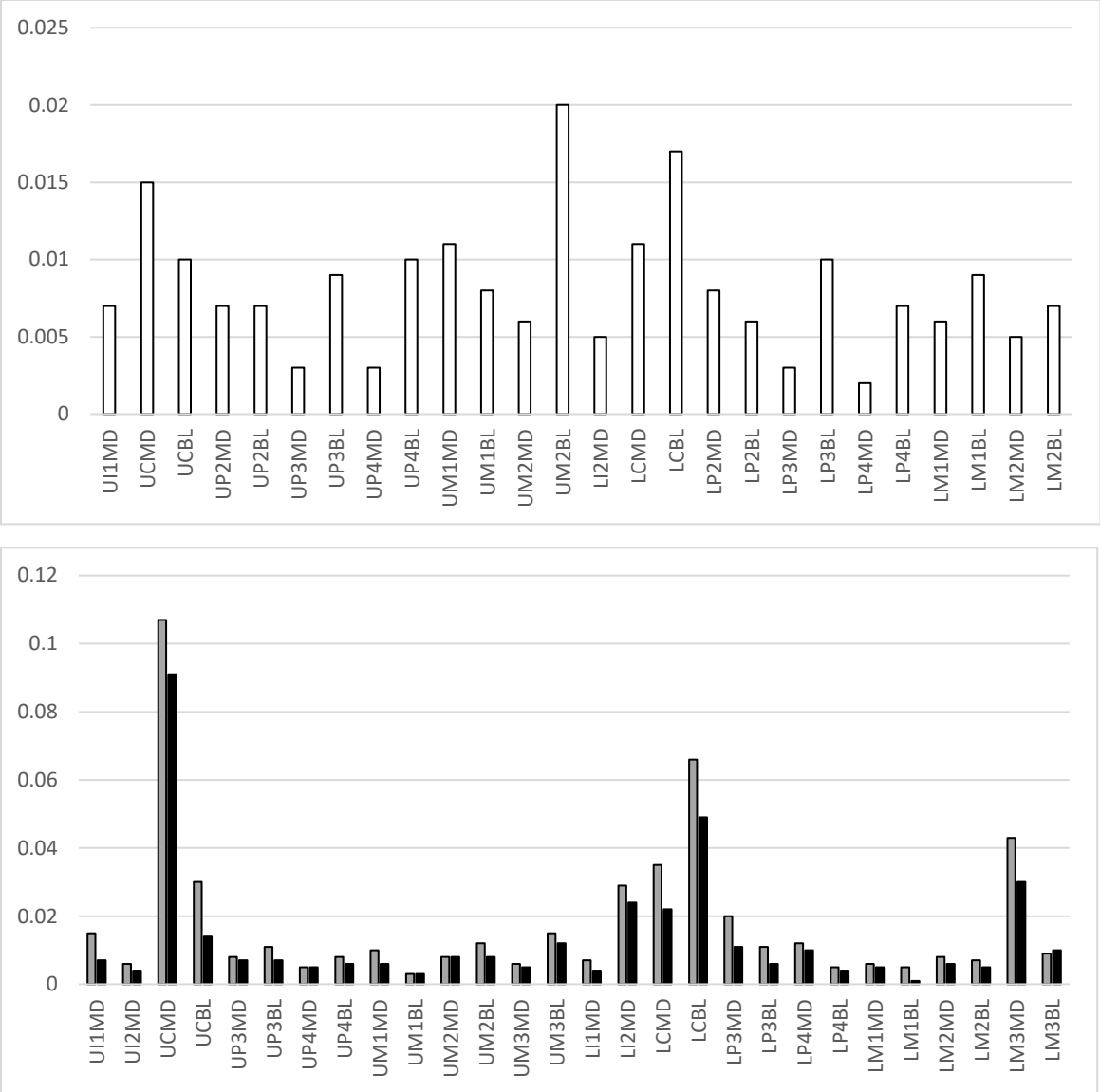

Figure 2.4. Tamarin (top) and macaque (bottom) evolvability estimates from dental measurement; macaque half-sibling analyses are shaded grey and macaque full-sibling analyses are shaded black.

some traits had markedly greater heritability estimates. There were no consistent patterns related to tooth type or tooth dimension in the macaque sample.

2.3.4 Evolvability

I_A estimates in the tamarin population range from 0.002 to 0.020. Evolvability estimates in the macaque population range from 0.001 to 0.107 for half-sibling pedigree models, and from 0.001 to 0.091 for full-sibling models. Comparisons of the evolvability estimates in these populations are shown in Figure 2.4. In the macaque population, the traits with the greatest evolvability estimates are canine dimensions, I_2 length and M_3 length. Canine dimension evolvability estimates are also large in tamarins relative to other traits.

2.4 Discussion

2.4.1 Heritability

These results broadly support the findings of previous studies (Hlusko et al., 2006; Koh et al., 2010; Stojanowski et al., 2017) showing high heritabilities for the dimensions of primate teeth. Although the Cayo Santiago macaque population might be expected to produce smaller heritability estimates – as a free-ranging population they are expected to encounter greater variation in environmental conditions than the captive tamarin population – any differences in environmental variance seem to have a small impact on the heritability of tooth size. This may indicate that environmental effects acting on the Cayo Santiago macaques are limited, perhaps due to provisioning or to general resistance of dental dimensions to environmental effects. The result could also indicate that reduced selection pressure on dental dimensions, due to provisioning and

lack of predation pressure, has allowed for an increase in the genetic variability of dental traits.

The overall impact of captivity on tooth dimensions and genetic variability of tooth dimensions is not straightforward. In the previously studied baboon population captive-born individuals had slightly larger dental measurements (Hlusko and Mahaney, 2007), whereas in the brown-mantled tamarin sample wild-born individuals had slightly larger dental measurements than their captive-born relatives. Similar patterns of phenotypic variance in the linear dental measurements from wild and captive baboons are used to support the application of research on the genetic architecture of dental traits in captive baboons to wild baboons (Hlusko and Mahaney, 2007). The significant impact of captive-birth on some but not all dental traits in the brown-mantled tamarin population indicates that extrapolation of quantitative genetic parameters from captive to wild populations should be performed cautiously.

The heritabilities estimated here likely reflect some common environmental effects that could not be separated from additive genetic effects. The captive tamarins had access to the same foods and socialization across the population, which likely minimized common environmental effects on dental phenotypes. The Cayo Santiago macaque population is also resistant to some confounding variables, such as migration between populations, but it seems likely that parental effects and other similarities in the environments of closely related individuals will inflate h^2 estimates in this population. Female rhesus macaques with the same mother fall near each other in the dominance hierarchy of females, meaning that closely related females will likely have access to

similar high-quality foods and will experience similar levels of aggression from other individuals. Future analyses could account for some of these common environmental effects by including rank information, birth order, or matriline as a covariate in quantitative genetic analyses.

Four dental measurements from this study produce h^2 estimates that are not significantly different from zero. Tamarin P_4 length has a low estimated h^2 value (h^2 = 0.185) with a standard error value similar to those of other traits, indicating that this result may accurately characterize low heritability of P_4 length in this tamarin population. The same conclusions may be drawn for macaque M^1 breadth (h^2 = 0.196-0.155) and P_3 length (h^2 = 0.176-0.214), which also have low h^2 estimates and low standard error values. The difference in full-sib and half-sib estimation of h^2 for M_1 breadth is considerable (h^2 = 0.080-0.498). These results should therefore not be interpreted as indicative of reduced additive genetic variability in M_1 breadth, and should instead be considered inconclusive.

Reduced genetic variability, represented by low h^2, theoretically indicates that selection has recently narrowed the genetic variance in the population (Fisher, 1930), and fitness-related traits typically have lower h^2 than morphological traits more indirectly related to fitness (Mousseau and Roff, 1987). The small h^2 estimates for tamarin P_4 length and macaque M^1 breadth and P_3 length could therefore indicate that these traits impact fitness more than other dimensions of the toothrow. Alternatively, the inheritance of these traits may be influenced by non-additive genetic effects that could not be estimated in this study. Low additive genetic variability in the macaque P_3 is of interest since the P_3 is

mesiodistally expanded in the males of most anthropoid primate taxa to hone the distal face of the maxillary canine, forming part of the canine-premolar honing complex. Average h^2 estimates across studies are not statistically significantly different for sexually selected morphological traits and non-sexually selected morphological traits (Prokuda and Roff, 2014), yet sex differences in genetic variability and in selection pressures are expected to influence the evolution of the trait (Lande, 1980; Leutenegger and Cheverud, 1982). The functional relationship between the honing premolar and the canine teeth may also impact the additive genetic variability of P_3 length in this population if the honing complex is integrated genetically as it is phenotypically (Greenfield, 1996; Delezene, 2015), The confounding influence of extreme sexual dimorphism in the mesiodistal length of the macaque P_3 may also impact our ability to accurately estimate the heritability of this trait, although h^2 estimates for canine dimensions are statistically significant despite the impact of extreme sexual dimorphism. Hlusko et al. (2011) also found that P_3 length h^2 was not significantly different from zero in the SNPRC baboons.

2.4.2 Evolvability

The coefficient of additive genetic variance, or evolvability (I_A), describes additive genetic variability of a trait in a population as a proportion of the total trait value rather than the phenotypic variance of the trait (Houle, 1992). According to Hansen et al. (2011), the low h^2 of fitness-related traits is produced not by reduced σ^2_A, but by large σ^2_P. Fitness-related traits are therefore associated with high I_A estimates, and low h^2

estimates (Houle, 1992). Because I_A and h^2 often produce very different patterns between fitness-related traits and traits less directly associated with fitness, it is useful to combine discussion of h^2 with discussion of I_A. I_A can also be useful for between-population comparisons of σ^2_A, since differences in σ^2_E will not directly impact I_A. Nevertheless, insofar as the mean trait value is impacted by non-genetic factors, I_A is limited in many of the same ways as h^2 as a measure of potential evolvability.

The evolvabilities of dental measurements are generally greater in the macaque population than in the tamarin population. Macaque canine dimensions have especially large I_A values, and although tamarin canine dimensions also have large I_A relative to other traits, the trait with the largest I_A in the tamarin sample is M^2 breadth. Of the traits with low h^2 estimates, tamarin P_4 length ($I_A = 0.002$) and macaque M^1 breadth ($I_A = 0.003$) have low I_A estimates, whereas macaque P_3 length has moderately high I_A estimates ($I_A = 0.011$-0.02). The high evolvability of P_3 length in the Cayo Santiago macaques could indicate that the low h^2 of this trait results from high environmental variance in P_3 length in this population, or it could result from sex differences in trait means skewing I_A estimates.

The traits that produced especially large evolvability estimates in the macaque population are generally characterized by extreme sexual dimorphism, and it is plausible that these differences in evolvability result from effects of scale and sexual dimorphism. Because male canines are much larger than female canines in the macaque sample, the phenotypic and additive genetic variance should be greater in males than females for

canine dimensions. By pooling the sexes and including sex as a covariate, both σ^2_A and σ^2_P are impacted by sex differences similarly during h^2 estimation. Because I_A was calculated as the σ^2_A after sex correction scaled by the mean of the male and female samples, the smaller female trait values depressed the mean trait value for the population resulting in very large I_A values for dimorphic traits. It is therefore not useful to compare the I_A of highly dimorphic traits to less dimorphic or monomorphic traits since, just as h^2 may be biased by σ^2_E, I_A is greatly influenced by the distribution of trait values in the population. This issue could be best resolved by estimating σ^2_A in males and females separately, so that male I_A can be calculated using the male mean trait value and female I_A can be calculated using the female mean trait value. Although the available pedigree and phenotype data for the Cayo Santiago rhesus macaques are not adequate for the estimation of quantitative genetic parameters separately in each sex, this may be possible in future studies.

2.4.3 Comparing macaques and tamarins to baboons and humans

Maximum-likelihood estimation of heritability has been performed previously for dental dimensions in the Southwest Primate Research Center baboon population (*Papio* spp.) (Hlusko and Mahaney, 2009) and a contemporary human population from James Island, South Carolina (Stojanowski et al., 2017). Analyses of baboon and human dentitions have produced a broad range of h^2 estimates similar to those produced here in tamarins and macaques (Table 2.4), indicating that dental dimensions are, for the most

part, highly heritable across several primate populations living in different settings. There persists, however, a dearth of information on the heritability of dental dimensions in wild non-human primate populations.

Table 2.4. Heritability estimates from baboons (using the largest estimate from antimeres) and humans (using average heritability of antimeres) compared to those of brown-mantled tamarins and rhesus macaques. Baboon data from Hlusko et al. 2011; human data from Stojanowski et al. 2017.

Measurement	Tamarin h^2 ± SE	Macaque half-sib h^2 ± SE	Macaque full-sib h^2 ± SE	Baboon h^2 ± SE	Human h^2 ± SE
I^1 MD	0.64±0.11	0.89±0.24	0.41±0.15	0.65±0.10	0.61±0.14
I^2 MD		0.40±0.22	0.26±0.15	0.61±0.11	0.62±0.14
C^1 MD	0.70±0.11	0.74±0.18	0.62±0.20		0.70±0.14
P^3 MD	0.29±0.13	0.52±0.15	0.42±0.13	0.32±0.15	0.77±0.14
P^3 BL	0.61±0.12	0.71±0.15	0.47±0.15	0.66±0.20	
P^4 MD	0.32±0.16	0.35±0.14	0.30±0.12	0.68±0.12	0.60±0.21
P^4 BL	0.68±0.11	0.57±0.14	0.45±0.14	0.61±0.12	
M^1 MD	0.88±0.09	0.70±0.19	0.45±0.17	0.75±0.12	0.46±0.14
M^1 BL	0.75±0.09	0.26±0.20	0.21±0.16		
M^1 mesial BL				0.72±0.11	
M^1 distal BL				0.79±0.12	
M^2 MD	0.31±0.13	0.46±0.15	0.46±0.14	0.85±0.10	
M^2 BL	0.88±0.07	0.72±0.16	0.48±0.15		
M^2 mesial BL				0.76±0.10	
M^2 distal BL				0.56±0.11	
M^3 MD		0.41±0.17	0.35±0.16	0.24±0.19	
M^3 BL		0.64±0.16	0.52±0.15		
M^3 mesial BL				0.56±0.13	
M^3 distal BL				0.33±0.19	
I_1 MD		0.54±0.20	0.34±0.16	0.67±0.11	0.46±0.13
I_2 MD	0.48±0.14	0.45±0.17	0.36±0.14	0.29±0.10	0.39±0.15
C_1 MD	0.57±0.11	0.52±0.26	0.33±0.22		0.46±0.13
P_3 MD	0.29±0.14	0.21±0.18	0.12±0.11	0.47±0.41	0.65±0.11
P_3 BL	0.82±0.10	0.54±0.23	0.31±0.16	0.44±0.16	
P_4 MD	0.19±0.16	0.64±0.14	0.55±0.13	0.67±0.10	0.37±0.18
P_4 BL	0.49±0.13	0.33±0.15	0.28±0.13	0.73±0.14	
M_1 MD	0.47±0.15	0.55±0.24	0.44±0.18	0.93±0.14	0.23±0.18
M_1 BL	0.99±0.10	0.50±0.43	0.080±0.18		
M_1 mesial BL				0.72±0.15	
M_1 distal BL				0.78±0.16	
M_2 MD	0.45±0.18	0.51±0.18	0.36±0.16	0.89±0.10	

M_2 BL	0.92±0.10	0.44±0.17	0.31±0.14		
M_2 mesial BL				0.76±0.10	
M_2 distal BL				0.62±0.12	
M_3 MD		1.0	0.68±0.18	0.72±0.22	
M_3 BL		0.59±0.15	0.64±0.16		
M_3 mesial BL				0.81±0.11	
M_3 distal BL				0.63±0.11	
Range of h^2	0.19-0.99	0.21-1.0	0.080-0.68	0.24-0.93	0.23-0.77

Stojanowski et al. (2017) point out that human maxillary tooth lengths yield consistently greater heritability estimates than the lengths of the homologous mandibular teeth, with maxillary permanent tooth length heritabilities ranging from 0.458 to 0.768 and mandibular permanent tooth length heritabilities ranging from 0.229 to 0.646. They hypothesize that maxillary trait heritabilities are greater than mandibular trait heritabilities due to greater constraints on the development of maxillary teeth. Taking standard error for h^2 estimates into account, this pattern is fairly weak in the human sample. The same pattern is also not observed in the Oak Ridge tamarins, Cayo Santiago macaques, or SNPRC baboons (data from Hlusko et al., 2011). Across these four human samples, the range of h^2 values estimated in the maxillary and mandibular dentition is broad, and it becomes even broader when error and uncertainty due to unaccounted for aspects of common environment and non-additive genetic effects are taken into consideration.

Stojanowski et al. (2017) also note that heritability estimates of human tooth lengths align with dental morphogenetic field theory (Butler, 1939), so that the h^2 estimate of a key or pole tooth tends to be greater than that of more distal teeth of the

same type. In the human sample, the heritability of the first incisor is greater than that of the second incisor, and the heritability of the mesial premolar is greater than that of the distal premolar. A similar trend is found in the heritabilities of tooth length in the Oak Ridge brown-mantled tamarin population. The h^2 estimate for the length of the mesial-most tamarin premolar, P^2, is greater than that of the other maxillary premolar lengths, although the h^2 of P^4 length is greater than that of $P^{3.}$ The pattern is more reliably held in the mandibular premolars, in which the P_2 length h^2 is greater than the h^2 of P_3 length, which is greater than the h^2 of P_4 length. The h^2 of M^1 length is greater than that of M^2, and the h^2 of M_1 length is marginally greater than that of M_2 length. As others have noted (Stojanowski et al., 2017), the considerable margins of error around these estimates of h^2 mean that these differences are not statistically significant, and much larger sample sizes would be necessary to generate h^2 estimates in which significant differences would be worth testing.

Comparisons of the Cayo Santiago macaque tooth length h^2 estimates show a similar pattern, albeit less consistently. The h^2 of I^1 is greater than that of I^2, the h^2 of P^3 is greater than that of P^4, and the h^2 of I_1 is greater than that of I_2, but the h^2 of P_3 is much less than that of $P_{4.}$ The maxillary molars follow the predicted pattern ($M^1>M^2>M^3$), and the h^2 of M_1 is slightly greater than that of M_2. The estimated h^2 of M_3 length is, however, greater than that of M_1 or M_2. Deviations from the predicted pattern in the mandibular premolars may be explained by the atypical eruption pattern and morphology of the honing premolar in *Macaca mulatta*. The macaque P_3 erupts before the P_4 in female rhesus macaques, but after the P_4 in male rhesus macaques in whom the P_3 is elongated as

part of the canine-premolar honing complex. The macaque population heritability estimates are therefore not entirely consistent with the findings from humans (Stojanowski et al., 2017) and tamarins, but still provide weak support for the hypothesis that h^2 estimates from tooth lengths reflect either increased genetic regulation or decreased environmental variance in the dimensions of the pole teeth (Dahlberg, 1945).

Assessment of this pattern using I_A in addition to h^2 indicates a similar trend. The I_A estimates for P^2, P_2, M^1, and M_1 length are greater than I_A estimates for lengths of more distal teeth of the same type in the tamarin sample. The pattern is also held observed in the maxillary incisors and premolars and mandibular premolars of the macaque sample, but is not consistent across both pedigree models in the maxillary molars or mandibular incisors and molars. While h^2 is more closely aligned to the pole tooth concept as described by Dahlberg (1945), h^2 estimates of tooth dimensions in these primate populations are heavily influenced by the specific environments in which these individuals lived and are not generalizable to primates in the past.

Estimates of h^2 and I_A may also be influenced by common environmental effects that were not fully considered in these and previous studies of the genetic architecture of primate dental dimensions; common environmental effects related to maternal identity, matriline, and litter have had observable impacts on h^2 estimates in other mammals (Asadi Fozi et al., 2005; Kruuk and Hadfield, 2007; Koivula et al., 2009). Teeth that initiate crown formation early in development might be expected to be more greatly influenced by maternal effects than teeth that develop later. These earlier-developing teeth also tend to be the pole teeth observed to produce greater tooth length h^2 estimates.

It is therefore possible that common environmental effects, such as maternal effects, explain the pattern that Stojanowski et al. (2017) interpret as evidence for the dental morphogenetic field theory. The estimation of genetic correlations between dental dimensions in these populations would bear more directly on these questions over the existence and manner of odontogenetic patterning in primates.

2.4.4 Challenges

The sampling variance that accompanies the estimation of h^2 of dental measurements in primate populations is large and limits the strength of conclusions that can be drawn from these analyses. Comparisons of h^2 and of I_A are nevertheless included in this paper so that the trends observed here may serve as hypotheses for future testing. As the Cayo Santiago skeletal collection grows to include more individuals with known paternity, it will be possible to estimate quantitative genetic parameters in this population with less error. Larger samples sizes may also be used to estimate parameters separately in males and females to study the role of sex differences in genetic architecture in the appearance and inheritance of sexually dimorphic features.

2.5 Conclusions

These results provide the first of estimates of tooth size heritability in a platyrrhine and in a free-ranging cercopithecoid population, and demonstrate that dental dimensions are highly heritable in multiple extant primate populations. The results

broadly resemble those of previous studies, although comparisons of h^2 and I_A estimates between populations should be performed cautiously and with full consideration of error in parameter estimation, and the impacts of environmental variance, selection, and common environment on quantitative genetic parameters. Future studies should account for these effects, and the impacts of sex differences in trait inheritance, and this will require the continued preservation of skeletal and dental material from captive and wild primate populations. The collection of pedigree data and skeletal material at long-term study sites is invaluable to future research into the genetic inheritance of primate skeletal and dental morphology.

3 Using genetic correlations to evaluate models of dental patterning

The preceding chapter demonstrates that, while most dental dimensions are highly heritable in different primate populations living in a range of conditions, interpretation of heritability estimates is limited by the uncertainty of the estimates, the possibility of common environmental effects, and the impact of selection and environment on genetic and environmental variance components. Heritability estimates are especially ill-suited to answer questions about genetic patterning, since they describe only the proportion of the phenotypic variance associated with genetic similarity. Estimates of genetic covariance, often expressed using the genetic correlation (ρ_G) between traits, may be more useful in investigations of dental patterning in primates.

The brown-mantled tamarin sample was selected for this quantitative genetic assessment of dental patterning because the tamarin pedigree is more complete than the macaque pedigree, and the tamarin sample exhibits very little sexual dimorphism, a factor that could greatly impact analyses (as discussed in Chapters 2 and 5). The tamarins are also distinct from the previously studied baboon and human populations in ways that could impact the genetic patterning of the dentition. Loss of the third molars and retention of the second premolars in the tamarin lineage could greatly impact the genetic relationships between teeth, making tamarins an excellent test of the homogeneity of the genetic correlation matrix in anthropoid primates.

The morphogenetic field model (Butler, 1939; Dahlberg, 1945) and the clone model (Osborn, 1978) are assessed in this paper following assumptions of the ways that genetic relationships will manifest in estimates of genetic correlations. It is, however, also possible that the morphogenetic field model and clone model would produce similar genetic correlations between estimates. The focus of this paper is therefore not on selecting one model, but on demonstrating how genetic correlations in the dentition may relate to both simultaneously. This approach is also consistent with recent models that recognize that both models likely influence the patterning of odontogenesis (Mitsiadis and Smith, 2006; Townsend et al., 2009a).

4 Genetic correlations between dental dimensions in *Saguinus fuscicollis*

4.1 Introduction

Models of mammalian dental patterning, such as morphogenetic field theory (Butler, 1939; Dahlberg, 1945), the dental clone model (Osborn, 1978), and the dental inhibitory cascade model (Kavanagh et al., 2007), use phenotypic covariance within and between species to identify developmental and genetic constraints on the evolution of the mammalian dentition. Some phenotypic variation observed in the size and morphology of primate teeth can be explained by these models (e.g. Greenfield, 1993; Townsend et al., 2009; Evans et al., 2016), although deviations have been observed in hominoid and cercopithecoid primates (Carter and Worthington, 2016). Experimental manipulations of developing teeth and their environments provide valuable additional evidence of basic mechanisms that impact tooth morphology, but these methods do not explain how phenotypic variation and covariation arise in the teeth of living primate populations. Research into the quantitative genetic parameters governing tooth size and morphology in living primate populations provides additional evidence in the investigation of dental patterning and its evolution in primates (Hlusko et al., 2016).

Traditional quantitative genetics methods break down population-level phenotypic variance into genetically- and environmentally-derived components. Resulting heritability and genetic correlation estimates can be used to predict response to selection in living populations using the breeder's equation (Lush, 1937), adapted for use

with genetically correlated traits under multivariate selection by Lande and Arnold (1983). Although the phenotypic changes predicted by these equations are often not realized in actual populations (Merilä et al., 2001; Kruuk et al., 2002; Pemberton, 2010), they are nevertheless useful heuristics for the process by which selection acts on heritable phenotypic variation. This is especially true of Lande and Arnold's multivariate breeder's equation (1983), which demonstrates that genetic correlations between traits do not necessarily constrain, and can even accelerate, evolutionary change. Estimates of genetic correlation are important for connecting research on genetic variation to the study of phenotypic variation to improve our understanding of the evolution of morphology and other complex traits (Hlusko et al., 2016).

Genetic integration is widespread due to the shared effects of genes on multiple traits through pleiotropy as well as the tendency for genes to be inherited together due to linkage disequilibrium. Traits with close functional relationships are expected to be more highly genetically or developmentally correlated when such integration increases the evolvability of the system (Olson and Miller, 1958; Lande, 1979; Cheverud, 1982; Wagner et al., 2007). Quantitative genetic analyses of cranial morphology in primates support the hypothesis that functionally integrated features are genetically correlated; these functional sets are also somewhat modular, meaning they are less genetically correlated with those features to which they are not functionally or embryologically linked (Cheverud, 1982, 1995; though see Sherwood et al., 2008a, b). Genetic correlations between dental measurements from the Southwest National Primate Research Center (SNPRC) baboon population (Hlusko and Mahaney, 2009; Hlusko et al.,

2011) are also modular, with greater genetic correlations within than between tooth types (Hlusko and Mahaney, 2009; Hlusko et al., 2011). Estimates of genetic correlations between mesiodistal tooth lengths in a modern human population, however, show widespread integration across dental dimensions with little evidence of the modularity identified in the SNPRC baboons (Stojanowski et al., 2017).

Based on these mixed results from baboons and humans, it is difficult to interpret which aspects of genetic integration and modularity in the dentition are population- or species-specific and which might be characteristic of primates more broadly. Quantitative genetic analyses of dental dimensions from additional primate populations will help, but few primate skeletal collections have the pedigree data and large samples necessary for traditional quantitative genetic analyses. The Oak Ridge brown-mantled tamarin (*Saguinus fuscicollis*) skeletal collection is well-suited to these analyses because of the size of the collection and completeness of the pedigree. It is also valuable to compare tamarins, a small-bodied platyrrhine, to previous analyses of humans and baboons. Tamarins lack both the derived bilophodonty of baboons and bunodonty of humans, and have neither the greatly expanded canine-premolar honing complex of baboons nor the greatly reduced canine-premolar honing complex of humans. For these reasons, this tamarin sample may be a particularly useful comparative model to further the study of genetic integration and modularity in the primate dentition.

Models of dental patterning and covariation must contend with the different manners in which teeth relate to each other. To function, teeth in the maxilla and mandible must occlude with each other to process food during mastication; this requires

that the jaws, teeth, cusps, and foveae are aligned properly during the chewing cycle. If genetic modularity is expected to evolve in functionally integrated parts, teeth that occlude may be more highly genetically correlated than teeth that do not occlude. In a morphological context, different tooth types have distinct morphologies that may be produced by differences in the morphogenetic field in which each tooth develops. If morphological similarities among teeth of the same type are produced by morphogenetic fields, it is expected that teeth of the same type are more highly genetically correlated than teeth of different types. The dental inhibitory cascade model (Kavanagh et al., 2007) also demonstrates that intercellular signaling in developing teeth influences crown size, even in primates (Evans et al., 2016). If tooth development is altered by signaling of surrounding teeth (Kangas et al., 2004), then genetic correlations between neighboring teeth are expected to be greater than genetic correlations in physically separated teeth.

This paper uses maximum likelihood estimation to estimate narrow-sense heritabilities of and genetic correlations between dental measurements from a captive, pedigreed brown-mantled tamarin population. The results of these analyses are compared to results from modern humans (Stojanowski et al., 2017) and hamadryas baboons (Hlusko and Mahaney, 2009) to determine whether teeth that occlude are more highly genetically correlated than teeth that do not occlude, whether teeth of the same type are more highly genetically correlated than teeth of different types, and whether neighboring teeth are more highly genetically correlated than teeth in different regions of the toothrow.

4.2 Methods

4.2.1 Measurement

The Oak Ridge brown-mantled tamarin (*Saguinus fuscicollis illigeri*) population was bred in captivity for use in medical research over several decades (Clapp and Tardif, 1985). The associated skeletal collection, housed at the Osteometric Variation Analysis Laboratory (OVAL) at the University of Tennessee, contains material from individuals that are part of an extended pedigree. 386 pedigreed individuals, spanning four generations, were included in this study. Dams and sires are known for 190 individuals, and the other 196 individuals are founders.

Linear dental measurements were collected from 302 of these pedigreed individuals using Mitutoyo nib-style digital calipers. Mesiodistal length was measured as the maximum dimension parallel to the lingual margin of the tooth crown. Buccolingual breadth was measured as the maximum dimension perpendicular to the lingual margin of the tooth crown. The left and right sides of the toothrow were considered interchangeable based on the evidence of complete pleiotropy between antimeres shown by previous studies (Hlusko et al., 2011; Stojanowski et al., 2017), so the half of the toothrow with the fewest missing teeth and least damage was measured for each individual. Incisor labio-lingual breadths were not measured due to the impact of wear on this trait in this population.

The estimated planar rectangular area of canine and postcanine tooth crowns, calculated as the product of the mesiodistal length and the buccolingual breadth, was also analyzed. Hlusko et al. (2002) demonstrated that quantitative genetic parameters of actual

crown area, measured using outlines of the occlusal surface of the tooth, are similar to those estimated for estimated crown areas in a captive baboon sample. Calculations of estimated crown area were performed in SOLAR.

4.2.2 Analyses

Intra-observer measurement reliability was assessed with repeated measurements of ten individuals. Calculation of measurement reliabilities was performed in MS Excel, where:

Reliability = 1 – (repeated measure variance / population variance)

The phenotypic variance in a trait, $\sigma^2_{P,}$ can be decomposed into genetic and environmental variance (σ^2_G and σ^2_E respectively) (Lynch and Walsh, 1998). There are not enough full sibling relationships in the pedigree to estimate variance related to dominance in this population. The additive genetic variance (σ^2_A) was estimated in place of σ^2_G and hence the resulting heritability estimates reflect the narrow-sense heritability ($h^2 = \sigma^2_A/ \sigma^2_P$), rather than the broad-sense heritability ($H^2 = \sigma^2_G/ \sigma^2_P$). Maximum likelihood-based variance decomposition was performed in the open-source software package SOLAR 6.2.2 (Almasy and Blangero, 1998) following estimation procedures described by Wang et al. (1997).

Likelihood-ratio tests are used in SOLAR to compare a restricted model, in which σ^2_A is constrained to zero, to a general model, in which σ^2_A is freely estimated. The likelihood-ratio test statistic determines the probability that the general model is

significantly more likely than the restricted model. In univariate h^2 estimation, the p-value resulting from likelihood-ratio tests is the probability that the null hypothesis holds, i.e. that h^2 equals zero. Estimates of h^2 from univariate models are considered significantly more likely than estimates of zero when $p<0.05$. The effects of sex and birth-in-captivity (scored as wild-born or captive-born) were estimated simultaneously using the SOLAR covariate screening function, which uses likelihood-ratio tests to compare models in which covariates are included to models in which covariates are excluded. Age-at-death was not known for the 190 founder individuals in the sample, so age was not included as a covariate. Sex and birth-in-captivity were included in univariate models as significant covariates at $p<0.10$ (as in Hlusko et al., 2002).

In addition to the estimation of h^2, the evolvability or mean-scaled additive variance ($I_A = \sigma^2_A$ / mean) was calculated in SAS/STAT 14.1 following the procedure described in the preceding chapter. I_A was formulated as a measure of genetic heritability that can be used in comparisons between populations, since it is not influenced by the population-specific σ^2_E (Houle, 1992). Since, however, I_A expresses the evolvability in proportion to the mean its interpretability across traits and populations is still somewhat limited. It is useful to examine both h^2 and I_A for patterns across traits since these parameters may be impacted by σ^2_E in different ways.

Because the sample size is insufficient for full multivariate analysis of all traits jointly, bivariate maximum likelihood estimation of quantitative genetic parameters was performed on three sets of measurements: maxillary length and breadth dimensions, mandibular length and breadth dimensions, and maxillary and mandibular estimated

crown areas. In each case, the genetic correlation (ρ_G) was estimated for every pair of traits in the set. Prior to estimation, the effective sample size (N_{eff}) was calculated for each pair using the equation from Cheverud (1995) following Robertson (1959):

$$N_{eff} = (2h^2_x h^2_y / (V(h^2_x)\ V(h^2_y))^{0.5}) + 1$$

where $V(h^2)$ is the squared standard error of the h^2 estimate. This calculation of N_{eff} assumes similar degrees of genetic correlation across families within the population; although this assumption cannot be tested, most individuals in this population are part of a single extended family rather than several separate family groups. N_{eff} is an estimate of the effective number of genetically independent individuals used to estimate ρ_G, and provides an additional measure of the statistical reliability of ρ_G estimates. N_{eff} is not more useful or reliable than the standard error estimated alongside ρ_G in SOLAR, but its calculation allows for comparison of the reliability of ρ_G estimates in this study and other studies that use N_{eff} to assess ρ_G reliability.

Genetic correlations (ρ_G), environmental correlations (ρ_E), and phenotypic correlations (ρ_P) between pairs of measurements were estimated through bivariate analyses in SOLAR. Likelihood ratio tests were used to calculate the probability that a bivariate model in which ρ_G is freely estimated is significantly more likely than a model in which ρ_G is restricted to zero. Additional likelihood ratio tests assess whether ρ_G is significantly different from 1. ρ_G estimates are considered significantly more likely than restricted models when $p<0.05$. In total, 248 bivariate analyses were performed, each including multiple likelihood ratio tests. Given the number of tests performed,

designating significance at $p<0.05$ risks the identification of many false positives. Rather than reducing the p-value or applying a correction for multiple tests, which may increase the risk of false negatives, values that are significant at $p<0.05$ are evaluated with associated standard error estimates. This approach has also been used in previous quantitative genetic studies of primate dental traits (Hlusko, 2000; Hlusko et al., 2002, 2011; Hlusko and Mahaney, 2009; Stojanowski et al., 2017). There is considerable uncertainty in the estimation of ρ_G in this population whether or not estimates differ significantly from zero. Covariates were included in bivariate models according to the results of covariate screening during univariate h^2 estimation.

4.3 Results

4.3.1 Reliability

Intra-observer measurement reliabilities are provided in Table 4.1. Reliability is quite low for measurements of the incisors, so measurements of I^2 length, I_1 length were excluded from further analysis. Reliability coefficients in the canines, premolars, and molars fall between 0.61 and 0.98, and six measurements have reliability coefficients

Table 4.1. Intra-observer measurement reliability, traits with reliability below 0.80 are shaded in grey.

	Maxillary		Mandibular	
	MD	BL	MD	BL
I1	0.55		0.32	
I2	0.17		0.65	
C	0.81	0.86	0.69	0.77
P2	0.91	0.76	0.88	0.75
P3	0.81	0.88	0.87	0.77
P4	0.80	0.91	0.82	0.88
M1	0.90	0.72	0.93	0.78
M2	0.91	0.98	0.88	0.61

greater than or equal to 0.90. Measurements with reliability below 0.80 are noted in additional analyses.

4.3.2 Heritability estimates

Results of univariate analyses of mesiodistal lengths, buccolingual breadths, and crown area estimates, are provided in Table 4.2. Birth-in-captivity is a statistically significant covariate ($p<0.10$) for 24 traits, while sex is a statistically significant covariate for five traits. Both birth-in-captivity and sex are statistically significant covariates for two traits (P^3 breadth and P^3area). Covariates account for between 0.2% and 7.8% of the phenotypic variance in a trait. For the 38 variables analyzed, 37 estimates of h^2 are statistically significantly greater than zero ($p<0.05$); only the h^2 of P_4 length is not statistically significantly different from zero. Estimates of h^2 range from 0.185 (P_4 length) to 0.985 (M_1 breadth).

Table 4.2. Results of univariate analyses. MD = mesiodistal length, BL = buccolingual breadth, area = estimated crown area, C = statistically significant covariates where WC is birth-in-captivity, $\sigma 2_C$ = percentage of $\sigma 2_P$ removed by statistically significant covariates. Grey-shaded rows indicate traits with measurement reliability below 0.80.

Tooth	Trait	N	Mean	σ^2_P	h^2	p	SE	C	σ^2_C	I_A
I^1	MD	263	2.17	0.024	**0.642**	<0.001	0.111	WC	2.97	0.007
C^1	MD	273	2.34	0.052	**0.697**	<0.001	0.110			0.015
	BL	271	1.95	0.030	**0.647**	<0.001	0.127	WC	0.93	0.010
	area	271	4.57	0.502	**0.984**	<0.001	0.073	WC	0.18	0.108
P^2	MD	271	1.80	0.026	**0.454**	<0.001	0.125	WC	7.63	0.007
	BL	274	2.14	0.026	**0.562**	<0.001	0.108	Sex	0.73	0.007
	area	269	3.85	0.219	**0.538**	<0.001	0.114	WC	4.77	0.031

P^3	MD	256	1.57	0.016	**0.285**	0.008	0.132			0.003
	BL	280	2.44	0.037	**0.609**	<0.001	0.115	Sex, WC	2.45	0.009
	area	255	3.83	0.241	**0.589**	<0.001	0.127	Sex, WC	1.31	0.037
P^4	MD	255	1.59	0.016	**0.315**	0.011	0.157			0.003
	BL^K	276	2.64	0.037	**0.678**	<0.001	0.110	WC	5.83	0.010
	area	252	4.22	0.265	**0.643**	<0.001	0.122	WC	1.58	0.040
M^1	MD	282	2.19	0.028	**0.876**	<0.001	0.089			0.011
	BL	282	2.74	0.029	**0.748**	<0.001	0.093	WC	2.59	0.008
	area	277	6.01	0.492	**0.946**	<0.001	0.083	WC	1.73	0.077
M^2	MD	250	1.43	0.027	**0.305**	0.003	0.132	Sex	1.35	0.006
	BL	270	2.27	0.051	**0.879**	<0.001	0.070			0.020
	area	247	3.28	0.332	**0.764**	<0.001	0.106	WC	1.02	0.077
I_2	MD	266	1.34	0.015	**0.482**	<0.001	0.137	WC	7.77	0.005
C_1	MD	270	2.16	0.041	**0.569**	<0.001	0.111	WC	3.5	0.011
	BL^K	270	2.46	0.050	**0.824**	<0.001	0.096	WC	1.04	0.017
	area	269	5.33	0.716	**0.830**	<0.001	0.093			0.111
P_2	MD	274	2.11	0.042	**0.385**	<0.001	0.127	Sex	2.04	0.008
	BL^K	279	1.95	0.026	**0.419**	<0.001	0.111	WC	0.92	0.006
	area	273	4.12	0.325	**0.628**	<0.001	0.125			0.050
P_3	MD	245	1.71	0.019	**0.286**	0.008	0.138			0.003
	BL	272	1.78	0.021	**0.815**	<0.001	0.099	WC	0.97	0.010
	area	245	3.06	0.136	**0.681**	<0.001	0.116	WC	0.45	0.030
P_4	MD	222	1.74	0.020	0.185	0.103	0.159	WC	4.13	0.002
	BL	242	1.84	0.028	**0.492**	<0.001	0.127	WC	6.17	0.007
	area	220	3.21	0.155	**0.538**	<0.001	0.146	WC	7.21	0.026
M_1	MD	235	2.11	0.027	**0.465**	0.0011	0.151	WC	6.39	0.006
	BL^K	241	1.91	0.018	**0.985**	<0.001	0.100	WC	2.64	0.009
	area	234	4.03	0.234	**0.759**	<0.001	0.123	WC	7.57	0.044
M_2	MD	218	1.97	0.024	**0.446**	0.0048	0.184			0.005
	BL	241	1.63	0.013	**0.915**	<0.001	0.095			0.007

	area	217	3.21	0.143	**0.761**	<0.001	0.129			0.034

[K] indicates traits that were inverse normalized prior to analysis to correct for skew

4.3.3 Genetic correlation estimates

Effective sample sizes (N_{eff}) for pairs of traits (following Cheverud, 1995 Robertson 1959) demonstrate that genetic correlations estimated from this population are reliable in comparison to previous ρ_G estimates in this population (Table 9.1). Across 248 trait combinations, N_{eff} ranges from 22 to 365. These are large N_{eff} values compared to those of previous studies; a study of cranial dimensions in the same tamarin population found N_{eff} values ranging from 1.08 to 239.43 (Cheverud, 1995). This difference likely results from the greater heritability estimates associated with dental dimensions. Estimation of ρ_G is appropriate for dental dimensions in this population based on N_{eff}, although P_4 length was excluded from ρ_G estimation due low h^2 for this trait resulting in low N_{eff}. N_{eff} for P_4 length ranges from 22 to 79.

Table 4.3. Within-maxilla bivariate analyses: The lower triangle contains ρ_G estimates, and the upper triangle contains the standard error of the ρ_G estimate. White: statistically significantly different from zero but not statistically significantly different from one; Pale grey: between zero and one ($p<0.05$); Dark grey: not statistically significantly different from zero; Black: not statistically significantly different from zero or one.

		I^1	C^1		P^2		P^3		P^4		M^1		M^2	
		MD	MD	BL	MD	BL	MD	BL	MD	BL	MD	BL	MD	BL
I^1	MD		0.16	0.16	0.19	0.15	0.29	0.15	0.24	0.13	0.14	0.12	0.20	0.13
C^1	MD	0.60		0.09	0.17	0.10	0.19	0.12	0.24	0.13	0.12	0.12	0.18	0.08
	BL	0.62	0.91		0.19	0.10	0.18	0.12	0.25	0.13	0.14	0.12	0.23	0.11
P^2	MD	0.39	0.44	0.26		0.19	0.27	0.18	-	0.17	0.15	0.15	0.21	0.13
	BL	0.52	0.77	0.73	0.19		0.21	-	0.26	0.10	0.12	0.12	0.22	0.11
P^3	MD	0.88	0.62	0.71	0.72	0.50		0.21	0.29	0.22	-	0.18	0.29	0.20
	BL	0.59	0.58	0.63	0.31	1.00	0.49		0.24	0.07	0.13	0.11	0.21	0.09
P^4	MD	0.55	0.55	0.48	1.00	0.56	0.94	0.61		0.25	0.13	0.16	0.23	0.16
	BL	0.58	0.60	0.54	0.44	0.92	0.58	0.91	0.41		0.13	0.08	0.20	0.06
M^1	MD	0.58	0.48	0.59	0.59	0.49	1.00	0.51	0.94	0.42		0.09	0.20	0.10
	BL	0.65	0.45	0.55	0.43	0.57	0.66	0.57	0.78	0.79	0.63		0.18	0.07

M^2	MD	0.63	0.64	0.06	0.80	0.45	0.83	0.38	0.74	0.45	0.58	0.47		0.16
	BL	0.61	0.75	0.58	0.62	0.69	0.75	0.75	0.65	0.84	0.63	0.76	0.61	

Statistically significant non-zero ρ_G values are estimated for 70 out of 78 within-maxilla bivariate analyses (Table 4.3). Two pairs of traits produce inconclusive ρ_G estimates that are not significantly different from zero or one (C^1 breadth-P^4 length, P^4 length-P^4 breadth). ρ_G estimates that are not significantly different from zero fail to reject the null hypothesis of genetic independence between dental dimensions for six pairs of traits. ρ_G estimates for 50 pairs of traits are significantly different from one and from zero and ρ_G estimates for 20 pairs of traits are significantly different from zero and are not significantly different from one. In both cases, these results suggest a role for pleiotropy and linkage disequilibrium in the associated dimensions.

In bivariate analyses of mandibular tooth dimensions, there are significant non-zero genetic correlations for 60 out of 66 pairs of traits (Table 4.4). The estimate of ρ_G for one pair of traits is inconclusive, meaning it is not significantly different from zero or from 1 (P_3 length-M_2 length). Five pairs of traits produce ρ_G estimates that are not statistically significantly different from zero, meaning that the null hypothesis of genetic independence is not rejected. Of the 60 trait pairs with statistically significant non-zero ρ_G estimates, 20 pairs of traits are incompletely genetically associated, meaning ρ_G is statistically significantly different from zero and from one, and 40 ρ_G estimates are not statistically significantly different from one.

Within-tooth genetic correlations are estimated between length and breadth measurements of all canines, premolars and molars except P_4. Of these eleven within-tooth ρ_G estimates, four teeth (C^1, P_2, P_3, M_1) show complete pleiotropy between length and breadth measurements and five teeth (P^3, M^1, M^2, C_1, M_2) show incomplete pleiotropy. Length and breadth measurements are genetically independent in P^2. The ρ_G estimate for P^4 length and breadth is not significantly different from zero or one, and is therefore inconclusive.

Table 4.4. Within-mandible bivariate analyses: The left diagonal contains ρ_G estimates, and the right diagonal contains the standard error of the ρ_G estimate. White: not statistically significantly different from one; Pale grey: between zero and one; Dark grey: not statistically significantly different from zero; Black: not statistically significantly different from zero or one.

		I_2	C_1		P_2		P_3		P_4	M_1		M_2	
		MD	MD	BL^K	MD	BL^K	MD	BL	BL	MD	BL^K	MD	BL
I_2	MD		0.18	0.21	0.20	0.34	-	0.17	0.24	0.21	0.17	0.25	0.15
C_1	MD	0.78		0.09	-	0.19	0.25	0.10	0.16	0.23	0.19	0.25	0.10
	BL	0.72	0.85		0.18	0.14	0.22	0.11	0.16	0.16	0.13	0.19	0.11
P_2	MD	0.65	1.00	0.53		0.23	0.24	0.15	0.19	0.21	0.21	0.23	0.17
	BL	0.95	0.55	0.80	0.66		0.31	0.15	-	0.21	0.16	0.25	0.16
P_3	MD	1.00	0.76	0.54	0.81	0.87		0.27	0.28	0.25	0.24	0.29	0.25
	BL	0.68	0.93	0.71	0.85	0.74	0.59		-	0.15	0.14	0.18	0.08
P_4	BL	0.73	0.94	0.90	0.96	1.00	0.92	1.00		0.20	0.10	0.22	0.10
M_1	MD	0.65	0.43	0.57	0.70	0.59	0.86	0.61	0.53		0.16	-	0.15
	BL	0.74	0.74	0.58	0.75	0.86	0.75	0.74	0.93	0.83		0.18	0.07
M_2	MD	0.65	0.52	0.21	0.93	0.27	0.55	0.43	0.44	1.00	0.37		0.19
	BL	0.56	0.89	0.56	0.98	0.44	0.72	0.74	0.78	0.81	0.82	0.45	

Table 4.5. Bivariate analyses of estimated crown areas: The left diagonal contains ρ_G estimates, and the right diagonal contains the standard error of the ρ_G estimate. White: not statistically significantly different from one; Pale grey: between zero and one ($p<0.05$).

	C^1	P^2	P^3	P^4	M^1	M^2	C_1	P_2	P_3	P_4	M_1	M_2
C^1		0.09	0.08	0.12	0.10	0.09	0.05	0.14	0.09	0.13	0.11	0.10
P^2	0.74		-	-	0.10	0.10	0.08	0.11	0.10	0.22	0.13	0.14
P^3	0.75	1.00		-	0.09	0.11	0.10	0.17	0.15	0.16	0.10	0.14
P^4	0.58	1.00	1.00		0.06	0.08	0.12	0.17	0.11	0.17	0.11	0.13
M^1	0.55	0.74	0.90	0.91		0.08	0.10	0.14	0.10	0.14	0.09	0.11
M^2	0.61	0.90	0.78	0.80	0.77		0.10	0.13	0.11	0.11	0.10	0.11
C_1	0.84	0.95	0.88	0.80	0.68	0.80		0.15	0.09	0.15	0.14	0.12
P_2	0.65	0.84	0.66	0.61	0.73	0.90	0.77		0.11	-	0.14	0.18

P_3	0.73	0.96	0.78	0.76	0.73	0.88	0.92	0.92		0.145	0.10	0.11
P_4	0.62	0.80	0.88	0.86	0.69	0.89	0.90	1.00	0.95		0.13	0.15
M_1	0.70	0.73	0.85	0.82	0.83	0.77	0.64	0.90	0.84	0.85		0.09
M_2	0.52	0.64	0.51	0.49	0.58	0.75	0.65	0.88	0.73	0.66	0.87	

Bivariate analyses of estimated crown areas produce 66 ρ_G estimates, all of which are statistically significantly different from zero (Table 4.5). 27 estimates are not statistically significantly different from one, indicating complete pleiotropy, and 39 estimates are statistically significantly different from one, indicating incomplete pleiotropy. Within the maxilla, six out of fifteen ρ_G estimates are not statistically significantly different from one, while nine out of fifteen ρ_G estimates are statistically significantly different from one. 12 out of 36 ρ_G estimates between maxillary and mandibular teeth are not statistically significantly different from one.

4.4 Discussion

Genetic correlations estimated across the toothrow in this brown-mantled tamarin population suggest a high degree of pleiotropy in the dentition, providing mixed support for findings from similar studies of baboons (Hlusko, 2000; Hlusko and Mahaney, 2009; Hlusko et al., 2011) and humans (Stojanowski et al., 2017). The interpretations of these results will be discussed as they relate to models of dental patterning in mammals and primates, before they are directly compared to results from similar studies of genetic correlations between primate dental dimensions.

4.4.1 Are teeth that occlude more highly genetically correlated than teeth that do not occlude?

To evaluate whether tooth dimensions that are functionally related are more genetically integrated than those that are not functionally related, genetic correlations between estimated tooth crown areas in the maxilla and mandible were estimated (Table 4.5). In platyrrhines with proper occlusion, maxillary teeth sit slightly anterior to their mandibular homologues so that C^1 occludes with C_1 and P_2, and P^2 occludes with P_2 and P_3. To assess whether the crown areas of teeth that occlude are more highly genetically correlated than those of teeth that do not occlude, ρ_G estimates were plotted with standard error in two sets: ρ_G between occluding teeth and ρ_G between non-occluding teeth. Figure 4.1 shows ρ_G for occluding teeth on the left side of the plot and ρ_G estimates for non-occluding teeth on the right side of the plot. The degree to which occluding teeth are genetically correlated is remarkably similar to genetic correlations between non-occluding teeth. For occluding teeth, ρ_G ranges from 0.583 to 0.955, while non-occluding tooth pair ρ_G estimates range from 0.493 to 0.953. Both sets of ρ_G estimates therefore indicate high genetic correlations between maxillary and mandibular estimate crown areas, but the hypothesis that the crown areas of teeth that are functionally integrated will be more highly genetically correlated than those that are not functionally integrated is not supported.

In addition to the lack of support for the stated hypothesis, it is not possible to separate functional integration that leads to genetic integration from genetic integration that results in functional integration. If functionally unrelated parts become genetically

integrated due to, for example, shared embryological origins, the genetic correlation could allow for functional integration between parts via exaptation. Close genetic correlations between functionally related parts therefore does not necessarily indicate that genetic integration or modularity result from functional integration.

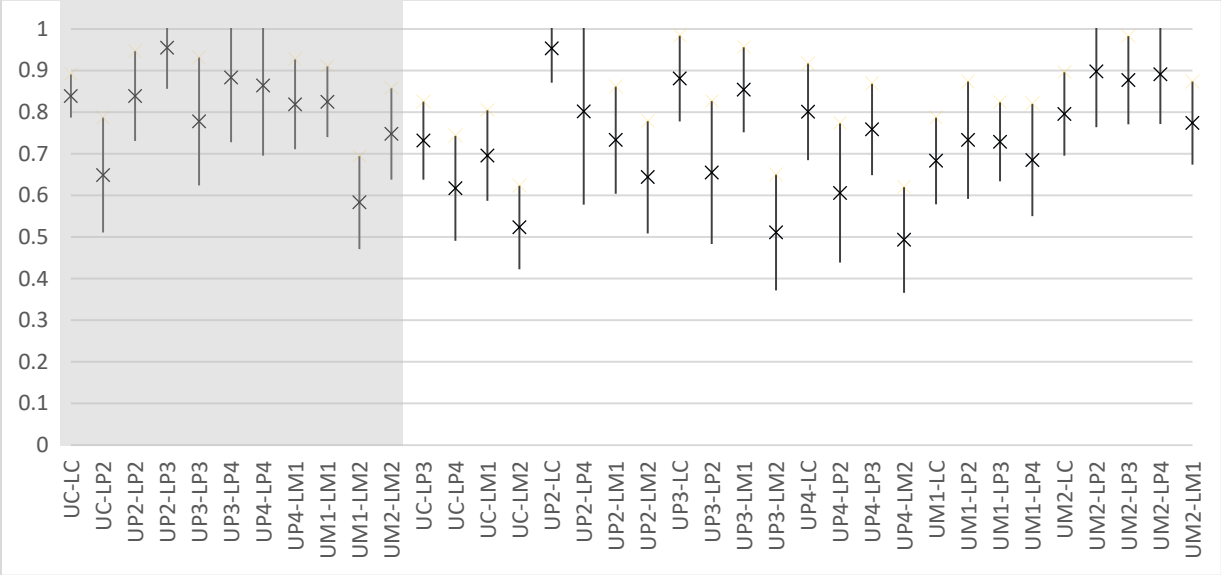

Figure 4.1. Genetic correlation estimates (+/- one standard error) from occluding (on the left, shaded in grey) and non-occluding (on the right, unshaded) tooth crown areas.

Previous studies have not estimated genetic correlations between maxillary and mandibular tooth areas, but genetic correlations of cusp proportions between maxillary and mandibular molars have been estimated in the SNPRC baboons (Koh et al., 2010). These analyses demonstrate that maxillary molar cusp proportions are statistically significantly genetically correlated with mandibular molar cusp proportions, and that these correlations are larger between cusps that do not occlude during mastication than between those that do. Koh et al. (2009) discuss the possibility that these genetic

correlations in modern baboon molar cusps are genetic byproducts of the ancestral tribosphenic molar. Results from this study of brown-mantled tamarin dental integration provide additional evidence that significant and large genetic correlations between maxillary and mandibular dental proportions may result from developmental or evolutionary, rather than or in addition to functional, relationships between teeth.

4.4.2 Are teeth of the same type more highly genetically correlated than teeth of different types?

According to morphogenetic field theory (Butler, 1939; Dahlberg, 1945; Townsend et al., 2009a) and the clone model of odontogenesis (Osborn, 1978), the morphological similarities by which teeth are divided into types result from genetic contributions that are shared according to the position of a tooth in the toothrow. These shared genetic contributions are estimated as genetic correlations in this population of brown-mantled tamarins to determine whether the dimensions of teeth of the same type are more highly genetically correlated than teeth of different types.

While the dimensions of a single tooth might be expected to be highly genetically correlated, within-tooth ρ_G estimates are not substantially greater than between-tooth ρ_G estimates in this population. One exception is the maxillary canine, in which the within-tooth ρ_G estimate is larger than all other ρ_G estimates for the tooth. Within-tooth analyses produce large ρ_G estimates that may indicate pleiotropy with other teeth as well (P_2, P_3, M_1). These analyses also demonstrate that length and breadth dimensions within a tooth

may often be characterized by incomplete pleiotropy. Length and breadth dimensions of a single tooth are not clearly more genetically integrated than linear dimensions in between-tooth comparisons.

Despite the appearance of morphogenetic fields underlying the differentiation of tooth types, genetic correlation estimates are not clearly greater between the dimensions of teeth of the same type than are ρ_G estimates between the dimensions of teeth of different types. The average ρ_G for analyses of two maxillary premolar dimensions is 0.637, which is essentially identical to the average ρ_G for analyses between maxillary premolar dimensions and dimensions of maxillary canines and molars in which the average is 0.628. The same comparison of averages for maxillary molars yields similarly close average ρ_G estimates; within-maxillary molar dimension analyses have an average ρ_G estimate of 0.611, compared to a between-tooth type average of 0.614. Premolar dimensions are more closely correlated in the mandibular toothrow, with an average ρ_G from analyses of two mandibular premolar dimensions of 0.790; between-tooth type analyses that include mandibular premolars average a ρ_G estimate of 0.664. Dimensions of mandibular molars are also highly genetically correlated with each other, with an average ρ_G between two mandibular molar dimensions of 0.714. The average ρ_G from analyses between mandibular molar dimensions and dimensions of mandibular canines and premolars is 0.640. These averages do not, however, represent the distribution of ρ_G estimates within and between tooth types, or the degree to which error impacts each ρ_G-estimate.

In both the maxilla and mandible, estimates of ρ_G between premolar dimensions span the entire range of possible values when standard error is included. Figure 4.2 demonstrates that the distribution of ρ_G is similar in within- and between-tooth type analyses centered on maxillary premolars, while Figure 4.3 demonstrates the same in analyses centered around mandibular premolars. Analyses of molar dimensions produce a smaller range of ρ_G values than analyses between the dimensions of molars and other tooth types, yet, as Figure 4.4 and Figure 4.5 demonstrate, within-molar ρ_G estimates fall very near the center of the entire range of ρ_G values.

Maxillary premolar area estimates are highly genetically correlated with the areas of other maxillary premolars, as are mandibular premolar areas with other mandibular premolar areas. The largest genetic correlations between maxillary and mandibular tooth areas are found between premolars and between maxillary premolars and the mandibular canine. Estimates of ρ_G between maxillary and mandibular canine areas and molar areas suggest moderate pleiotropy with high genetic correlations between the toothrows.

The dimensions and crown areas of teeth tend to be highly genetically correlated within the maxilla and mandible in this tamarin population, but genetic correlations between linear dimensions are not consistently larger between teeth of the same type. Between the maxilla and mandible, premolar crown areas also tend to have large ρ_G estimates, suggesting high degree of pleiotropy between maxillary and mandibular premolar crown areas. The hypothesis that dimensions of teeth of the same type are more highly genetically correlated than dimensions across tooth types is weakly supported in the mandibular premolars and molars, based on the greater average ρ_G values from

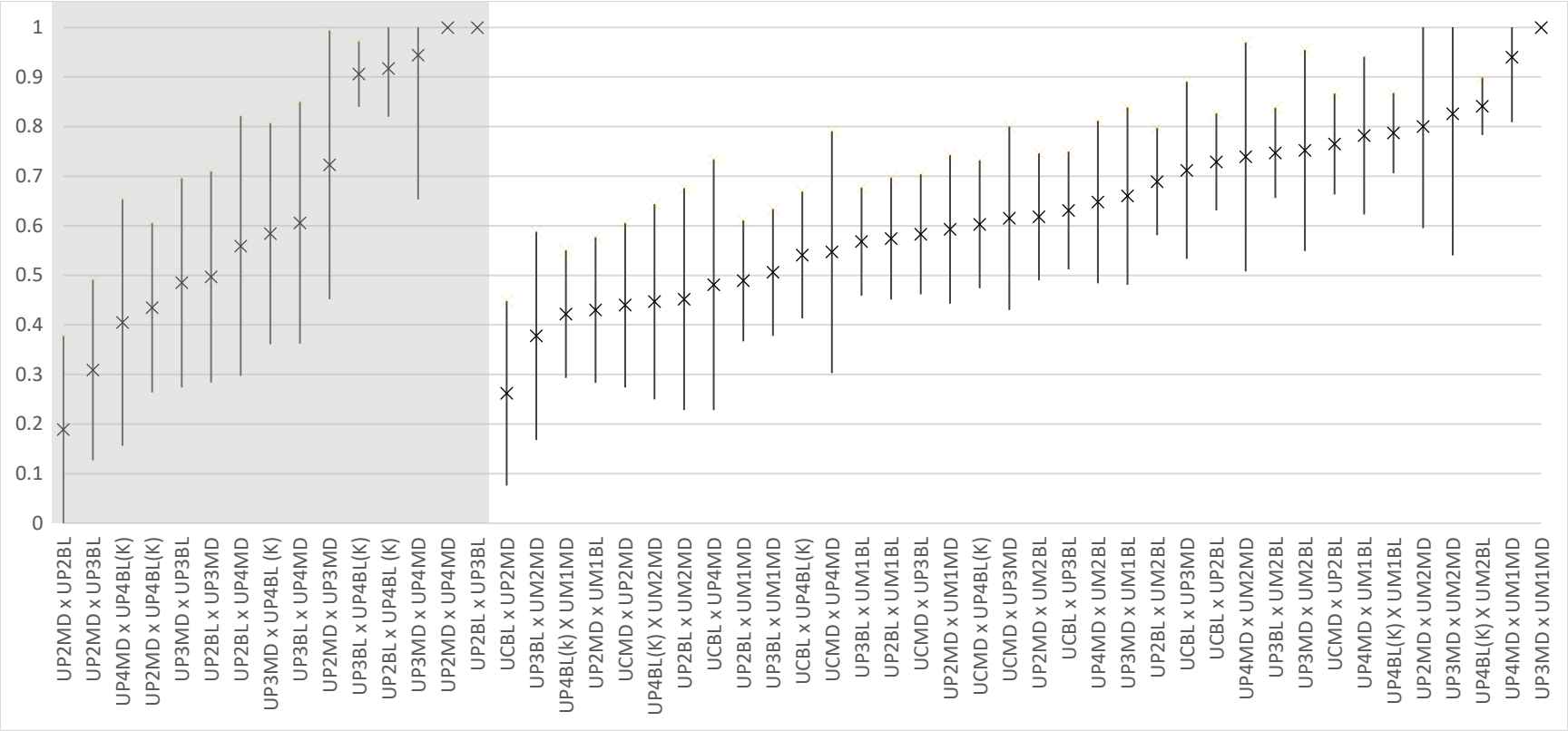

Figure 4.2. Genetic correlation estimates (+/- one standard error) within maxillary premolar dimensions (on the left, shaded in grey) and between maxillary premolars and other maxillary tooth types (on the right, unshaded) ordered from left to right by smallest to largest h^2 value.

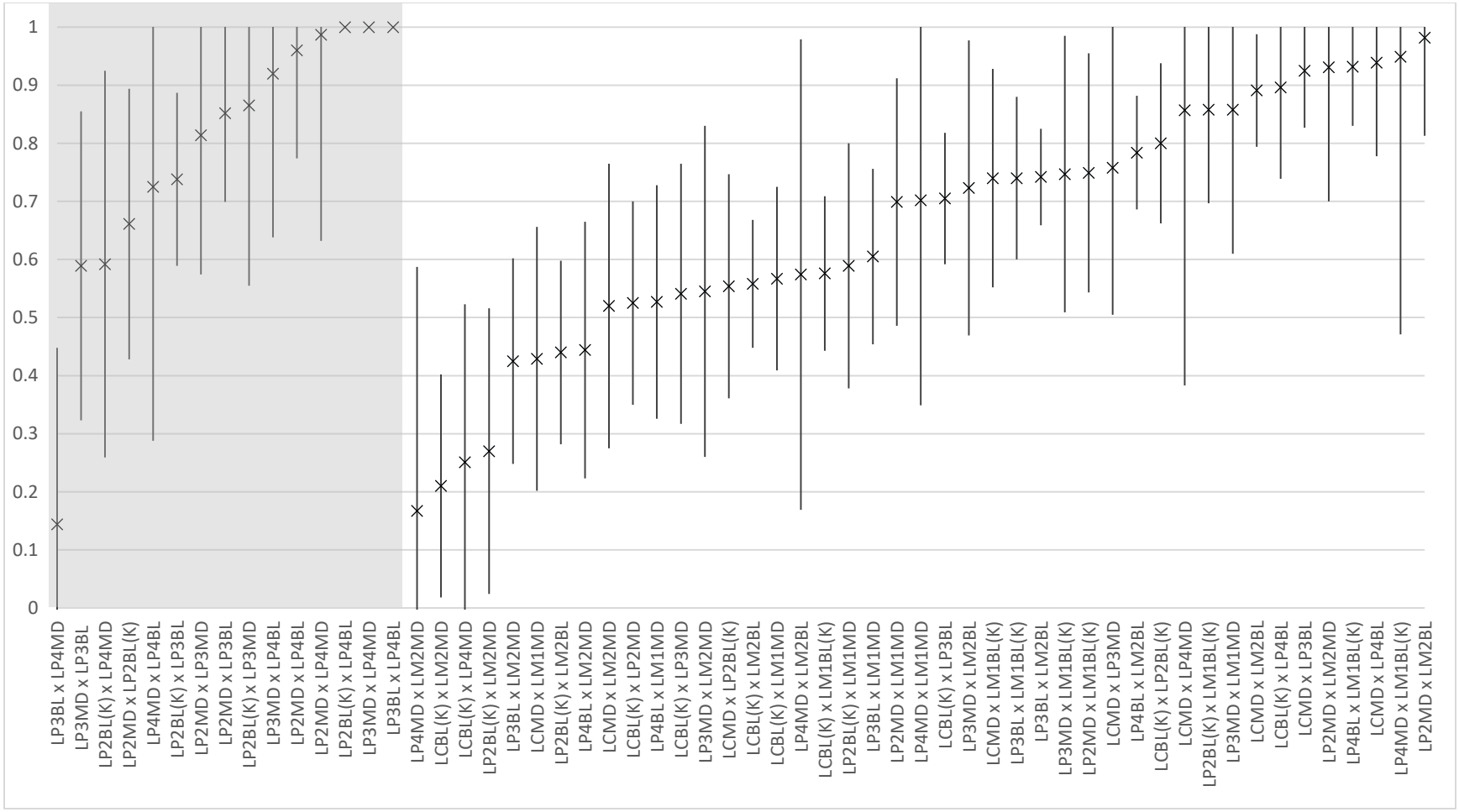

Figure 4.3. Genetic correlation estimates (+/- one standard error) within mandibular premolar dimensions (on the left, shaded in grey) and between mandibular premolars and other mandibular tooth types (on the right, unshaded) ordered from left to right by smallest to largest h^2 value.

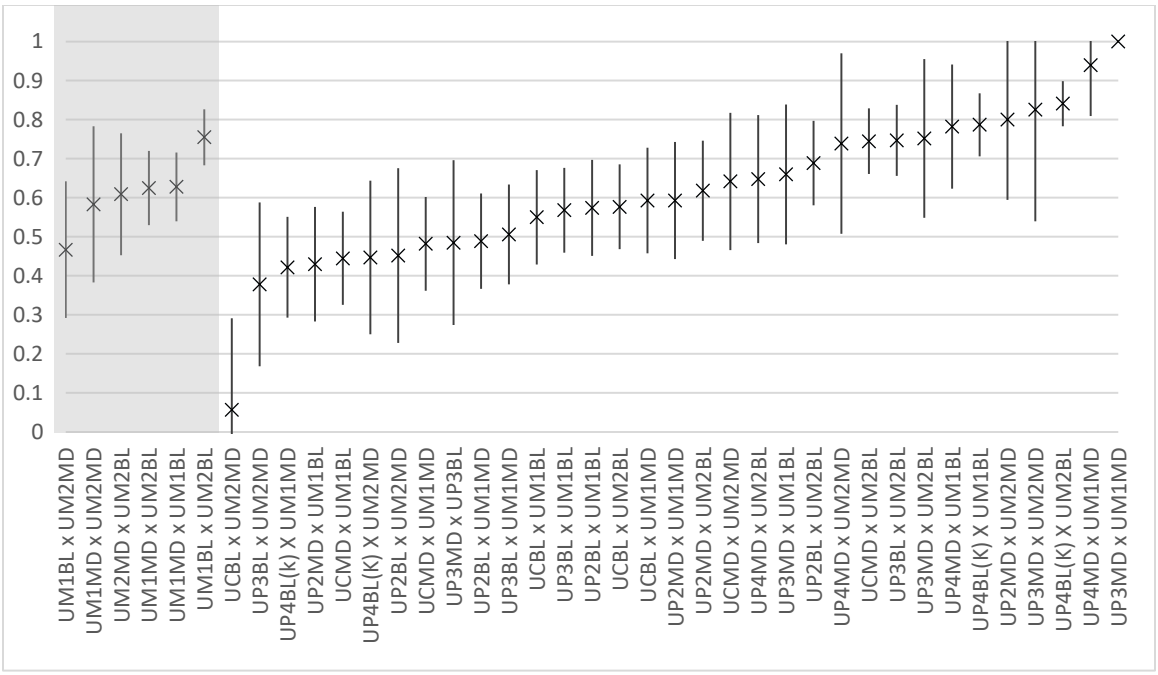

Figure 4.4. Genetic correlation estimates (+/- one standard error) within maxillary molar dimensions (on the left, shaded in grey) and between maxillary molars and other maxillary tooth types (on the right, unshaded) ordered from left to right by smallest to largest h^2 value.

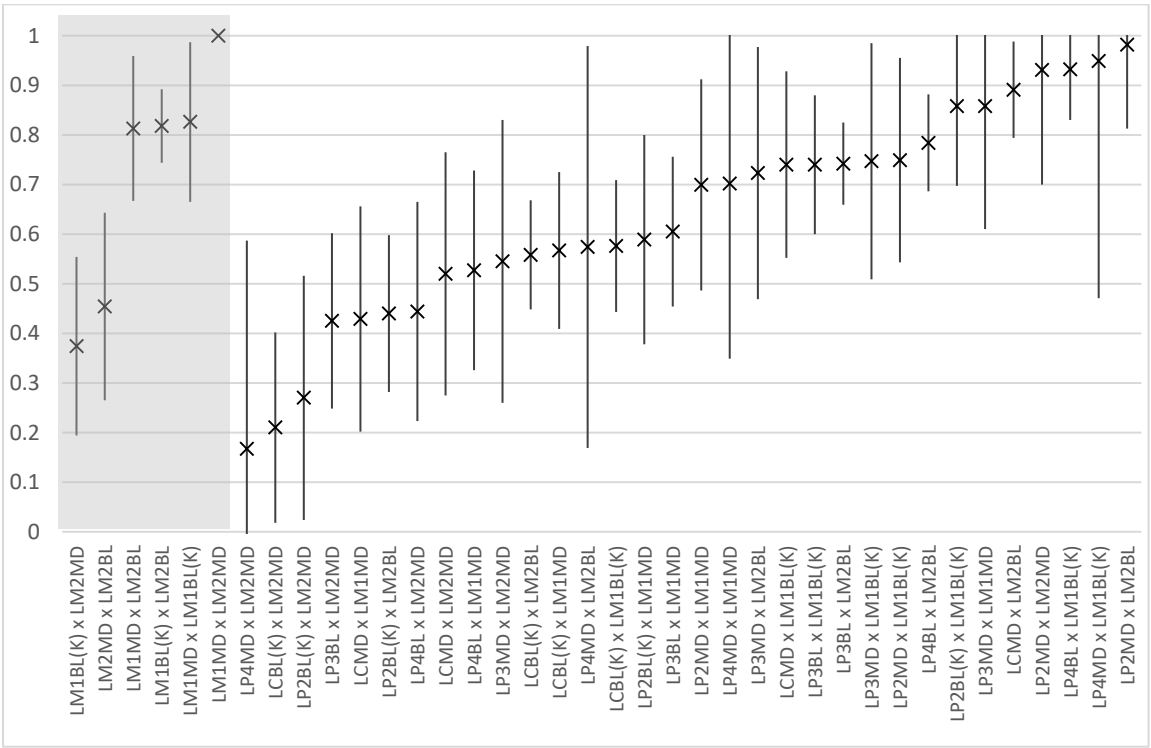

Figure 4.5. Genetic correlation estimates (+/- one standard error) within mandibular molar dimensions (on the left, shaded in grey) and between mandibular molars and other maxillary tooth types (on the right, unshaded) ordered from left to right by smallest to largest h^2 value.

within-tooth type analyses in the mandible. The same hypothesis is not supported in the maxilla based on average ρ_G values, and is not supported in the maxillary or mandibular teeth based on the distribution of ρ_G values. The high degree of genetic integration between premolars and molars in the maxilla and mandible described in this population provides a possible genetic explanation for morphological integration observed in extant primate postcanine teeth (Ribeiro et al., 2013).

4.4.3 Are neighboring teeth more highly genetically correlated than non-neighboring teeth?

Morphogenetic field theory, as described by Butler (1939) and applied to the human dentition by Dahlberg (1945), divides the toothrow into fields, each described as a "sphere of influence" (Dahlberg, 1945: 687). According to this theory, a morphogenetic signal is expressed most strongly within each field at the location of a 'key' tooth and dissipates in teeth more physically removed from this pole. The morphogenetic signal, and its dissipation, is expected to produce genetic correlations that are greater between the key tooth and its neighbors and decrease in teeth more distant from the key tooth. Comparisons of ρ_G estimates between key postcanine teeth (P^2, M^1, P_2, M_1) and their neighbors to ρ_G estimates between key postcanine teeth and more distant teeth in the same postcanine region (Figure 4.6) demonstrate the predicted pattern in the first molars, but not in the second premolars. This may indicate the presence of a strong molar morphogenetic field centered around the first molar in maxilla and mandible as predicted from mammalian patterns of dental evolution. Genetic correlations between the molars

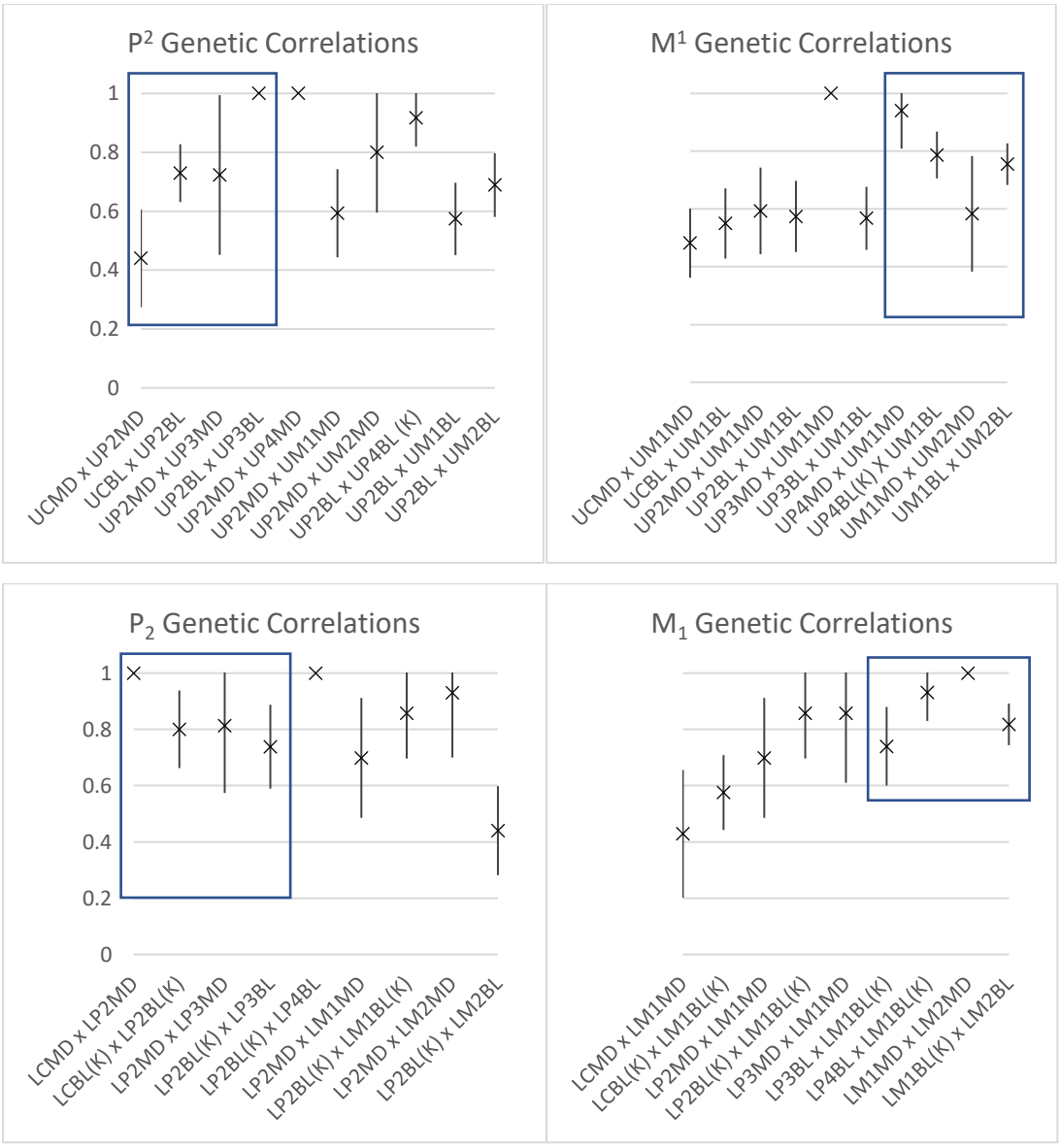

Figure 4.6. Estimates of ρ_G in key teeth (P^2, M^1, P_2, M_1) with standard errors. Results are ordered from left to right by the mesiodistal position of the tooth being analyzed with the key tooth. Blue squares indicate analyses with teeth that neighbor the key tooth

and premolars may indicate the presence of a postcanine morphogenetic field instead of discrete premolar and molar fields. These results may also indicate differences in the

pattern of genetic contribution to tooth size and tooth morphology. Since we are only testing simple linear dimensions in this study, additional analyses of morphological characteristics such as those performed in the SNPRC baboons (Hlusko and Mahaney, 2003; Koh et al., 2010) should be performed on additional primate populations.

4.4.4 Comparing Saguinus to other primates

Estimates of ρ_G between linear dental measurements have been estimated in a captive baboon population (*Papio* spp.) (Hlusko et al., 2006, 2011, 2016; Hlusko and Mahaney, 2009; Willmore et al., 2009) and a modern human population (Stojanowski et al., 2017) using similar maximum likelihood estimation methods. This study of genetic correlations between dental measurements in *Saguinus* may provide a useful comparison for assessing the results of these previous studies. With only two primate samples available for comparison, it is impossible to extract differences resulting from population structure and sample size from those resulting from evolutionary differences in the genetic architecture of tooth size. In addition, the degree to which environmental variance contributes to phenotypic variance in dental traits will impact estimates of both h^2 and ρ_G. Nevertheless, comparisons across populations may still indicate patterns and differences that can be investigated with greater control over these confounds in future research.

There are also challenges in comparing results across these studies due to differences in the measurements collected. Stojanowski et al. (2017) analyze lengths, but not breadths or areas, of incisors, premolars, and first molars, while Hlusko et al. (2011)

analyze lengths and breadths of all teeth except canines. This study of *Saguinus* includes lengths of all teeth and breadths and areas of canines, premolars and molars, but measurements were taken from one set of antimeres (left or right) while measurements were taken from both sides of the toothrow in previous studies. In addition, *Saguinus* has a different dental formula from *Papio* and *Homo,* which likely impacts the pattern of correlation, both phenotypic and genetic, across teeth. The addition of this third population nevertheless clarifies the variation in the patterns of genetic correlation present in primate tooth size and demonstrates some patterns that are consistent across all three populations.

The baboon results demonstrate a weak pattern of modularity in which the incisors are largely genetically independent from the post-canine teeth, and the premolars are not highly integrated with the molars (Hlusko and Mahaney, 2009). Because this pattern is also observed in mice, it is thought to be an ancestral mammalian pattern of tooth development and regulation (Hlusko et al., 2011). In a human sample, however, this pattern is not clearly observed; instead large genetic correlations are estimated between teeth in different parts of the toothrow in both the maxilla and mandible. The tamarin results presented here show greater genetic correlations throughout the toothrow than were found in the previously studied baboon population (Table 4.6).

The ρ_G values estimated by Stojanowski et al. (2017) from a human population are larger on average than ρ_G estimates from the baboon sample analyzed by Hlusko et al. (2009, 2011, 2016). The tamarin sample analyzed here yields larger ρ_G estimates than the previously analyzed human and baboon populations. This may be due to differences in

pedigree structure and family-level environmental effects that cannot be separated from genetic effects in the model. The estimation of quantitative genetic parameters from additional platyrrhine primates, and primates living in a broader range of environments, would allow for further interpretation of these results.

Table 4.6. Genetic correlation estimates of tooth lengths in modern humans (Stojanowski et al. 2017), hamadryas baboons (Hlusko et al. 2011), and brown-mantled tamarins. White: ρ_G is statistically significantly different from 0 but not from 1; Light grey: ρ_G is statistically significantly different from 0 and 1; Dark grey: ρ_G is statistically significantly from 1 but not from 0.

Human	P^4	M^1	Baboon	P^4	M^1	Tamarin	P^3	P^4	M^1
P^3	0.94	0.68	P^3	0.53	0.41	P^2	0.72	1.0	0.59
P^4		0.65	P^4		0.67	P^3		0.94	1.0
						P^4			0.94
	P_4	M_1		P_4	M_1		P_3		M_1
P_3	0.98	0.79	P_3	0.21	-0.070	P_2	0.81		0.70
P_4		0.59	P_4		0.72	P_3			0.86

The differences in ρ_G estimated from these three different populations could result from uncertainty in the estimates, with the true genetic correlations of all three populations being similar. Alternatively, these differences could be the result of different genetic architecture underlying the tooth dimensions of tamarins, baboons, and humans. Just as dental dimensions are under selective pressure, so too are the genetic correlations between dental dimensions, although the evolution of genetic correlation is as yet poorly understood (Cheverud, 1988a; Griswold, 2006; Wagner et al., 2007; Agrawal and Stinchcombe, 2009; Watson et al., 2014; Melo and Marroig, 2015). Genetic correlation estimates from additional primate species can be used to determine whether this pattern of reduced pleiotropy observed in *Papio* (Hlusko et al., 2009, 2011) is typical of

cercopithecoid primates, and whether platyrrhines are more generally characterized by high degrees of pleiotropy as seen in this *Saguinus fuscicollis* population.

If the variation in genetic integration between *Papio*, *Homo*, and *Saguinus* represents species- or family-level differences in the genetic relationships between teeth, then we can expect the teeth of these taxa to follow different evolutionary trajectories due to varied patterns of modularity and integration. Grieco et al. (2012) have shown, for example, that the evolution of the cercopithecoid dentition largely conforms to the modular framework predicted by genetic correlations from the SNPRC baboon population. Similar studies of extant and fossil platyrrhine dental morphology could determine the degree to which the platyrrhine dentition is characterized by genetic integration, as predicted by estimates of genetic correlations from this population of brown-mantled tamarins.

4.5 Conclusion

Genetic correlation estimates between dental dimensions in a brown-mantled tamarin population demonstrate a high degree of genetic integration throughout the maxillary and mandibular dentition. While sets of teeth that occlude might be expected to covary genetically more so than teeth that are not directly functionally related, there is no clear difference in the magnitude of genetic correlations between occluding teeth and non-occluding teeth. Genetic correlation estimates are not consistently larger for teeth of the same type than for the dimensions of teeth of different types. Teeth that sit near the

first mandibular molar are more highly genetically correlated than teeth that are more physically removed from the molar field. The influence of a molar field is not observed as clearly in the maxillary molars, and no clear influence of a premolar field is observed. Dental dimensions in this population of brown-mantled tamarins are highly genetically integrated relative to previously studied baboons (Hlusko and Mahaney, 2009; Hlusko et al., 2011). Altogether, these results indicate that there is considerable variation in the degree of genetic integration and modularity in the teeth of extant primates, and that this variation could impact the evolution of dental morphology.

5 Modularity and integration in the canine-premolar honing complex

Chapter 4 presented genetic correlation estimates for dental dimensions of a captive brown-mantled tamarin population and discussed the relationships between these correlation estimates and two theoretical models of odontogenesis. These analyses indicate that the teeth of this tamarin population are more genetically integrated across the toothrow than was observed in the previously studied baboon population (Hlusko and Mahaney, 2009; Hlusko et al., 2011), and are, in terms of genetic integration, more similar to the previously studied human population (Stojanowski et al., 2017). There is therefore variation in the pattern of genetic correlations between dental measurements in anthropoid primates, with the baboon population tending towards greater positive correlations within than between tooth types (Hlusko and Mahaney, 2009; Hlusko et al., 2011), and the human and tamarin populations tending toward moderately positive genetic correlations within and between tooth types.

Previous analyses of genetic correlations in baboons were not able to include canine dimensions because the canines of the SNPRC baboon population are clipped (Hlusko, 2000; Hlusko and Mahaney, 2009). Genetic integration in the canine-premolar honing complex has not been assessed using quantitative genetic analyses, although phenotypic correlation across taxa indicate that maxillary and mandibular canine dimensions are largely independent from dimensions of incisors and postcanine teeth (Delezene, 2015). To test the assumption that cross-taxon phenotypic correlations

accurately reflect genetic correlations, and that the canines are genetically independent from other teeth, the third paper estimates genetic correlations between dental dimensions in the free-ranging Cayo Santiago rhesus macaque (*Macaca mulatta*). The results also provide a useful comparison to similar analyses in the captive SNPRC baboon population.

6 Morphological and genetic integration in the canine-premolar honing complex of *Macaca mulatta*

6.1 Introduction

The canines and mesial-most mandibular premolar of most anthropoid primates form a functionally integrated structure called the canine-premolar honing complex or simply honing complex. The teeth that form this complex maintain a sharp edge along the distolingual surface of the maxillary canine by honing during occlusion. The functional relationships of these teeth are maintained across anthropoid primates despite considerable sex- and taxon-based variation in the proportions of the teeth, including differences in dental formula. Selection on canines is primarily associated with their use in threat displays and agonistic encounters in extant primates (Plavcan et al., 1995; Plavcan and Kelley, 1996; Plavcan, 1998), meaning they have some functional independence from teeth that are primarily used for mastication. Given the functional relationships among the teeth of the honing complex, and the degree to which they are functionally independent from other teeth, genetic or developmental integration, and possibly modularity, could contribute to the maintenance of the honing complex across diverse anthropoid taxa (Wagner et al., 2007; Delezene, 2015).

Reduction of the honing complex is characteristic of the hominin lineage. This reduction occurred through mosaic evolutionary change in the honing complex, based on reduction in the maxillary canine in early hominins (Haile-Selassie, 2001; Haile-Selassie et al., 2004; Manthi et al., 2012) and continued reduction of the honing premolar in *Australopithecus anamensis* and *Australopithecus afarensis* (Ward et al., 2010; Delezene

and Kimbel, 2011). As Delezene (2015) has argued previously, this pattern of evolutionary change indicates that the honing complex is not tightly genetically integrated in the hominin lineage. Studies of phenotypic covariance in tooth dimensions have shown a high degree of phenotypic integration within the anthropoid honing complex and weak yet positive phenotypic correlations between the canines and other tooth types (Cochard, 1981; Scott, 2010; Grieco et al., 2013; Delezene, 2015). These phenotypic patterns may reflect underlying genetic relationships between tooth dimensions, and many phenotypic observations are consistent with the pattern of genetic correlations identified in the dental dimensions of the Southwest National Primate Research Center (SNPRC) hamadryas baboons (*Papio hamadryas*) (Hlusko and Mahaney, 2009; Hlusko et al., 2011). It has not been possible, however, to include canine dimensions in previous quantitative genetic analyses of nonhuman primates' dental dimensions, so it remains unclear if this pattern of phenotypic correlations in the honing complex results from genetic integration between certain pairs of dimensions and genetic independence of others.

The need for the teeth that make up the honing complex to maintain their occlusal relationships may produce selection on the underlying genetic architecture. It is theorized that genetic and co-developmental integration evolves in functionally related traits (Wagner et al., 2007), although the impact of genetic integration on trait evolvability is highly context-dependent and is the focus of a large body of theoretical and empirical research (e.g. Hansen, 2003, 2006; Griswold, 2006; Melo and Marroig, 2015). A set of structures or processes in an organism that are highly correlated with each other, while

remaining largely independent from other structures or processes, can be referred to as a module (Klingenberg, 2014). The integration of parts within a module is expected to influence the evolution of these parts individually and of the module as a whole (Lande, 1979). Modularity also evolves in response to selective pressure, and it is expected that functionally integrated parts will become correlated, whether through genetic or developmental links, while genetic independence may be maintained in units with separate functions (Wagner, 1996; Wagner et al., 2007; Watson et al., 2014; Melo et al., 2016). While selection on traits is often discussed as a direct and univariate process, genetically correlated traits, whether modular or not, are acted upon by multivariate selection pressures (Lande, 1979; Lande and Arnold, 1983). Correlated response to selection can constrain the response to selection when opposing selection pressures impact positively correlated traits, but it can also accelerate the response when positively correlated traits are impacted by similarly directed selection. Estimates of the genetic correlations between traits can be usefully applied to plant and animal breeding, and may help to realistically model evolutionary change in the past based on patterns observed in modern populations.

Estimation of genetic correlations generally requires phenotypic data from large populations with known pedigrees. Samples with the necessary data to estimate genetic correlations in primate dental traits are rare, largely because primates reproduce slowly. Due to the limited application of quantitative genetic analyses, the phenotypic correlation matrix is often substituted for the genetic correlation matrix in primates (e.g., Cheverud, 1988, 2009; Delezene, 2015; Grabowski, 2016). There are structural similarities between

the phenotypic and genetic correlation matrices describing dental measurements of the SNPRC hamadryas baboon population (Hlusko and Mahaney, 2009; Hlusko et al., 2011; Grieco et al., 2013). These similarities indicate that phenotypic integration between dental features could be rooted in genetic correlation. Yet, because the honing complex differs functionally and evolutionarily from the rest of the dentition, the degree to which genetic integration contributes to observed phenotypic relationships between the canines and honing premolar should not be assumed based on similarities between the genetic and phenotypic correlations in the rest of the toothrow. This study uses genetic correlation estimations of dental dimensions in the Cayo Santiago rhesus macaques (*Macaca mulatta*) to test whether genetic correlations between dimensions of the honing complex are more highly genetically correlated than are genetic correlations between honing complex dimensions and dimensions of teeth outside the honing complex.

6.2 Materials

6.2.1 Population and pedigree

Approximately 400 rhesus macaques from near Lucknow, India were introduced to Cayo Santiago in 1938 as a free-ranging population for biomedical and behavioral research (Dunbar, 2012). The population fluctuated throughout the 1940s, and at its smallest the population held approximately 200 individuals (Dunbar, 2012). Records of maternal parentage have been collected since the early 1950s and skeletal materials have been collected and maintained since 1971 (Rawlins and Kessler, 1986). The skeletal collection, housed at the Caribbean Primate Research Center Laboratory of Primate

Morphology and Genetics at the University of Puerto Rico, now contains hundreds of *Macaca mulatta* specimens from the Cayo Santiago population and the Sabana Seca field station. The rhesus macaque population has been systematically maintained since 1969, and the population today contains approximately 1,000 individuals (Dunbar, 2012).

Although many paternal identities in the Cayo Santiago macaque population have been determined through genetic testing (Widdig et al., 2016; Ruiz, personal communication), paternities are not known for most individuals in the skeletal collection. To maximize the use of the known maternities from this population, individuals with known dams were assigned a distinct "dummy sire" assuming that all individuals with the same dam are half-siblings (following Konigsberg and Cheverud, 1992; Joganic et al., 2012; though see Myers et al. 2006; Adams, 2011). The impact of assuming half-siblings compared to full-siblings was assessed during heritability estimation, and while full-sibling h^2 estimates are smaller than those from half-sibling analyses, different dummy sire configurations do not alter the significance or interpretation of the results. The pedigree used in the following analyses consists of 66 founders, 334 individuals with known dams, and 334 dummy sires.

6.2.2 Measurements

Measurements of the mesiodistal crown length and buccolingual crown breadth of permanent teeth were collected from 365 rhesus macaques (*Macaca mulatta*) at the Caribbean Primate Research Center at the University of Puerto Rico. All specimens were measured using Mitutoyo nib-style digital calipers with a digital input tool to minimize

error during data transcription. Mesiodistal crown length was measured as the maximum length perpendicular to the lingual edge of the tooth crown. Buccolingual crown breadth was measured as the maximum width perpendicular to the mesiodistal length measurement. Canine mesiodistal lengths were measured as the maximum mesiodistal length, and the buccolingual breadth of the canine was perpendicular to the length measurement. Previous studies have consistently shown that antimeres are highly genetically correlated, with genetic correlation estimates ranging from 0.89 to 1.0 in baboons (Hlusko et al., 2011) and from 0.96 to 1.0 in humans (Stojanowski et al., 2017), so halves of the toothrow were considered interchangeable and the side with the least damage or fewest missing teeth was measured for each individual. There were no statistically significant differences between dimensions from the left and right sides of the toothrow based on t-tests performed in SAS/STAT 14.1. Due to wear and damage, the sample for any individual trait was often fewer than the total number of individuals measured. Measurements were not collected from any teeth with noticeable wear or enamel breakage that could have altered the size of the tooth.

Intra-observer measurement reliability was assessed with repeated measurements as described in Chapters 2 and 4. Those measurements with reliability greater than 0.80 are considered reliable in the following analyses.

Prior to quantitative genetic parameter estimation, all traits were standardized to correct for sex differences in means and variance. There is considerable sexual dimorphism in rhesus macaques, both in body size and in dental dimensions. Heritabilities of non-standardized dental measurements from this population are provided

in Chapter 2, and are slightly different from those presented here. Standardizing by sex ensures that the larger phenotypic variance among males does not bias the heritability estimates for the population, in case male and female heritabilities differ. Estimating heritabilities separately for males and females in this population would provide a more robust assessment of sex differences in trait heritabilities, but unfortunately sex-specific heritability values cannot be reliably estimated with the current sample size . Previous studies have included sex as a covariate during maximum likelihood estimation (Hlusko et al., 2002, 2011; Hlusko and Mahaney, 2009; Stojanowski et al., 2017) which adjusts mean trait-values for each sex but does not correct for sex differences in phenotypic variance. The use of different software packages to correct for sex in phenotypic correlation and genetic correlation estimation could also result in slight differences in the manner of sex correction, thereby producing inaccurate phenotypic and genetic correlation estimates. Manual standardization ensures that the same trait values are analyzed during estimation of quantitative genetic parameters and phenotypic correlations, and that sex differences in variance do not bias phenotypic and genetic correlation estimates. Data were screened for outliers and standardized using SAS/STAT 14.1.

6.2.3 Phenotypic correlations

Phenotypic correlations were estimated in SAS/STAT 14.1 using the same standardized trait values from which quantitative genetic parameters were estimated. The five matrices of phenotypic correlations were not compared statistically to the five

genetic correlation matrices because the sample is likely too small to yield interpretable results from statistical comparisons of the genetic and phenotypic covariance matrices (Mezey and Houle, 2003; Cheverud and Marroig, 2007).

6.2.4 Quantitative genetic parameter estimation

Narrow-sense heritabilities (h^2) were estimated in SOLAR v. 6.2.2 (Almasy and Blangero, 1998) using maximum likelihood. Although all traits were standardized by sex prior to analysis, covariate screening was performed in SOLAR for sex, estimated age at death, and age-by-sex interaction. Likelihood ratio tests were used to assess the difference in likelihood between models in which parameters (covariate effects or h^2) were constrained to zero to those in which parameters were estimated, providing the probability that the estimation of a given parameter statistically significantly impacted the model. Covariate effects were included in the final model at $p<0.10$ and h^2 is statistically significantly different from zero at $p<0.05$ (as in Hlusko et al. 2002; Stojanowski et al. 2017). Trait distributions with high kurtosis as estimated in SOLAR were inverse normalized before analysis. Although h^2 estimates generally express the proportion of the total phenotypic variance in the sample population that can be attributed to the additive genetic variance (σ^2_A), the h^2 of a standardized trait instead describes the degree to which individuals' deviation from the mean for each sex is attributable to breeding values in this population.

Genetic correlation (ρ_G) estimation was performed between traits within the canine-premolar honing complex, and between maxillary tooth lengths, maxillary tooth

breadths, mandibular tooth lengths, and mandibular tooth breadths. The estimation of a single genetic correlation matrix including all possible trait combinations is possible, but would produce more ρ_G estimates than are necessary to test the hypothesis that genetic correlations are greater within the honing complex than between the honing complex and the rest of the dentition. Instead, five smaller genetic correlation matrices were used to assess genetic integration and modularity in the dental dimensions of this population. To determine whether the sample was adequate for ρ_G estimation, the effective sample size (N_{eff}) was calculated for each pair of traits using the equation from Cheverud (1995) following Robertson (1959):

$$N_{eff} = (2h^2_x h^2_y / (V(h^2_x)\ V(h^2_y))^{0.5}) + 1$$

Genetic correlations and environmental correlations (ρ_E) between pairs of measurements were estimated through bivariate maximum likelihood in SOLAR 6.2.2. The phenotypic covariance is modeled as the sum of the additive genetic covariance and environmental covariance in a population, so that the phenotypic correlation (ρ_P) is equal to:

$$\rho_P = h_x h_y \rho_A + e_x e_y \rho_E$$

where h is the square root of h^2 (for traits x and y), ρ_A is the additive genetic correlation between traits x and y, e is the square root of e^2 where e^2 is equal to $1-h^2$ (for traits x and y), and ρ_E is the environmental correlation between traits x and y (Falconer and Mackay, 1996: 314). Covariates that were statistically significant in h^2 estimation were included in bivariate models, and likelihood ratio tests were used to assess whether a restricted

model, in which ρ_A was equal to zero or one, fit the data as well as the unrestricted model. When the unrestricted ρ_A fit the data better than the restricted ρ_A such that $p<0.05$, ρ_A was considered statistically significantly different from the restricted value (zero or one). The additive genetic correlation (ρ_A) is referred to as the genetic correlation (ρ_G) going forward.

6.3 Results

6.3.1 Reliability

Of the twenty-eight dental measurements collected, two have measurement reliability below 0.80 (Table 6.1). I_1 length and P_4 length are excluded from additional analyses due to poor measurement reliability.

Table 6.1. Measurement reliability for dental dimensions, grey shaded cells indicate measurements with poor reliability that are excluded from additional analyses.

	Maxillary		Mandibular	
	MD	BL	MD	BL
I1	0.964		0.685	
I2	0.989		0.987	
C	0.965	0.988	0.969	0.994
P3	0.832	0.974	0.925	0.954
P4	0.848	0.947	0.691	0.909
M1	0.933	0.882	0.953	0.934
M2	0.951	0.911	0.962	0.905
M3	0.971	0.970	0.980	0.942

6.3.2 Heritabilities

Results of h^2 estimation are provided in Table 6.2. Twenty-six heritability estimates are statistically significantly greater than zero, and h^2 estimates range from

0.215 (P_3 length) to 1.000 (I^1 length). The estimates for three measurements (M^1 width, P_3 length, and P_3 breadth) are not statistically significantly different from zero. Age is a statistically significant covariate for eleven traits, and age-by-sex interaction is a statistically significant covariate for six traits. Covariates together account for between 0.4% and 14.1% of the standardized phenotypic variance in a trait. Nine traits (M^1 breadth, M^3 breadth, I_2 length, C_1 length and breadth, P_4 breadth, M_1 length, M_2 breadth, M_3 length) were inverse normalized prior to h^2 estimation to correct for skew.

Table 6.2. Univariate analyses of all standardized measurements. MD = mesiodistal length, BL = buccolingual breadth, C = statistically significant covariates, σ^2_C = percentage of σ^2_P removed by statistically significant covariates. Grey shaded cells have measurement reliability below 0.90.

Tooth	Trait	N	Male mean	Female mean	h^2	p	SE	C	σ^2_C
I^1	MD	258	6.38	6.10	**1.000**	<0.001	-	-	-
I^2	MD	266	5.10	4.67	**0.372**	0.033	0.217	-	-
C^1	MD	245	9.16	5.98	**0.791**	<0.001	0.175	-	-
	BL	251	7.38	5.18	**0.771**	<0.001	0.194	AGE, AGE*SEX	0.141
P^3	MD	332	5.40	5.07	**0.538**	<0.001	0.146	AGE*SEX	0.044
	BL	337	6.54	6.27	**0.779**	<0.001	0.155	-	-
P^4	MD	337	5.38	5.23	**0.426**	0.002	0.167	-	-
	BL	332	7.06	6.75	**0.590**	<0.001	0.137	AGE*SEX	0.004
M^1	MD	335	7.74	7.52	**0.737**	<0.001	0.199	AGE	0.089
	BL^K	263	7.36	7.06	0.317	0.058	0.206	-	-
M^2	MD	341	8.98	8.62	**0.544**	<0.001	0.153	-	-
	BL	306	8.71	8.21	**0.781**	<0.001	0.139	AGE	0.012
M^3	MD	259	9.16	8.57	**0.501**	<0.001	0.176	AGE, AGE*SEX	0.024
	BL^K	252	8.70	8.10	**0.871**	<0.001	0.166	AGE, AGE*SEX	0.050
I_2	MD^K	241	4.06	3.97	**0.585**	0.001	0.226	-	-
C_1	MD^K	235	5.53	3.79	**0.513**	0.034	0.272	AGE	0.027
	BL^K	213	9.11	5.54	0.280	0.111	0.239	AGE	0.049
P_3	MD	310	10.68	6.99	0.215	0.115	0.190	AGE,	0.140

								AGE*SEX	
	BL	303	4.83	4.21	**0.401**	0.020	0.232	-	-
P_4	BL^K	318	5.19	5.04	**0.284**	0.021	0.166	-	-
M_1	MD^K	299	7.58	7.34	**0.600**	0.011	0.258	AGE	0.079
	BL	236	5.98	5.76	**0.683**	0.026	0.356	-	-
M_2	MD	332	8.73	8.43	**0.571**	<0.001	0.177	-	-
	BL^K	305	7.30	7.01	**0.544**	<0.001	0.185	AGE	0.070
M_3	MD^K	257	10.92	10.55	**0.925**	<0.001	0.163	-	-
	BL	253	7.69	7.29	**0.547**	<0.001	0.162	AGE	0.021

^{K} indicates traits that were inverse normalized prior to analysis to correct for skew

Table 6.3. Phenotypic correlations within the honing complex, all values are statistically significantly different from zero at $p<0.05$.

N=191-291	C^1 MD	C^1 BL	C_1 MD	C_1 BL	P_3 MD
C^1 MD					
C^1 BL	0.181				
C_1 MD	0.302	0.385			
C_1 BL	0.394	0.467	0.538		
P_3 MD	0.246	0.293	0.344	0.331	
P_3 BL	0.263	0.339	0.325	0.323	0.156

Table 6.4. Phenotypic correlations between maxillary tooth lengths, all values are statistically significantly different from zero at $p<0.05$.

N=82-170	I^1MD	I^2MD	C^1MD	P^3MD	P^4MD	M^1MD	M^2MD
I^1MD							
I^2MD	0.403						
C^1MD	0.408	0.369					
P^3MD	0.554	0.540	0.442				
P^4MD	0.293	0.377	0.197	0.539			
M^1MD	0.282	0.277	0.352	0.395	0.457		
M^2MD	0.452	0.412	0.424	0.574	0.563	0.660	
M^3MD	0.354	0.231	0.329	0.507	0.494	0.375	0.695

6.3.3 Phenotypic correlations

Phenotypic correlations (ρ_P) between dental measurements are positive and statistically significantly different from zero across the canine-premolar honing complex (Table 6.3). In maxillary tooth lengths and breadths, all phenotypic correlations are positive and statistically significantly different from zero. Within maxillary tooth lengths, P^3 length and M^2 length are especially closely correlated with other maxillary tooth lengths (Table 6.4). Maxillary tooth breadths are generally highly phenotypically correlated, although C^1 breadth is less closely correlated with postcanine tooth breadths (Table 6.5). For mandibular tooth lengths and breadths, all phenotypic correlations are positive, and all but one, the phenotypic correlation between I_2 length and P_3 length, are statistically significantly different from zero (Table 6.6). Phenotypic correlations are generally greater between mandibular tooth breadths than mandibular tooth lengths, although this trend does not extend to the mandibular molars (Table 6.7).

Table 6.5. Phenotypic correlations between maxillary tooth breadths, all values are statistically significantly different from zero at $p<0.05$.

N=88-166	C^1BL	P^3BL	P^4BL	M^1BL	M^2BL
C^1BL					
P^3BL	0.259				
P^4BL	0.192	0.811			
M^1BL	0.167	0.618	0.641		
M^2BL	0.218	0.623	0.652	0.728	
M^3BL	0.310	0.527	0.488	0.220	0.677

Table 6.6. Phenotypic correlations between mandibular tooth lengths. Unshaded cells are statistically significantly different from zero at $p<0.05$, cells shaded in grey are not statistically significantly different from zero.

N=79-151	I_2MD	C_1MD	P_3MD	M_1MD	M_2MD
I_2MD					
C_1MD	0.382				
P_3MD	0.131	0.413			
M_1MD	0.420	0.287	0.180		
M_2MD	0.396	0.396	0.384	0.712	
M_3MD	0.269	0.381	0.312	0.468	0.641

Table 6.7. Phenotypic correlations between mandibular tooth breadths, all values are statistically significantly different from zero at $p<0.05$.

N=81-152	C_1BL	P_3BL	P_4BL	M_1BL	M_2BL
C_1BL					
P_3BL	0.276				
P_4BL	0.428	0.582			
M_1BL	0.500	0.490	0.571		
M_2BL	0.446	0.454	0.521	0.689	
M_3BL	0.406	0.360	0.455	0.639	0.819

6.3.4 Bivariate analyses

Results of ρ_G estimation in the dimensions of the canine-premolar honing complex are provided in Table 6.8. Detailed results of ρ_G estimation are provided in Table 9.2. The h^2 estimates for two measurements in the honing complex (C_1 breadth and P_3 length) are not statistically significantly different from zero, and these traits also produce low and inconclusive estimates of ρ_G. The other canine dimensions generate statistically significant non-zero estimates of ρ_G, while ρ_G values between P_3 breadth and canine dimensions are not statistically significantly different from zero. The ρ_G estimate between C_1 breadth and P_3 length is likely indicative of the low genetic variability in both traits, rather than a large degree of pleiotropy between these dimensions.

Table 6.8. Results of genetic correlation estimation within the honing complex: left of diagonal cells contain genetic correlation estimates, right of diagonal cells contain corresponding standard error estimates. White: not statistically significantly different from one; Pale grey: between zero and one ($p<0.05$); Dark grey: not statistically significantly different from zero; Black: not statistically significantly different from zero or one.

N=182-326	C^1 MD	C^1 BL	C_1 MD	C_1 BL	P_3 MD	P_3 BL
C^1 MD		0.167	0.189	0.261	0.380	0.288
C^1 BL	0.429		0.200	0.318	0.481	0.237
C_1 MD	0.615	0.804		0.331	0.330	0.309
C_1 BL	0.708	0.453	0.801		-	0.685
P_3 MD	0.254	-0.001	0.631	1.000		0.376
P_3 BL	0.285	0.633	0.493	-0.289	0.531	

Table 6.9. Results of genetic correlation estimation between maxillary tooth lengths: left of diagonal cells contain genetic correlation estimates, right of diagonal cells contain corresponding standard error estimates. White: not statistically significantly different from one; Pale grey: between zero and one ($p<0.05$); Dark grey: not statistically significantly different from zero; Black: not statistically significantly different from zero or one.

N=310-347	I^1MD	I^2MD	C^1MD	P^3MD	P^4MD	M^1MD	M^2MD	M^3MD
I^1MD		0.309	0.124	0.164	-	0.275	0.154	0.184
I^2MD	0.717		0.285	0.225	0.277	0.34	0.218	0.341
C^1MD	0.518	0.360		0.172	0.228	0.222	0.166	0.194
P^3MD	0.528	0.810	0.465		0.160	0.170	0.161	0.170
P^4MD	0.640	0.553	0.295	0.626		0.172	0.137	0.211
M^1MD	0.584	0.345	0.517	0.532	0.630		0.070	0.184
M^2MD	0.571	0.664	0.516	0.543	0.725	0.916		0.131
M^3MD	0.781	0.743	0.477	0.628	0.654	0.573	0.749	

Table 6.10. Results of genetic correlation estimation between maxillary tooth breadths: left of diagonal cells contain genetic correlation estimates, right of diagonal cells contain corresponding standard error estimates. White: not statistically significantly different from one; Pale grey: between zero and one ($p<0.05$); Dark grey: not statistically significantly different from zero; Black: not statistically significantly different from zero or one.

N=306-342	C^1BL	P^3BL	P^4BL	M^1BL	M^2BL	M^3BL
C^1BL		0.190	0.194	0.365	0.190	0.205
P^3BL	0.331		0.055	0.207	0.097	0.099
P^4BL	0.288	0.903		0.207	0.096	0.115
M^1BL	-0.091	0.991	0.848		0.129	0.154

M^2BL	0.016	0.637	0.677	0.797		0.074
M^3BL	0.587	0.749	0.775	0.786	0.974	

Out of twenty-eight estimates of ρ_G between maxillary tooth lengths, twenty-four are statistically significantly different from zero (Table 6.9). Seventeen are statistically significantly different from both zero and one, and seven are statistically significantly different from zero but not from one.

Eleven of fifteen ρ_G estimates between maxillary tooth breadths are statistically significantly different from zero (Table 6.10). Six of these are statistically significantly different from zero and one, and five are statistically significantly different from zero but not from one. Three ρ_G estimates are statistically significantly different from one but not from zero. The ρ_G estimate between C^1 breadth and M^1 breadth is not statistically significantly different from zero or one, and is therefore an inconclusive estimate. All M^1 breadth ρ_G estimates should be viewed as somewhat inconclusive since the h^2 for M^1 breadth is not statistically significantly different from zero, and M^1 breadth therefore shows low genetic variability in this population.

Table 6.11. Results of genetic correlation estimation between mandibular tooth lengths: left of diagonal cells contain genetic correlation estimates, right of diagonal cells contain corresponding standard error estimates. White: not statistically significantly different from one; Pale grey: between zero and one ($p<0.05$); Dark grey: not statistically significantly different from zero; Black: not statistically significantly different from zero or one.

N=308-341	I_2MD	C_1MD	P_3MD	M_1MD	M_2MD	M_3MD
I_2MD		0.293	0.373	0.296	0.257	0.238
C_1MD	0.508		0.330	0.190	0.193	0.197
P_3MD	0.494	0.631		-	0.287	0.842
M_1MD	0.355	0.763	1.000		0.062	0.173
M_2MD	0.320	0.989	0.895	0.954		0.132
M_3MD	0.411	0.525	0.901	0.374	0.828	

Table 6.12. Results of genetic correlation estimation between mandibular tooth breadths: left of diagonal cells contain genetic correlation estimates, right of diagonal cells contain corresponding standard error estimates. White: not statistically significantly different from one; Pale grey: between zero and one ($p<0.05$); Dark grey: not statistically significantly different from zero; Black: not statistically significantly different from zero or one.

N=290-338	C_1BL	P_3BL	P_4BL	M_1BL	M_2BL	M_3BL
C_1BL		0.685	0.441	0.672	0.485	0.337
P_3BL	-0.289		0.236	0.271	0.222	0.465
P_4BL	-0.065	0.990		0.390	0.205	0.294
M_1BL	0.040	0.736	0.164		0.094	0.160
M_2BL	0.147	0.705	0.856	0.931		-
M_3BL	0.400	0.408	0.690	0.839	1.000	

Excluding I_1 and P_4 lengths from bivariate analyses due to poor measurement reliability, fifteen ρ_G values were estimated between mandibular tooth lengths (Table 6.11). Of these, one ρ_G estimate is statistically significantly different from zero and one, and six are statistically significantly different from zero but not from one. Four ρ_G estimates are statistically significantly different from one but not from zero, and four are not statistically significantly different from zero or one and are therefore inconclusive. Given the low h^2 estimate for P_3 length, ρ_G values for P_3 length may also be viewed as inconclusive. Seven out of fifteen ρ_G estimates between mandibular tooth breadths are statistically significantly different from zero but not from one, and no estimates are statistically significantly different from zero and one (Table 6.12). Two ρ_G estimates are statistically significantly different from one but not from zero. A large proportion of ρ_G estimates between mandibular tooth breadths, six in total and all five estimates related to C_1 breadth, are not statistically significantly different from zero or one and are therefore

inconclusive. This outcome is an expected result of the low h^2 estimate associated with C_1 breadth.

6.3.5 Comparing estimates of ρ_G and ρ_P

Estimates of ρ_G are greater than estimates of ρ_P for 71 out of 88 trait pairs, and the average ρ_G value (average $\rho_G = 0.577$) is larger than the average ρ_P value (average $\rho_P = 0.475$). Of the seventeen instances in which ρ_P exceeds estimated ρ_G, ten occur for inconclusive estimates of ρ_G and five occur for ρ_G values that are not statistically significantly different from zero. In the remaining two instances, the difference between ρ_G and ρ_P is less than 0.100.

Figure 6.1 shows that ρ_G and ρ_P estimates within the honing complex are similar when inconclusive ρ_G estimates are excluded. All ρ_P values in the honing complex are statistically significantly different from zero, whereas four of the ρ_G estimates are statistically significantly different from zero. The same comparisons between ρ_G and ρ_P - are shown for maxillary tooth lengths (Figure 6.2), maxillary tooth breadths (Figure 6.3), mandibular tooth lengths (Figure 6.4), and mandibular tooth breadths (Figure 6.5). Phenotypic correlations are generally less variable than genetic correlations; excluding inconclusive estimates, ρ_G values range from 0.016 to 1.000 with a mean of 0.652. For the same trait pairs, ρ_P values range from 0.180 to 0.819 with a mean of 0.449.

6.4 Discussion

Overall, the genetic correlations estimated here conform to phenotypic patterns of covariation in that greater correlations are identified throughout the toothrow than within the honing complex. Strong genetic correlations between dimensions of the maxillary and mandibular canines do not extend to the honing premolar, although the low heritability of

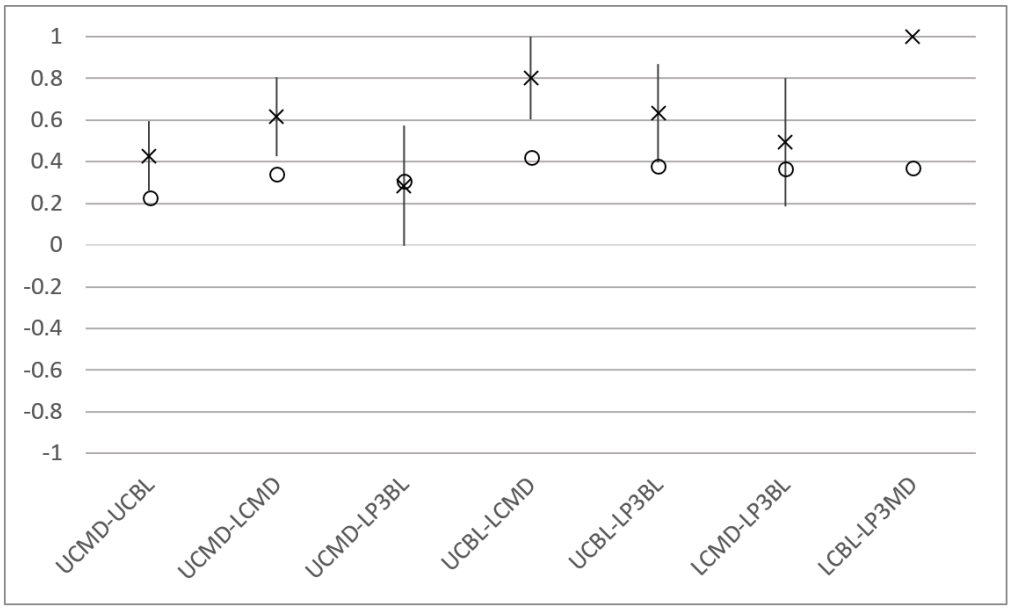

Figure 6.1. Comparison of genetic and phenotypic correlations between dimensions of the honing complex. X indicates ρ_G with bars representing standard error margins. Circles indicate ρ_P.

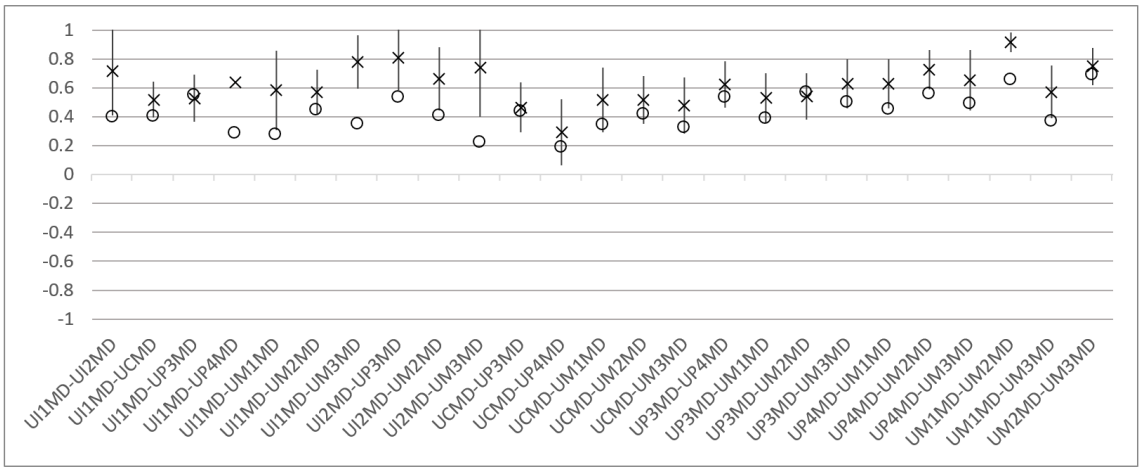

Figure 6.2. Comparison of genetic and phenotypic correlations between maxillary tooth lengths. X indicates ρ_G with bars representing standard error margins. Circles indicate ρ_P.

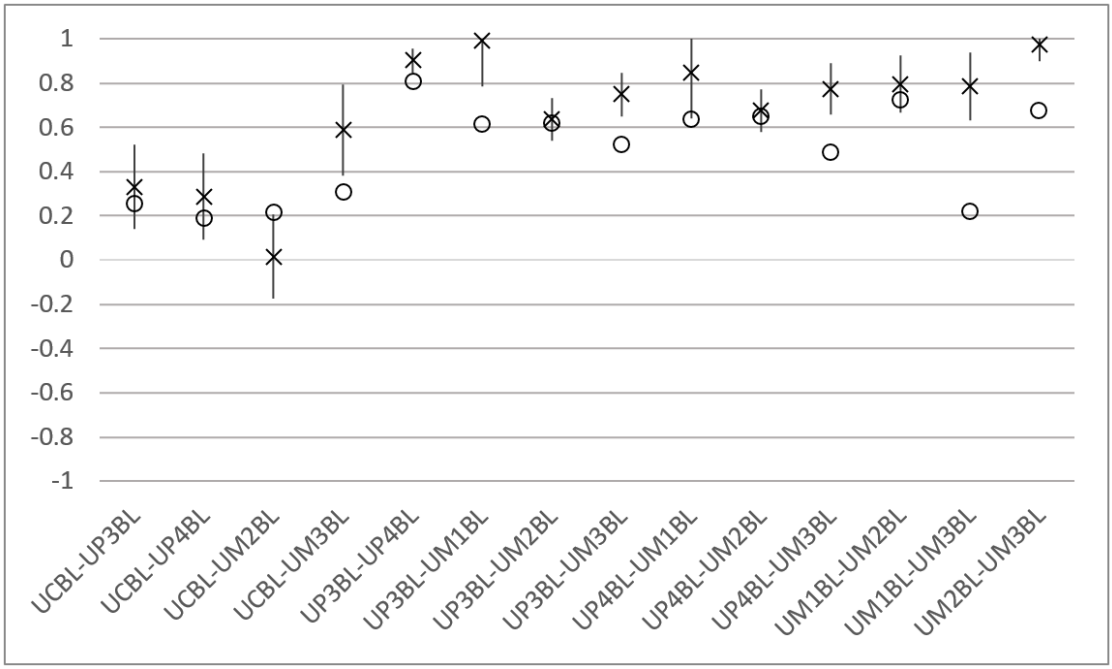

Figure 6.3. Comparison of genetic and phenotypic correlations between maxillary tooth breadths. X indicates ρ_G with bars representing standard error margins. Circles indicate ρ_P.

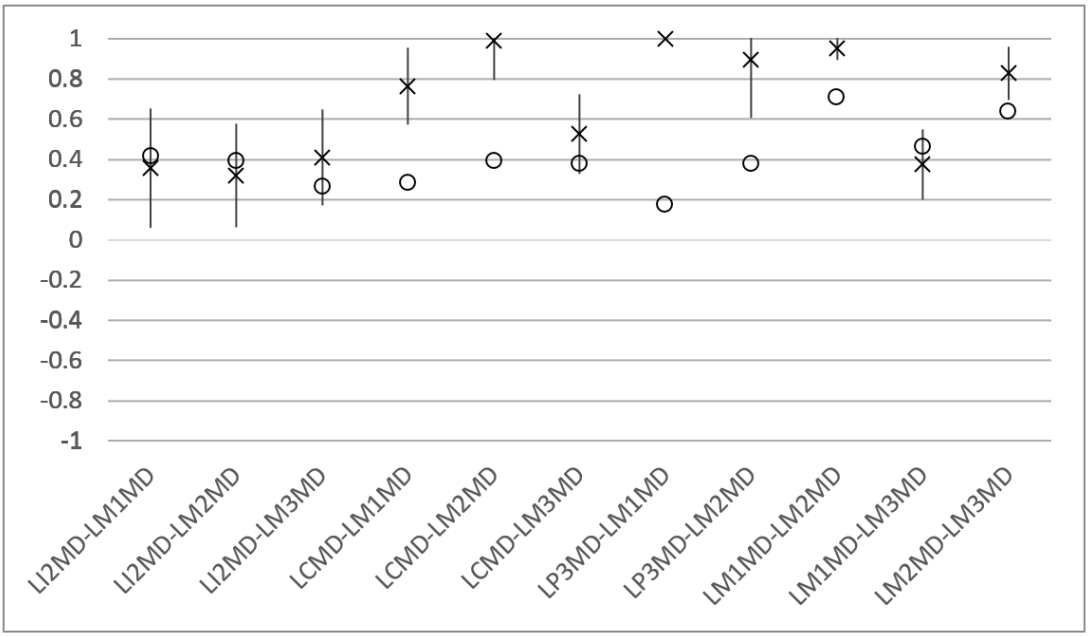

Figure 6.4. Comparison of genetic and phenotypic correlations between mandibular tooth lengths. X indicates ρ_G with bars representing standard error margins. Circles indicate ρ_P.

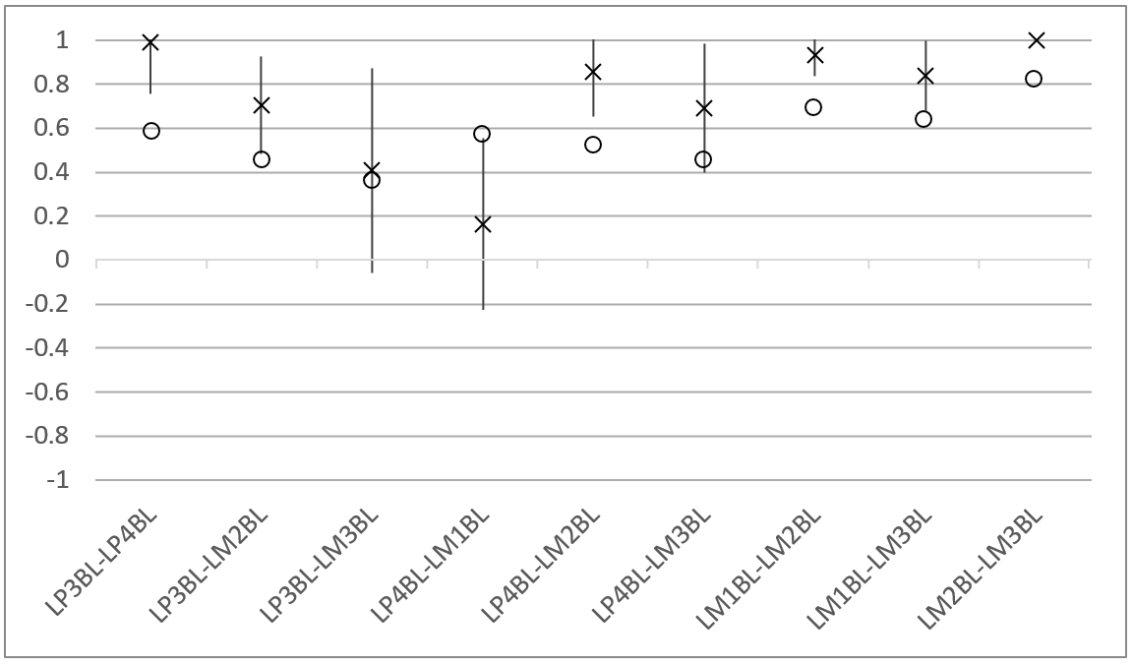

Figure 6.5. Comparison of genetic and phenotypic correlations between mandibular tooth breadths. X indicates ρ_G with bars representing standard error margins. Circles indicate ρ_P.

the honing premolar length limits the interpretation of these results. These results indicate that a degree of genetic independence between the canines and honing premolar is not unique to hominins. Outside the honing complex, the macaque dentition is somewhat genetically modular by tooth type, although to a lesser degree than the dental dimensions of the SNPRC baboon population.

6.4.1 Heritability

Differences in h^2 estimates can be difficult to interpret, since low h^2 values may indicate the large influence of σ^2_P or low additive genetic variability, represented by $\sigma^2_{A,}$ in the population. Primate dental traits produce, for the most part, high h^2 estimates in this and previous studies (Townsend and Brown, 1978; Hlusko et al., 2002, 2004, 2011; Hlusko and Mahaney, 2009; Townsend et al., 2009c; Koh et al., 2010). Of the 26 standardized dental measurements analyzed here, 19 produce h^2 values greater than 0.50. The degree to which the environment is expected to impact dental phenotypic variation certainly varies according to tooth position and the timing of tooth development, yet the dimensions of a single tooth can vary considerably in h^2, as in M^1, C_1, and P_3. As demonstrated in *Saguinus fuscicollis* in Chapter 4, genetic correlations between the dimensions of a single tooth are not necessarily greater than between-tooth genetic correlations, and it is possible that environmental factors may impact, for instance, the mesiodistal dimensions more than the buccolinguals dimension for certain teeth. It nevertheless seems unlikely that the observed differences in heritabilities of dimensions

in the M^1, C_1, and P_3 result solely from differences in σ^2_P, and the role of the additive genetic variability of dental dimensions should be considered.

Recent natural or artificial selection can, in principle, reduce σ^2_A in a population (Falconer and Mackay, 1996), yet long-term selection experiments have generally failed to support this hypothesis (Houle, 1992). Likewise, reduced additive genetic variability does not necessarily limit how a trait responds to natural selection due to the often significant role of non-additive genetic variability (Waldmann, 2001). Non-additive genetic contributions to phenotypes, such as epistasis or dominance-related interactions between genes, could not, however, be estimated in this population. If it is assumed that dental dimensions under neutral selection yield high h^2 estimates, the low h^2 values estimated for M^1 breadth, C_1 breadth, and P_3 length could indicate that selection pressures on these dental dimensions have led to reduction of σ^2_A, and therefore reduction of h^2. Alternative explanations cannot be ruled out, however. For example, the low measurement reliability for M^1 breadth is impacting the h^2 estimate for this trait. Additionally, wear associated with C^1 honing against C_1 and P_3 could introduce greater environmental variability to C_1 breadth and P_3 length.

Common environmental effects on related individuals could explain some of the variation in h^2 as well and should be examined more closely in studies of wild and free-ranging populations (Pemberton, 2010). Female rhesus macaques inherit their rank through their mothers, meaning that closely related individuals may also have access to similar foods and experience similar social and environmental stresses during odontogenesis. Birth order may also have a significant impact on dental development, as

female macaques are ranked below their mothers but above their older sisters. These common environmental effects could elevate h^2 for some dental traits, producing differences in h^2 that reflect environmental differences between matrilines or between individuals rather than differences in genetic variability or evolvability. Provisioning of the rhesus macaques at Cayo Santiago may moderate the impact of rank on differences in dental development, but this should nevertheless be taken into account in future analyses and discussion. Further analysis of the impact of common environment on dental development, and of how these dimensions have changed in this population over the course of 80 years on Cayo Santiago are necessary to answer these questions.

6.4.2 Genetic correlations

Bivariate quantitative genetic parameter estimation shows that morphological integration between maxillary and mandibular canines may be rooted in genetic integration, supporting the conclusions of some previous studies of the anthropoid honing complex (Grieco et al., 2013; Delezene, 2015). These results do not, however, indicate that genetic integration between the canines extends to the honing premolar. Results related to P_3 are not easy to interpret, since the low h^2 estimate for P_3 length could have numerous causes as discussed above, but low genetic correlations between canine dimensions and P_3 breadth indicate that there is some degree of genetic independence between the canines and honing premolar. It is worth noting, however, that P_3 breadth is not as directly associated with the honing function of the complex as the mesiodistally-oriented P_3 honing surface. Genetic correlations between the estimated areas of teeth in

the honing complex are estimated in *Saguinus fuscicollis* in Chapter 4, and all values are statistically significantly different from zero. Results of genetic correlation estimation in this rhesus macaque population therefore indicate that genetic structures underlie the lesser phenotypic correlations between the canines and honing premolar in anthropoids (Delezene, 2015), whereas dimensions of the honing complex in the brown-mantled tamarin population are closely genetically correlated.

Maxillary tooth dimensions are highly correlated throughout the toothrow, and high ρ_G estimates between the maxillary incisors and maxillary postcanine teeth differ from estimates acquired from *Papio hamadryas*, in which there are few statistically significant non-zero genetic correlations between incisor and postcanine dimensions (Hlusko et al., 2011). Within maxillary tooth lengths, estimates of ρ_G within regions of the toothrow are not greater than estimates between anterior and postcanine teeth. For example, the range of genetic correlations between incisor length and molar length (range: 0.571-0.781, excluding one inconclusive result) largely overlaps with the range of ρ_G estimates between molar lengths (range: 0.573-0.916) and between incisor lengths (0.717). The breadths of teeth of the same type and neighboring teeth in the maxilla are, however, more highly genetically correlated than other pairings. C^1 breadth is genetically independent from other maxillary tooth breadths.

Genetic correlations between mandibular tooth dimensions are consistent with the pattern observed in the maxillary tooth breadths. I_1 length is not statistically significantly genetically correlated with any postcanine tooth lengths, and postcanine tooth lengths are generally highly genetically correlated with each other. Although genetic correlations are

inconclusive between C_1 breadth and all other mandibular tooth breadths, the remaining ρ_G estimates tend to be statistically significantly different from zero and most are not statistically significantly different from one. This indicates a moderate to high degree of pleiotropy between mandibular postcanine tooth breadths.

Excepting maxillary tooth lengths, ρ_G estimates between dental dimensions of the Cayo Santiago rhesus macaques indicate a degree of genetic independence between incisors and postcanines. In most cases, ρ_G estimates are greater within the postcanines than between postcanines and incisors or canines. The canines are also generally not highly genetically correlated with the incisors. These results generally support the findings of Hlusko et al. (2011) that dental dimensions of the SNPRC baboons are weakly genetically modular by tooth type. Genetic correlations estimated in maxillary tooth lengths show a broader pattern of integration across the toothrow in this population, and may indicate important differences between the patterning of tooth lengths and tooth breadths, and between the patterning of the maxillary and mandibular teeth.

6.4.3 Comparing phenotypic and genetic correlations

The standardized dental dimensions of the Cayo Santiago macaques are all positively phenotypically correlated with each other, and correlations are statistically significantly different from zero for all but one pair of dimensions (I_2 length and P_3 length). Tooth breadths are generally more highly correlated with each other than are tooth lengths. Contrary to the hypothesis that dimensions of the honing complex are closely correlated due to functional integration, phenotypic correlations within the honing

complex are reduced relative to correlations between tooth dimensions throughout the maxilla or mandible.

The tendency towards statistically significant positive correlations between dental measurements is also seen in the ρ_G estimates. Heritability estimates for the standardized dental measurements are moderate to high, so, given the theoretical relationship between ρ_G and ρ_P, the two correlation estimates should be generally similar (Falconer and Mackay, 1996). However, since h^2 values are not equal to one for most measurements, ρ_P are still expected to differ from ρ_G due to environmental variance and covariance.

The comparisons of ρ_G and ρ_P provided here, while not statistically rigorous, could support the concept that well-estimated genetic correlations may not differ substantially from phenotypic correlations for highly heritable traits like dental dimensions (Cheverud, 1988b). Alternatively, similarity between ρ_P and ρ_G also depends upon the sign and magnitude of ρ_E. Given that individuals in the Cayo Santiago rhesus macaques are provisioned and experience less variation in food quality than might be typical in the environment of a wild rhesus macaque population, it may be that ρ_E values in this population are not typical of a natural population. In addition, low h^2 estimates for dental traits such as C_1 breadth and P_3 length demonstrate that dental traits are not necessarily highly heritable in every population. Since ρ_G and ρ_P may differ substantially when h^2 is low, there is a need for caution when using phenotypic correlations as proxies for ρ_G even in traits that are generally highly heritable like tooth dimensions.

6.4.4 Sexual dimorphism

Extreme sex differences in rhesus macaque tooth dimensions are sure to impact the genetic inheritance of tooth size. By standardizing each measurement within each sex, then pooling the data for quantitative genetic parameter estimation, I accounted for sex differences in means and variance, but did not account for sex differences in heritability or genetic correlation. To understand the influence of sex on these quantitative genetic parameters, it might be best to estimate h^2 separately in males and females, and to estimate the intersexual genetic correlation (Wolak et al., 2015). At present, there are not adequate phenotypic and pedigree data to reliably estimate these parameters in males and females separately in the Cayo Santiago rhesus macaques, but the pedigree information is constantly improving though ongoing genetic testing (Widdig et al., 2016) and it may be possible to estimate these parameters in the future.

6.4.5 Evolution of the canine-premolar honing complex

Interpretations of genetic correlation estimates should account for both the uncertainty surrounding the results and the changeability of genetic correlations over generations. Selection pressures and other evolutionary mechanisms impact the genetic structures underlying genetic correlations, primarily pleiotropic genes, just as they impact the genetic heritability of traits. Consistent patterns of genetic correlations across species can, however, indicate stability in the genetic covariance matrix over evolutionary time periods (Lynch and Walsh, 1998:650-653). The genetic correlations between dental dimensions in the Cayo Santiago rhesus macaques broadly resemble estimates from the

SNPRC hamadryas baboons (Hlusko et al., 2011), demonstrating slight genetic modularity between tooth types that is stable across two papionin species. ρ_G estimates between dimensions of the honing premolar and dimensions of other teeth in the SNPRC baboon population are very low, with only five out of sixty ρ_G estimates statistically significantly differing from zero, while four out of ten ρ_G estimates associated with P_3 dimensions are statistically significantly different from zero in the Cayo Santiago rhesus macaque population. The greater genetic integration between P_3 dimensions and premolar and molar dimensions in this macaque sample could indicate slight differences in the genetic regulation of P_3 odontogenesis at the species- or population-level.

Table 6.13. Genetic correlations associated with canine mesiodistal lengths in humans (data from Stojanowski et al. 2017), tamarins, and rhesus macaques. Black = not statistically significantly different from zero or one, dark gray = different from one but not from zero, light gray = different from zero and one, white = different from zero but not from one.

	Tamarin ρ_G (SE)	Human ρ_G (SE)	Macaque ρ_G (SE)
I^1 length – C^1 length	0.599 (0.156)	0.580 (0.134)	0.518 (0.124)
I^2 length – C^1 length	0.239 (0.181)	0.258 (0.164)	0.360 (0.285)
C^1 length – P^2 length	0.440 (0.166)		
C^1 length – P^3 length	0.615 (0.185)	0.595 (0.158)	0.465 (0.172)
C^1 length – P^4 length	0.547 (0.244)	0.752 (0.168)	0.295 (0.228)
C^1 length – M^1 length	0.482 (0.120)	0.532 (0.184)	0.517 (0.222)
C^1 length – M^2 length	0.642 (0.176)		0.516 (0.166)
C^1 length – M^3 length			0.477 (0.194)
I_1 length – C_1 length	0.628 (0.256)	0.657 (0.184)	
I_2 length – C_1 length	0.784 (0.183)	0.643 (0.200)	0.508 (0.293)
C_1 length – P_2 length	1 (nc)		
C_1 length – P_3 length	0.758 (0.253)	0.659 (0.184)	0.631 (0.330)
C_1 length – P_4 length	0.857 (0.474)	0.661 (0.514)	
C_1 length – M_1 length	0.429 (0.227)	0.438 (0.402)	0.763 (0.190)
C_1 length – M_2 length	0.520 (0.245)		0.989 (0.193)
C_1 length – M_3 length			0.525 (0.197)
C^1 length – C_1 length		0.704 (0.144)	0.615 (0.189)

A comparison of ρ_G estimates associated with canine lengths between the Cayo Santiago rhesus macaques and a human sample (Stojanowski et al., 2017) shows that both human and macaque canine lengths are closely genetically correlated with other tooth lengths; tamarin canine dimensions are also highly genetically correlated with other tooth dimensions (Table 6.13). C^1 breadth is, however, genetically independent from most other dimensions in this macaque population, and C_1 breadth yields inconclusive results. The tendency for canine mesiodistal length to covary genetically with other tooth dimensions across three distantly related primate species may indicate some evolutionary stability in the shared genetic contributions to canine length and other tooth lengths. Given the stability of this pattern, it may be important to consider the impact of genetic integration between teeth on the evolution of primate canine size and shape.

The dimensions of the honing complex are not strongly modular based on the genetic correlations estimated using standardized dental measurements from the Cayo Santiago rhesus macaque population. Instead, dimensions of the canines covary genetically with each other and dimensions of the canines and honing premolar covary genetically with dimensions of the incisors, premolars, and molars. This is perhaps to be expected based on the structural similarities between teeth and the shared developmental processes that contribute to odontogenesis. The pattern of phenotypic covariation in the anthropoid honing complex is broadly consistent with the genetic correlations estimated here, as both methods identify statistically significant positive correlations within the honing complex and between dimensions of the honing complex and the incisors and postcanine teeth (Delezene, 2015). However, phenotypic correlations are of greater

magnitude within the honing complex than between the honing complex and other incisors or postcanine teeth and therefore provide stronger evidence of variational modularity of the honing complex in anthropoid primates (Delezene, 2015) than is evident from genetic correlation estimates. Genetic correlations demonstrate that the honing complex is not necessarily genetically independent from other dental dimensions and therefore may be affected by selection acting upon other regions in the toothrow. Because it contains a honing complex that is functionally distinct, yet developmentally and genetically integrated with teeth that function as part of the masticatory apparatus, the anthropoid dentition may be a very useful model for understanding the evolution of genetic modularity and integration.

6.5 Conclusions

Genetic correlations in the canine-premolar honing complex of the Cayo Santiago macaques are consistent with significant genetic integration of maxillary and mandibular canine dimensions, but demonstrate that the canines may be genetically independent from the honing premolar. Strong genetic correlations between dimensions of the honing complex and incisors and postcanine teeth provide evidence of genetic integration across tooth types and functional modules within the dentition. The degree to which genetic integration throughout the toothrow varies across additional primate and mammal populations should be examined further to determine how the patterns identified here and in the previously analyzed baboon and tamarin populations relate to the evolution of the dentition. The Cayo Santiago macaques provide a rare opportunity to estimate

quantitative genetic parameters of skeletal and dental morphology. Continued collection of behavioral data, genetic material, and skeletal remains from the Cayo Santiago macaques will increase the power with which quantitative genetic parameters can be estimated, which will be necessary to understand the role of genes, sex, and environment in the evolution of the canine-premolar honing complex in anthropoid primates.

7 Summary

Previous quantitative genetic analyses of tooth size in non-human primates have indicated that variation in tooth size is highly heritable and the teeth are somewhat genetically modular by tooth type. Similarities between the genetic structure of the baboon and mouse dentitions have, furthermore, led some to conclude that this modular genetic architecture of the dentition is characteristic of mammals. This would indicate that the evolution of incisor and molar dimensions can occur largely independently, without pleiotropy between the teeth leading to strong correlated response to selection. The interpretation of any quantitative genetic analyses is limited, however, by the structure and environment of the study population. Using quantitative genetic methods to integrate our understanding of dental phenotypes with genetic and developmental studies of dental patterning therefore requires greater knowledge of the degree to which the genetic structure of dental traits vary across living primate populations.

Heritability estimates from previously studied human and baboon dental dimensions are generally moderate to high, indicating that there is a substantial additive genetic contribution to phenotypic variation in tooth size. Estimates of heritability from tamarins and macaques show that moderate heritability values are common in the primate dentition across a range of taxa, body sizes, and environmental conditions. Interpretations of heritability as they relate to the potential for a trait to evolve or the recent evolutionary history of a trait are more difficult, although the high evolvability of canine dimensions in

tamarins and macaques indicate greater genetic variability in the canines than in other tooth types.

Greater understanding of the genetic correlations between teeth is necessary to interpret how genetic patterning of the dentition has influenced the evolution of primate teeth. Models of odontogenesis, such as the morphogenetic field model (Butler, 1939) and clone theory (Osborn, 1978), explain morphological similarities between teeth as resulting from the genetic profile of the tissues in which and from which teeth form. Using genetic correlation estimates from a tamarin population, hypotheses generated from these odontogenetic models were not widely supported. Instead, the tamarin dentition is highly genetically integrated across regions and tooth types. Genetic modularity of tooth types, identified in baboons and mice and expected based on models of odontogenesis, is therefore not supported in the dental dimensions of a tamarin sample. The genetic patterning of tooth dimensions is more variable in extant primates than has been previously recognized, and differences in this patterning could influence how the dentition adapts and evolves.

Genetic correlations in the dimensions of the canine-premolar honing complex, and across the dentition, of rhesus macaques indicate that while there is a pattern of genetic modularity by tooth type in this population as in the previously studied baboons, the honing complex itself is not genetically independent from teeth outside the honing complex and is not particularly closely genetically integrated within itself. Since these are the first quantitative genetic analyses of the honing complex in a cercopithecoid primate, the results may reflect patterns that are limited to the Cayo Santiago rhesus macaque

population. The genetic integration observed between the maxillary and mandibular canines is, however, consistent with genetic correlations estimated in tamarins and phenotypic correlations observed in anthropoid primates (Delezene, 2015). While the macaque honing complex forms a functional unit that is largely independent from the masticatory function of the surrounding teeth, this has not resulted in a pattern of genetic modularity in which canine dimensions are genetically independent from the incisor and molar dimensions. It is possible that selection acting on the masticatory function of the dentition could impact canine morphology in non-adaptive ways.

Quantitative genetic methods provide a powerful toolkit for bridging study of the phenotype and morphological change over evolutionary timescales with the field of molecular genetics. While heritabilities and genetic correlations of dental dimensions in additional primate populations will need to be estimated to understand more fully how patterns of genetic inheritance impact the evolution of tooth morphology in primates broadly, this research provides the first evidence that there is variation in the degree to which dental traits are genetically integrated across primate populations. Given the large genetic contribution to tooth size variation, and the utility of dental traits in the study of primate evolution, the combined study of quantitative genetics and complex dental morphology could contribute greatly to our understanding of primate evolution.

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9 Appendix

Table 9.1. Detailed results of bivariate genetic correlation estimation in *Saguinus fuscicollis*. P-values below 0.05 are bolded. ρ_P estimates shown here are calculated in SOLAR during ρ_G estimation.

Traits	Covariates	N_{eff}	ρ_E	SE ρ_E	ρ_G	SE ρ_G	P $\rho_G=0$	P $\rho_G=1$	ρ_P
UI1MD x UI2MD	WC	65	-0.370	0.236	0.800	0.155	**<0.05**	>0.05	0.300
UI1MD x UCMD	WC(UI1MD)	104	-0.337	0.206	0.599	0.156	**<0.05**	**<0.05**	0.247
UI1MD x UCBL	WC	90	-0.352	0.221	0.624	0.16	**<0.05**	**<0.05**	0.241
UI1MD x UP2MD	WC	68	0.190	0.185	0.388	0.186	**<0.05**	**<0.05**	0.292
UI1MD x UP2BL	WC(UI1MD) Sex(UP2BL)	95	-0.165	0.194	0.522	0.152	**<0.05**	**<0.05**	0.239
UI1MD x UP3MD	WC(UI1MD)	56	-0.248	0.195	0.877	0.292	**<0.05**	>0.05	0.221
UI1MD x UP3BL	WC Sex(UP3BL)	93	-0.437	0.257	0.589	0.147	**<0.05**	**<0.05**	0.222
UI1MD x UP4MD	WC(UI1MD)	50	-0.071	0.193	0.545	0.240	**<0.05**	>0.05	0.200
UI1MD x UP4BL(K)	WC	103	-0.295	0.278	0.577	0.129	**<0.05**	**<0.05**	0.295
UI1MD x UM1MD	WC(UI1MD)	144	-0.558	0.330	0.576	0.135	**<0.05**	**<0.05**	0.288
UI1MD x UM1BL	WC	127	-0.217	0.233	0.647	0.120	**<0.05**	**<0.05**	0.367
UI1MD x UM2MD	WC(UI1MD) Sex(UM2MD)	58	-0.060	0.185	0.627	0.202	**<0.05**	**<0.05**	0.254
UI1MD x UM2BL	WC(UI1MD)	183	-0.493	0.255	0.610	0.130	**<0.05**	**<0.05**	0.298
UI2MD x UCMD	WC(UI2MD)	72	0.208	0.207	0.239	0.181	>0.05	**<0.05**	0.223
UI2MD x UCBL	WC	63	0.118	0.205	0.443	0.184	**<0.05**	**<0.05**	0.298
UI2MD x UP2MD	WC	47	0.009	0.181	0.516	0.210	**<0.05**	**<0.05**	0.249
UI2MD x UP2BL	WC(UI2MD) Sex(UP2BL)	66	0.026	0.186	0.354	0.189	>0.05	**<0.05**	0.201
UI2MD x UP3MD	WC(UI2MD)	39	0.130	0.169	0.625	0.265	**<0.05**	>0.05	0.312
UI2MD x UP3BL	WC Sex(UP3BL)	65	0.310	0.191	0.296	0.183	>0.05	**<0.05**	0.300
UI2MD x UP4MD	WC(UI2MD)	35	0.202	0.188	0.150	0.303	>0.05	**<0.05**	0.176
UI2MD x UP4BL(K)	WC	71	0.085	0.216	0.379	0.176	**<0.05**	**<0.05**	0.256
UI2MD x UM1MD	WC(UI2MD)	100	-0.506	0.312	0.706	0.159	**<0.05**	**<0.05**	0.292
UI2MD x UM1BL	WC	88	0.184	0.226	0.375	0.165	**<0.05**	**<0.05**	0.292

UI2MD x UM2MD	WC(UI2MD) Sex(UM2MD)	40	-0.262	0.220	0.622	0.223	**<0.05**	**<0.05**	0.143
UI2MD x UM2BL	WC(UI2MD)	127	-0.446	0.396	0.518	0.147	**<0.05**	**<0.05**	0.241
UCMD x UCBL	WC (UCBL)	101	-0.759	0.337	0.905	0.088	**<0.05**	>0.05	0.409
UCMD x UP2MD	WC(UP2MD)	76	0.045	0.181	0.440	0.166	**<0.05**	**<0.05**	0.260
UCMD x UP2BL	Sex(UP2BL)	106	-0.035	0.195	0.765	0.102	**<0.05**	**<0.05**	0.467
UCMD x UP3MD		62	-0.101	0.217	0.615	0.185	**<0.05**	**<0.05**	0.253
UCMD x UP3BL	WC(UP3BL) Sex(UP3BL)	104	0.086	0.205	0.583	0.121	**<0.05**	**<0.05**	0.406
UCMD x UP4MD		55	0.019	0.204	0.547	0.244	**<0.05**	>0.05	0.252
UCMD x UP4BL(K)	WC(UP4BL)	115	-0.137	0.241	0.603	0.129	**<0.05**	**<0.05**	0.356
UCMD x UM1MD		161	-0.281	0.331	0.482	0.120	**<0.05**	**<0.05**	0.308
UCMD x UM1BL	WC(UM1BL)	142	0.270	0.222	0.445	0.119	**<0.05**	**<0.05**	0.395
UCMD x UM2MD	Sex(UM2MD)	65	-0.325	0.230	0.642	0.176	**<0.05**	**<0.05**	0.192
UCMD x UM2BL		204	-0.851	0.425	0.745	0.084	**<0.05**	**<0.05**	0.420
UCBL x UP2MD	WC	65	-0.006	0.194	0.262	0.186	>0.05	**<0.05**	0.140
UCBL x UP2BL	WC(UCBL) Sex(UP2BL)	92	-0.072	0.237	0.729	0.098	**<0.05**	**<0.05**	0.439
UCBL x UP3MD	WC(UCBL)	54	-0.183	0.189	0.712	0.179	**<0.05**	>0.05	0.235
UCBL x UP3BL	WC Sex(UP3BL)	90	-0.115	0.251	0.631	0.119	**<0.05**	**<0.05**	0.369
UCBL x UP4MD	WC(UCBL)	48	0.039	0.187	0.481	0.253	>0.05	>0.05	0.222
UCBL x UP4BL(K)	WC	99	0.064	0.234	0.541	0.128	**<0.05**	**<0.05**	0.378
UCBL x UM1MD	WC(UCBL)	139	-0.574	0.277	0.593	0.135	**<0.05**	**<0.05**	0.265
UCBL x UM1BL	WC	123	-0.217	0.291	0.550	0.121	**<0.05**	**<0.05**	0.329
UCBL x UM2MD	WC(UCBL) Sex(UM2MD)	56	0.215	0.189	0.057	0.234	>0.05	**<0.05**	0.129
UCBL x UM2BL	WC(UCBL)	177	-0.305	0.435	0.577	0.109	**<0.05**	**<0.05**	0.380
UP2MD x UP2BL	WC (UP2MD), sex(UP2BL)	190	0.065	0.159	0.189	0.189	>0.05	**<0.05**	0.127
UP2MD x UP3MD	WC(UP2MD)	111	0.294	0.132	0.723	0.271	**<0.05**	>0.05	0.428
UP2MD x UP3BL	WC Sex(UP3BL)	185	0.105	0.176	0.309	0.182	>0.05	**<0.05**	0.211
UP2MD x UP4MD	WC(UP2MD)	98	0.002	0.151	1.000	nc	**<0.05**	nc	0.364
UP2MD x UP4BL(K)	WC	204	-0.057	0.191	0.435	0.171	**<0.05**	**<0.05**	0.215
UP2MD x	WC(UP2MD)	287	-0.420	0.29	0.593	0.150	**<0.05**	**<0.05**	0.256

UM1MD									
UP2MD x UM1BL	WC	254	0.084	0.197	0.430	0.147	**<0.05**	**<0.05**	0.285
UP2MD x UM2MD	WC(UP2MD) Sex(UM2MD)	115	-0.159	0.178	0.800	0.205	**<0.05**	>0.05	0.228
UP2MD x UM2BL	WC(UP2MD)	365	-0.677	0.311	0.618	0.128	**<0.05**	**<0.05**	0.233
UP2BL x UP3MD	Sex(UP2BL)	41	-0.003	0.163	0.497	0.213	**<0.05**	**<0.05**	0.204
UP2BL x UP3BL	WC(UP3BL) Sex	68	0.239	0.152	1.000	nc	**<0.05**	>0.05	0.676
UP2BL x UP4MD	Sex(UP2BL)	36	0.101	0.159	0.559	0.262	**<0.05**	>0.05	0.268
UP2BL x UP4BL (K)	WC(UP4BL) Sex(UP2BL)	75	0.092	0.181	0.917	0.097	**<0.05**	>0.05	0.570
UP2BL x UM1MD	Sex(UP2BL)	104	-0.344	0.393	0.489	0.122	**<0.05**	**<0.05**	0.282
UP2BL x UM1BL	WC(UM1BL) Sex(UP2BL)	92	0.286	0.188	0.574	0.123	**<0.05**	**<0.05**	0.464
UP2BL x UM2MD	Sex	42	-0.170	0.166	0.452	0.224	**<0.05**	**<0.05**	0.099
UP2BL x UM2BL	Sex(UP2BL)	133	-0.167	0.271	0.689	0.108	**<0.05**	**<0.05**	0.426
UP3MD x UP3BL	sex (UP3BL), WC (UP3BL)	95	0.074	0.163	0.485	0.211	**<0.05**	**<0.05**	0.242
UP3MD x UP4MD		51	0.107	0.146	0.944	0.291	**<0.05**	>0.05	0.349
UP3MD x UP4BL (K)	WC(UP4BL)	105	-0.065	0.182	0.584	0.223	**<0.05**	>0.05	0.218
UP3MD x UM1MD		147	-0.271	0.216	1	nc	**<0.05**	nc	0.392
UP3MD x UM1BL	WC(UM1BL)	130	-0.357	0.232	0.660	0.179	**<0.05**	**<0.05**	0.193
UP3MD x UM2MD	Sex(UM2MD)	59	-0.086	0.150	0.826	0.286	**<0.05**	>0.05	0.198
UP3MD x UM2BL		187	-0.542	0.305	0.752	0.203	**<0.05**	>0.05	0.207
UP3BL x UP4MD	WC(UP3BL)	47	0.052	0.172	0.606	0.244	**<0.05**	>0.05	0.275
UP3BL x UP4BL(K)	WC	97	0.512	0.131	0.906	0.066	**<0.05**	**<0.05**	0.748
UP3BL x UM1MD	WC(UP3BL)	136	-0.222	0.297	0.506	0.128	**<0.05**	**<0.05**	0.302
UP3BL x UM1BL	WC	121	0.473	0.170	0.568	0.109	**<0.05**	**<0.05**	0.529
UP3BL x UM2MD	WC(UP3BL) Sex(UM2MD)	55	0.055	0.176	0.378	0.210	>0.05	**<0.05**	0.197
UP3BL x UM2BL	WC(UP3BL)	173	-0.305	0.350	0.747	0.091	**<0.05**	**<0.05**	0.471
UP4MD x UP4BL(K)	WC (UP4BL)	62	0.199	0.190	0.405	0.249	>0.05	>0.05	0.270
UP4MD x UM1MD		86	-0.415	0.255	0.940	0.131	**<0.05**	>0.05	0.369
UP4MD x UM1BL	WC(UM1BL)	76	-0.127	0.224	0.782	0.159	**<0.05**	>0.05	0.35

UP4MD x UM2MD	Sex(UM2MD)	35	-0.066	0.185	0.739	0.231	**<0.05**	>0.05	0.232
UP4MD x UM2BL		109	-0.794	0.517	0.648	0.164	**<0.05**	**<0.05**	0.207
UP4BL(k) X UM1MD	WC(UP4BL)	81	-0.218	0.312	0.422	0.129	**<0.05**	**<0.05**	0.267
UP4BL(K) X UM1BL	WC	182	0.173	0.217	0.787	0.081	**<0.05**	**<0.05**	0.602
UP4BL(K) X UM2MD	WC(UP4BL) Sex(UM2MD)	67	0.182	0.187	0.447	0.197	>0.05	**<0.05**	0.293
UP4BL(K) X UM2BL	WC(UP4BL)	185	-0.443	0.547	0.841	0.058	**<0.05**	**<0.05**	0.608
UM1MD x UM1BL	WC (UM1BL)	111	-0.474	0.554	0.628	0.088	**<0.05**	**<0.05**	0.453
UM1MD x UM2MD	Sex(UM2MD)	51	-0.114	0.291	0.583	0.200	**<0.05**	**<0.05**	0.262
UM1MD x UM2BL		160	-1.000	nc	0.625	0.095	**<0.05**	**<0.05**	0.348
UM1BL x UM2MD	WC(UM1BL) Sex(UM2MD)	31	0.326	0.186	0.467	0.175	**<0.05**	**<0.05**	0.365
UM1BL x UM2BL	WC(UM1BL)	97	-0.123	0.319	0.755	0.072	**<0.05**	**<0.05**	0.570
UM2MD x UM2BL	sex (UM2MD)	202	0.163	0.242	0.609	0.156	**<0.05**	**<0.05**	0.363
LI1MD x LI2MD	WC	36	0.251	0.150	0.248	0.271	>0.05	**<0.05**	0.244
LI1MD x LCMD	WC	53	-0.126	0.167	0.628	0.256	**<0.05**	>0.05	0.175
LI1MD x LCBL(K)	WC	73	-0.211	0.232	0.550	0.212	**<0.05**	>0.05	0.179
LI1MD x LP2MD	WC(LI1MD) Sex(LP2MD)	37	0.002	0.143	0.858	0.230	**<0.05**	>0.05	0.290
LI1MD x LP2BL(K)	WC	46	-0.087	0.143	0.544	0.239	**<0.05**	**<0.05**	0.142
LI1MD x LP3MD	WC(LI1MD)	31	-0.249	0.148	0.828	0.312	**<0.05**	>0.05	0.086
LI1MD x LP3BL	WC	71	-0.388	0.243	0.546	0.218	**<0.05**	>0.05	0.119
LI1MD x LP4MD	WC	22	-0.270	0.151	1.000	nc	**<0.05**	nc	0.111
LI1MD x LP4BL	WC	40	0.055	0.157	0.320	0.274	>0.05	**<0.05**	0.151
LI1MD x LM1MD	WC	35	-0.011	0.165	0.760	0.262	**<0.05**	>0.05	0.277
LI1MD x LM1BL(K)	WC	77	-0.006	0.926	0.312	0.213	>0.05	**<0.05**	0.165
LI1MD x LM2MD	WC(LI1MD)	29	-0.247	0.181	0.773	0.303	**<0.05**	>0.05	0.124
LI1MD x LM2BL	WC(LI1MD)	78	-0.023	0.356	0.394	0.207	>0.05	**<0.05**	0.193
LI2MD x LCMD	WC	63	-0.169	0.179	0.784	0.183	**<0.05**	>0.05	0.291
LI2MD x LCBL(K)	WC	87	-0.567	0.246	0.722	0.205	**<0.05**	>0.05	0.182
LI2MD x LP2MD	WC(LI2MD) Sex(LP2MD)	44	0.034	0.160	0.653	0.196	**<0.05**	**<0.05**	0.297
LI2MD x	WC	54	-0.215	0.161	0.952	0.341	**<0.05**	>0.05	0.234

LP2BL(K)									
LI2MD x LP3MD	WC(LI2MD)	36	-0.566	0.194	1.000	nc	**<0.05**	nc	0.090
LI2MD x LP3BL	WC	84	-0.297	0.313	0.683	0.165	**<0.05**	>0.05	0.328
LI2MD x LP4MD	WC	26	-0.12	0.192	0.993	0.32	**<0.05**	>0.05	0.254
LI2MD x LP4BL	WC	47	-0.022	0.178	0.73	0.242	**<0.05**	>0.05	0.309
LI2MD x LM1MD	WC	41	-0.13	0.197	0.651	0.21	**<0.05**	>0.05	0.248
LI2MD x LM1BL(K)	WC	91	-0.698	0.731	0.736	0.169	**<0.05**	>0.05	0.337
LI2MD x LM2MD	WC(LI2MD)	34	-0.384	0.223	0.65	0.254	**<0.05**	>0.05	0.110
LI2MD x LM2BL	WC(LI2MD)	93	-0.435	0.536	0.562	0.145	**<0.05**	**<0.05**	0.289
LCMD x LCBL(K)	WC	130	-0.203	0.299	0.845	0.087	**<0.05**	**<0.05**	0.515
LCMD x LP2MD	WC(LCMD) Sex(LP2MD)	65	-0.151	0.148	1.000	nc	**<0.05**	nc	0.328
LCMD x LP2BL(K)	WC	80	0.157	0.154	0.554	0.193	**<0.05**	**<0.05**	0.335
LCMD x LP3MD	WC(LCMD)	54	-0.194	0.179	0.758	0.253	**<0.05**	>0.05	0.195
LCMD x LP3BL	WC	125	-0.203	0.286	0.925	0.098	**<0.05**	>0.05	0.533
LCMD x LP4MD	WC	38	-0.200	0.178	0.857	0.474	**<0.05**	>0.05	0.144
LCMD x LP4BL	WC	70	-0.153	0.181	0.939	0.161	**<0.05**	>0.05	0.384
LCMD x LM1MD	WC	61	0.026	0.186	0.429	0.227	>0.05	**<0.05**	0.221
LCMD x LM1BL(K)	WC	136	-0.750	0.590	0.740	0.188	**<0.05**	>0.05	0.326
LCMD x LM2MD	WC(LCMD)	50	-0.106	0.193	0.520	0.245	**<0.05**	>0.05	0.189
LCMD x LM2BL	WC(LCMD)	138	-0.560	0.377	0.891	0.097	**<0.05**	>0.05	0.456
LCBL(K) x LP2MD	WC(LCBL) Sex (LP2MD)	90	-0.084	0.233	0.525	0.175	**<0.05**	**<0.05**	0.252
LCBL(K) x LP2BL(K)	WC	111	0.191	0.209	0.8	0.138	**<0.05**	>0.05	0.500
LCBL(K) x LP3MD	WC(LCBL)	74	-0.167	0.242	0.541	0.224	**<0.05**	>0.05	0.193
LCBL(K) x LP3BL	WC	173	-0.134	0.342	0.705	0.113	**<0.05**	**<0.05**	0.508
LCBL(K) x LP4MD	WC	52	0.38	0.238	0.251	0.272	>0.05	>0.05	0.237
LCBL(K) x LP4BL	WC	98	-0.476	0.255	0.896	0.157	**<0.05**	>0.05	0.347
LCBL(K) x LM1MD	WC	84	-0.664	0.438	0.567	0.158	**<0.05**	**<0.05**	0.190
LCBL(K) x LM1BL(K)	WC	189	-0.821	0.886	0.576	0.133	**<0.05**	**<0.05**	0.380
LCBL(K) x LM2MD	WC(LCBL)	70	-0.04	0.313	0.21	0.192	>0.05	**<0.05**	0.117

LCBL(K) x LM2BL	WC(LCBL)	191	-0.637	0.609	0.558	0.11	**<0.05**	**<0.05**	0.376
LP2MD x LP2BL(K)	sex (LP2MD), WC (LP2BL)	115	-0.139	0.143	0.661	0.233	**<0.05**	>0.05	0.168
LP2MD x LP3MD	Sex(LP2MD)	77	0.023	0.161	0.814	0.24	**<0.05**	>0.05	0.295
LP2MD x LP3BL	Sex (LP2MD) WC(LP3BL)	180	-0.251	0.256	0.852	0.153	**<0.05**	>0.05	0.358
LP2MD x LP4MD	Sex(LP2MD) WC(LP4MD)	54	-0.015	0.179	0.987	0.355	**<0.05**	>0.05	0.289
LP2MD x LP4BL	Sex (LP2MD) WC(LP4BL)	101	-0.228	0.174	0.96	0.186	**<0.05**	>0.05	0.271
LP2MD x LM1MD	Sex(LP2MD) WC(LM1MD)	87	0.166	0.174	0.699	0.213	**<0.05**	>0.05	0.387
LP2MD x LM1BL(K)	Sex(LP2MD) WC(LM1BL)	195	-0.373	2.217	0.749	0.206	**<0.05**	>0.05	0.392
LP2MD x LM2MD	Sex(LP2MD)	72	-0.236	0.209	0.931	0.231	**<0.05**	>0.05	0.239
LP2MD x LM2BL	Sex (LP2MD)	198	-0.318	0.299	0.982	0.169	**<0.05**	>0.05	0.363
LP2BL(K) x LP3MD	WC(LP2BL)	38	-0.086	0.138	0.865	0.31	**<0.05**	>0.05	0.214
LP2BL(K) x LP3BL	WC	87	0.309	0.205	0.738	0.149	**<0.05**	**<0.05**	0.506
LP2BL(K) x LP4MD	WC	26	0.016	0.149	0.592	0.333	>0.05	>0.05	0.180
LP2BL(K) x LP4BL	WC	49	-0.034	0.135	1	nc	**<0.05**	nc	0.380
LP2BL(K) x LM1MD	WC	42	-0.041	0.173	0.589	0.211	**<0.05**	**<0.05**	0.234
LP2BL(K) x LM1BL(K)	WC	95	-0.58	0.495	0.858	0.161	**<0.05**	>0.05	0.369
LP2BL(K) x LM2MD	WC(LP2BL)	35	0.065	0.174	0.27	0.246	>0.05	**<0.05**	0.153
LP2BL(K) x LM2BL	WC(LP2BL)	96	0.186	0.323	0.44	0.158	**<0.05**	**<0.05**	0.307
LP3MD x LP3BL	WC (LP3BL)	107	-0.301	0.211	0.589	0.266	**<0.05**	>0.05	0.135
LP3MD x LP4MD	WC(LP4MD)	33	0.18	0.129	1	nc	**<0.05**	nc	0.361
LP3MD x LP4BL	WC(LP4BL)	61	-0.221	0.193	0.92	0.282	**<0.05**	>0.05	0.207
LP3MD x LM1MD	WC(LM1MD)	52	-0.168	0.212	0.858	0.248	**<0.05**	>0.05	0.240
LP3MD x LM1BL(K)	WC(LM1BL)	117	-1	nc	0.747	0.238	**<0.05**	>0.05	0.245
LP3MD x LM2MD		43	0.153	0.177	0.545	0.285	>0.05	>0.05	0.291
LP3MD x LM2BL		118	-0.168	0.384	0.723	0.254	**<0.05**	>0.05	0.296
LP3BL x LP4MD	WC	33	0.23	0.23	0.144	0.304	>0.05	>0.05	0.142
LP3BL x LP4BL	WC	61	-0.141	0.295	1	nc	**<0.05**	nc	0.606
LP3BL x LM1MD	WC	52	-0.129	0.294	0.605	0.151	**<0.05**	**<0.05**	0.327

LP3BL x LM1BL(K)	WC	117	-0.581	0.474	0.74	0.14	<**0.05**	<**0.05**	0.472
LP3BL x LM2MD	WC(LP3BL)	43	-0.124	0.291	0.425	0.177	<**0.05**	<**0.05**	0.221
LP3BL x LM2BL	WC(LP3BL)	119	-0.631	0.59	0.742	0.083	<**0.05**	<**0.05**	0.519
LP4MD x LP4BL	WC	41	-0.158	0.167	0.725	0.437	>0.05	>0.05	0.105
LP4MD x LM1MD	WC	35	0.05	0.2	0.702	0.353	>0.05	>0.05	0.250
LP4MD x LM1BL(K)	WC	78	-0.857	1.246	0.949	0.478	<**0.05**	>0.05	0.216
LP4MD x LM2MD	WC(LP4MD)	29	0.301	0.186	0.167	0.42	>0.05	>0.05	0.249
LP4MD x LM2BL	WC(LP4MD)	79	-0.105	0.382	0.574	0.405	>0.05	>0.05	0.183
LP4BL x LM1MD	WC	81	0.183	0.187	0.527	0.201	<**0.05**	<**0.05**	0.345
LP4BL x LM1BL(K)	WC	182	-0.503	0.753	0.932	0.102	<**0.05**	>0.05	0.542
LP4BL x LM2MD	WC(LP4BL)	67	-0.042	0.22	0.444	0.221	>0.05	<**0.05**	0.197
LP4BL x LM2BL	WC(LP4BL)	185	-0.431	0.67	0.784	0.098	<**0.05**	<**0.05**	0.469
LM1MD x LM1BL(K)	WC	147	-0.977	1.829	0.826	0.161	<**0.05**	>0.05	0.404
LM1MD x LM2MD	WC(LM1MD)	54	-0.183	0.249	1	nc	<**0.05**	nc	0.380
LM1MD x LM2BL	WC(LM1MD)	149	-1	nc	0.813	0.146	<**0.05**	>0.05	0.307
LM1BL(K) x LM2MD	WC (LM1BL)	21	0.432	0.811	0.374	0.18	>0.05	<**0.05**	0.306
LM1BL(K) x LM2BL	WC(LM1BL)	55	-1	nc	0.818	0.074	<**0.05**	<**0.05**	0.606
LM2MD x LM2BL		104	-0.084	0.444	0.454	0.189	<**0.05**	<**0.05**	0.266
UCarea x UP2area	WC	176	-0.156	0.492	0.738	0.089	<**0.001**	<**0.001**	0.506
UCarea x UP3area	WC, Sex(UP3area)	162	-1	nc	0.748	0.084	<**0.001**	<**0.05**	0.492
UCarea x UP4area	WC	180	0.061	0.487	0.582	0.116	<**0.001**	<**0.001**	0.444
UCarea x UM1area	WC	319	-0.611	0.907	0.546	0.101	<**0.001**	<**0.001**	0.450
UCarea x UM2area	WC	216	-1	nc	0.611	0.09	<**0.001**	<**0.001**	0.410
UP2area x UP3area	WC, Sex(UP3area)	77	0.196	0.168	1	nc	<**0.001**	nc	0.635
UP2area x UP4area	WC	86	0.067	0.17	1	nc	<**0.001**	nc	0.592
UP2area x UM1area	WC	152	-0.214	0.43	0.743	0.098	<**0.001**	<**0.001**	0.493
UP2area x UM2area	WC	103	-0.732	0.342	0.895	0.096	<**0.001**	>0.05	0.404
UP3area x UP4area	WC, Sex(UP3area)	79	0.071	0.196	1	nc	<**0.001**	nc	0.623

UP3area x UM1area	WC, Sex(UP3area)	140	-0.563	0.499	0.903	0.086	<**0.001**	>0.05	0.528
UP3area x UM2area	WC, Sex(UP3area)	95	-0.368	0.304	0.779	0.111	<**0.001**	<**0.05**	0.421
UP4area x UM1area	WC	155	-0.517	0.457	0.906	0.064	<**0.001**	>0.05	0.583
UP4area x UM2area	WC	105	-0.711	0.675	0.801	0.081	<**0.001**	<**0.05**	0.501
UM1area x UM2area	WC	186	-1	nc	0.768	0.075	<**0.001**	<**0.001**	0.551
LCarea X LP2area		115	0.02	0.251	0.766	0.146	<**0.001**	<**0.05**	0.491
LCarea x LP3area	WC(LP3area)	145	-0.304	0.332	0.918	0.086	<**0.001**	>0.05	0.576
LCarea x LP4area	WC(LP4area)	99	-0.124	0.27	0.896	0.15	<**0.001**	>0.05	0.478
LCarea x LM1area	WC(LM1area)	129	-0.409	0.347	0.636	0.136	<**0.001**	<**0.05**	0.362
LCarea x LM2area		133	-0.377	0.385	0.653	0.119	<**0.001**	<**0.001**	0.415
LP2area x LP3area	WC(LP3area)	87	0.039	0.218	0.919	0.111	<**0.001**	>0.05	0.569
LP2area x LP4area	WC(LP4area)	60	-0.139	0.196	1	nc	<**0.001**	nc	0.468
LP2area x LM1area	WC(LM1area)	77	-0.244	0.291	0.899	0.138	<**0.001**	>0.05	0.488
LP 2area x LM2area		80	-0.281	0.246	0.879	0.18	<**0.001**	>0.05	0.400
LP3area x LP4area	WC	75	0.172	0.194	0.945	0.149	<**0.001**	>0.05	0.565
LP3area x LM1area	WC	97	-0.249	0.349	0.835	0.103	<**0.001**	<**0.05**	0.516
LP3area x LM2area	WC(LP3area)	100	0.036	0.264	0.734	0.111	<**0.001**	<**0.05**	0.513
LP4area x LM1area	WC	66	-0.086	0.329	0.847	0.125	<**0.001**	>0.05	0.517
LP4area x LM2area	WC(LP4area)	69	0.12	0.268	0.658	0.146	<**0.001**	<**0.05**	0.454
LM1area x LM2area	WC(LM1area)	89	-0.846	0.937	0.874	0.087	<**0.001**	>0.05	0.562
UCarea x LCarea	WC(UCarea)	267	-0.845	1.386	0.839	0.052	<**0.001**	<**0.001**	0.671
UCarea x LP2area	WC(UCarea)	160	-0.701	0.744	0.649	0.138	<**0.001**	<**0.05**	0.368
UCarea x LP3area	WC	201	-1	nc	0.732	0.094	<**0.001**	<**0.05**	0.441
UCarea x LP4area	WC	138	-0.402	0.747	0.617	0.126	<**0.001**	<**0.05**	0.380
UCarea x LM1area	WC	178	-1	nc	0.696	0.109	<**0.001**	<**0.05**	0.408
UCarea x LM2area	WC(UCarea)	185	-0.653	1.561	0.523	0.1	<**0.001**	<**0.001**	0.413
UP2area x LCarea	WC(UP2area)	127	-0.298	0.273	0.953	0.082	<**0.001**	>0.05	0.517
UP2area x LP2area	WC(UP2area)	76	0.064	0.191	0.839	0.108	<**0.001**	>0.05	0.507

UP2area x LP3area	WC	96	0.116	0.183	0.955	0.099	<**0.001**	>0.05	0.577
UP2area x LP4area	WC	66	0.302	0.154	0.802	0.224	<**0.001**	>0.05	0.509
UP2area x LM1area	WC	85	-0.257	0.277	0.733	0.129	<**0.001**	<**0.05**	0.372
UP2area x LM2area	WC(UP2area)	88	-0.09	0.296	0.644	0.135	<**0.001**	<**0.05**	0.385
UP3area x LCarea	Sex(UP3area) WC(UP3area)	117	-0.365	0.338	0.881	0.103	<**0.001**	>0.05	0.482
UP3area x LP2area	Sex(UP3area) WC(UP3area)	70	0.124	0.195	0.655	0.172	<**0.001**	<**0.05**	0.414
UP3area x LP3area	WC Sex(UP3area)	88	0.09	0.215	0.778	0.154	<**0.001**	>0.05	0.492
UP3area x LP4area	WC Sex(UP3area)	61	-0.174	0.224	0.883	0.155	<**0.001**	>0.05	0.399
UP3area x LM1area	WC Sex(UP3area)	78	-0.459	0.395	0.854	0.102	>**0.001**	>0.05	0.478
UP3area x LM2area	Sex(UP3area) WC(UP3area)	81	0.228	0.251	0.511	0.139	<**0.05**	<**0.001**	0.412
UP4area x LCarea	WC(UP4area)	130	-0.056	0.266	0.801	0.116	>**0.001**	<**0.05**	0.510
UP4area x LP2area	WC(UP4area)	78	0.097	0.207	0.606	0.167	<**0.05**	<**0.05**	0.391
UP4area x LP3area	WC	98	0.11	0.229	0.759	0.11	<**0.001**	<**0.05**	0.534
UP4area x LP4area	WC	67	0.019	0.191	0.864	0.168	<**0.001**	>0.05	0.463
UP4area x LM1area	WC	87	-0.348	0.31	0.819	0.108	<**0.001**	<**0.05**	0.461
UP4area x LM2area	WC(UP4area)	90	0.427	0.213	0.493	0.127	<**0.05**	<**0.001**	0.469
UM1area x LCarea	WC(UM1area)	231	-0.658	0.439	0.683	0.104	<**0.001**	<**0.001**	0.436
UM1area x LP2area	WC(UM1area)	138	-0.384	0.367	0.733	0.141	<**0.001**	<**0.05**	0.416
UM1area x LP3area	WC	173	-0.501	0.569	0.729	0.095	<**0.001**	<**0.001**	0.489
UM1area x LP4area	WC	119	-0.172	0.393	0.685	0.135	<**0.001**	<**0.05**	0.419
UM1area x LM1area	WC	154	-1	nc	0.825	0.085	<**0.001**	<**0.05**	0.521
UM1area x LM2area	WC(UM1area)	159	0.114	0.589	0.583	0.112	<**0.001**	<**0.001**	0.504
UM2area x LCarea	WC(UM2area)	156	-0.933	0.479	0.796	0.1	<**0.001**	<**0.05**	0.413
UM2area x LP2area	WC(UM2area)	93	-1	nc	0.898	0.134	<**0.001**	>0.05	0.344
UM2area x LP3area	WC	117	-0.345	0.305	0.877	0.106	<**0.001**	>0.05	0.498
UM2area x LP4area	WC	80	-0.622	0.368	0.891	0.119	<**0.001**	>0.05	0.415
UM2area x LM1area	WC	104	-0.945	0.593	0.774	0.100	<**0.001**	<**0.05**	0.447
UM2area x LM2area	WC (UM2area)	108	-0.208	0.122	0.748	0.110	<**0.001**	<**0.05**	0.505

Table 9.2. Detailed results of bivariate genetic correlation estimation in *Macaca mulatta*. P-values below 0.05 are bolded. ρ_P estimates shown here are calculated in SOLAR during ρ_G estimation and differ from the ρ_P values described in Chapter 6.

Traits	Covariates	N_{eff}	ρ_E	SE ρ_E	ρ_G	SE ρ_G	P $\rho_G=0$	P $\rho_G=1$	ρ_P
UCMD x UCBL	Age(UCBL), Sex*Age(UCBL)	58	-0.783	1.288	0.429	0.167	**0.043**	**<0.001**	0.24
UCMD x LCMD(K)	Age(LCMD)	29	-0.111	0.608	0.615	0.189	**0.042**	**0.043**	0.376
UCMD x LCBL(K)	Age(LCBL)	24	0.412	0.288	0.708	0.261	0.052	0.216	0.485
UCMD x LP3MD	Age(LP3MD), Sex*Age(LP3MD)	23	0.375	0.307	0.254	0.380	0.506	0.141	0.268
UCMD x LP3BL		27	0.287	0.399	0.285	0.288	0.396	**0.015**	0.269
UCBL x LCMD(K)	Age, Sex*Age(UCBL)	32	-0.438	0.640	0.804	0.200	**0.005**	0.164	0.399
UCBL x LCBL(K)	Age, Sex*Age(UCBL)	20	0.546	0.294	0.453	0.318	0.269	0.093	0.461
UCBL x LP3MD	Age, Sex*Age	18	0.557	0.267	-0.001	0.481	0.997	0.166	0.286
UCBL x LP3BL	Age(UCBL), Sex*Age(UCBL)	26	0.093	0.426	0.633	0.237	0.062	**0.037**	0.401
LCMD(K) x LCBL(K)	Age	8	0.468	0.196	0.801	0.331	0.358	0.259	0.557
LCMD(K) x LP3MD	Age, Sex*Age(LP3MD)	16	0.198	0.229	0.631	0.330	0.175	0.148	0.343
LCMD(K) x LP3BL	Age(LCMD)	19	0.284	0.318	0.493	0.309	0.185	**0.045**	0.387
LCBL(K) x LP3MD	Age, Sex*Age(LP3MD)	16	0.039	0.25	1.000		**0.037**		0.356
LCBL(K) x LP3BL	Age(LCBL)	13	0.626	0.192	-0.289	0.685	0.627	0.231	0.346
LP3MD x LP3BL	Age(LP3MD), Sex*Age(LP3MD)	16	0.068	0.227	0.531	0.376	0.253	0.129	0.222
UI1MD x UI2MD		359	1.000		0.717	0.309	**0.016**	0.214	0.422
UI1MD x UCMD		790	1.000		0.518	0.124	**0.007**	**<0.001**	0.465
UI1MD x UP3MD	Sex*Age(UP3MD)	702	1.000		0.528	0.164	**0.011**	**<0.001**	0.421
UI1MD x UP4MD(K)			0.046		0.640		**0.010**	**<0.001**	0.431
UI1MD x UM1MD	Age(UM1MD)	74	-1.000		0.584	0.275	**<0.001**	0.107	0.333
UI1MD x UM2MD		714	1.000		0.571	0.154	**0.003**	**0.002**	0.450
UI1MD x UM3MD	Age(UM3MD), Sex*Age(UM3MD)	151	-1.000		0.781	0.184	**<0.001**	0.108	0.401
UI2MD x UCMD		26	0.465	0.291	0.360	0.285	0.315	0.064	0.361

UI2MD x UP3MD	Sex*Age(UP3MD)	31	0.194	0.221	0.810	0.225	**0.009**	0.220	0.460
UI2MD x UP4MD(K)		24	0.247	0.199	0.553	0.277	0.103	0.062	0.371
UI2MD x UM1MD	Age(UM1MD)	22	0.291	0.342	0.345	0.340	0.346	0.070	0.289
UI2MD x UM2MD		32	0.178	0.237	0.664	0.218	**0.022**	0.072	0.409
UI2MD x UM3MD	Age(UM3MD), Sex*Age(UM3MD)	24	-0.093	0.270	0.743	0.341	**0.029**	0.244	0.268
UCMD x UP3MD	Sex*Age(UP3MD)	49	0.350	0.285	0.465	0.172	**0.031**	**<0.001**	0.414
UCMD x UP4MD(K)		40	0.397	0.301	0.295	0.228	0.278	**0.002**	0.313
UCMD x UM1MD	Age(UM1MD)	39	0.054	0.520	0.517	0.222	**0.026**	**0.018**	0.391
UCMD x UM2MD		53	0.364	0.334	0.516	0.166	**0.016**	**<0.001**	0.450
UCMD x UM3MD	Age(UM3MD), Sex*Age(UM3MD)	47	-0.058	0.482	0.477	0.194	**0.044**	**0.001**	0.302
UP3MD x UP4MD(K)	Sex*Age(UP3MD)	41	0.508	0.150	0.626	0.160	**0.018**	**0.003**	0.562
UP3MD x UM1MD	Age(UM1MD), Sex*Age(UP3MD)	42	0.173	0.308	0.532	0.170	**0.021**	**0.005**	0.396
UP3MD x UM2MD	Sex*Age(UP3MD)	49	0.476	0.171	0.543	0.161	**0.018**	**<0.001**	0.512
UP3MD x UM3MD	Age(UM3MD), Sex*Age	43	0.371	0.193	0.628	0.170	**0.009**	**0.007**	0.503
UP4MD(K) x UM1MD	Age(UM1MD)	29	0.366	0.258	0.630	0.172	**0.050**	**0.002**	0.507
UP4MD(K) x UM2MD		39	0.449	0.166	0.725	0.137	**0.008**	**0.012**	0.581
UP4MD(K) x UM3MD	Age(UM3MD), Sex*Age(UM3MD)	33	0.361	0.186	0.654	0.211	**0.017**	**0.049**	0.493
UM1MD x UM2MD	Age(UM1MD)	50	0.108	0.364	0.916	0.070	**<0.001**	0.087	0.650
UM1MD x UM3MD	Age, Sex*Age(UM3MD)	36	0.176	0.342	0.573	0.184	**0.027**	**0.004**	0.418
UM2MD x UM3MD	Age(UM3MD), Sex*Age(UM3MD)	41	0.492	0.167	0.749	0.131	**0.003**	**0.015**	0.624
UCBL x UP3BL	Age(UCBL), Sex*Age(UCBL)	43	0.476	0.389	0.331	0.190	0.163	**0.002**	0.369
UCBL x UP4BL	Age(UCBL), Sex*Age	46	0.323	0.300	0.288	0.194	0.187	**0.001**	0.299
UCBL x UM1BL(K)	Age(UCBL), Sex*Age(UCBL)	25	0.520	0.391	-0.091	0.365	0.798	0.072	0.168
UCBL x UM2BL	Age, Sex*Age(UCBL)	56	0.949	0.445	0.016	0.190	0.934	**<0.001**	0.246
UCBL x UM3BL(K)	Age, Sex*Age	72	-1.000		0.587	0.205	**<0.001**	**0.038**	0.242
UP3BL x UP4BL	Sex*Age(UP4BL)	66	0.520	0.210	0.903	0.055	**<0.001**	**0.029**	0.785
UP3BL x UM1BL(K)		36	0.242	0.283	0.991	0.207	**<0.001**	0.482	0.621
UP3BL x UM2BL	Age(UM2BL)	72	0.562	0.289	0.637	0.097	**<0.001**	**<0.001**	0.620
UP3BL x	Age(UM3BL),	187	-1.000		0.749	0.099	**<0.001**	**0.006**	0.532

UM3BL(K)	Sex*Age(UM3BL)								
UP4BL x UM1BL(K)	Sex*Age(UP4BL)	35	0.429	0.176	0.848	0.207	**0.005**	0.258	0.599
UP4BL x UM2BL	Age(UM2BL), Sex*Age(UP4BL)	76	0.568	0.215	0.677	0.096	**<0.001**	**<0.001**	0.628
UP4BL x UM3BL(K)	Age(UM3BL), Sex*Age	80	-0.604	0.993	0.775	0.115	**<0.001**	**0.021**	0.486
UM1BL(K) x UM2BL	Age(UM2BL)	37	0.627	0.171	0.797	0.129	**0.006**	0.128	0.654
UM1BL(K) x UM3BL(K)	Age(UM3BL), Sex*Age(UM3BL)	48	-0.330	1.138	0.786	0.154	**0.001**	0.119	0.463
UM2BL x UM3BL(K)	Age, Sex*Age(UM3BL)	218	-1.000		0.974	0.074	**<0.001**	0.361	0.683
LI2MD(K) x LCMD(K)	Age(LCMD)	20	0.128	0.388	0.508	0.293	0.144	0.064	0.345
LI2MD(K) x LP3MD	Age(LP3MD), Sex*Age(LP3MD)	20	0.079	0.268	0.494	0.373	0.224	0.141	0.232
LI2MD(K) x LM1MD(K)	Age(LM1MD)	18	0.339	0.322	0.355	0.296	0.340	**0.009**	0.347
LI2MD(K) x LM2MD		31	0.633	0.316	0.320	0.257	0.253	**0.004**	0.366
LI2MD(K) x LM3MD(K)		42	-0.357	1.047	0.411	0.238	0.089	**0.010**	0.244
LCMD(K) x LP3MD	Age, Sex*Age(LP3MD)	16	0.198	0.229	0.631	0.330	0.175	0.148	0.343
LCMD(K) x LM1MD(K)	Age	28	-0.648	0.845	0.763	0.190	**0.017**	0.098	0.340
LCMD(K) x LM2MD	Age(LCMD)	33	-0.539	0.425	0.989	0.193	**<0.001**	0.478	0.356
LCMD(K) x LM3MD(K)	Age(LCMD)	41	-0.949	3.014	0.525	0.197	**<0.001**	**0.027**	0.290
LP3MD x LM1MD(K)	Age, Sex*Age(LP3MD)	30	-0.446	0.343	1.000		**0.001**		0.243
LP3MD x LM2MD	Age(LP3MD), Sex*Age(LP3MD)	26	0.013	0.210	0.895	0.287	**0.012**	0.366	0.334
LP3MD x LM3MD(K)	Age(LP3MD), Sex*Age(LP3MD)	19	0.212	0.513	0.901	0.842	0.069	0.459	0.328
LM1MD(K) x LM2MD	Age(LM1MD)	49	-0.022	0.504	0.954	0.062	**<0.001**	0.217	0.671
LM1MD(K) x LM3MD(K)	Age(LM1MD)	53	1.000		0.374	0.173	0.078	**0.005**	0.453
LM2MD x LM3MD(K)		55	-0.158	0.815	0.828	0.132	**<0.001**	0.106	0.581
LCBL(K) x LP3BL	Age(LCBL)	13	0.626	0.192	-0.289	0.685	0.627	0.231	0.346
LCBL(K) x LP4BL(K)	Age(LCBL)	18	0.536	0.220	-0.065	0.441	0.880	0.075	0.324
LCBL(K) x LM1BL	Age(LCBL)	9	0.667	0.301	0.040	0.672	0.953	0.059	0.439
LCBL(K) x LM2BL(K)	Age	15	0.693	0.197	0.147	0.485	0.789	0.179	0.467
LCBL(K) x	Age	22	0.399	0.250	0.400	0.337	0.284	0.130	0.384

LM3BL									
LP3BL x LP4BL(K)		19	0.404	0.146	0.990	0.236	**0.021**	0.483	0.582
LP3BL x LM1BL		18	-0.051	0.805	0.736	0.271	0.067	0.133	0.434
LP3BL x LM2BL(K)	Age(LM2BL)	25	0.221	0.269	0.705	0.222	**0.042**	0.081	0.455
LP3BL x LM3BL	Age(LM3BL)	24	0.336	0.225	0.408	0.465	0.213	**0.033**	0.365
LP4BL(K) x LM1BL		18	0.927	0.204	0.164	0.390	0.700	**0.013**	0.554
LP4BL(K) x LM2BL(K)	Age(LM2BL)	25	0.314	0.187	0.856	0.205	**0.015**	0.236	0.521
LP4BL(K) x LM3BL	Age(LM3BL)	30	0.195	0.192	0.690	0.294	**0.037**	0.169	0.365
LM1BL x LM2BL(K)	Age(LM2BL)	23	0.118	0.601	0.931	0.094	**0.005**	0.224	0.673
LM1BL x LM3BL	Age(LM3BL)	23	0.095	0.459	0.839	0.160	**0.009**	0.175	0.535
LM2BL(K) x LM3BL	Age	32	0.518	0.130	1.000		**<0.001**		0.726