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Genetic correlations among dental, mandibular and post-cranial dimensions in rhesus macaques (*Macaca mulatta*):

Tooth and body size genetic correlations

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Abstract

Objectives: Tooth dimensions typically scale with mandibular and post-cranial size in primates, although the exact pattern of scaling varies. This study assesses whether correlations by tissue type, anatomical region, or function (mastication or intrasexual competition) are present and could therefore act as evolutionary constraints on tooth-jaw-body size relationships by estimating genetic and phenotypic correlations between dental, mandibular, and post-cranial dimensions in rhesus macaques (*Macaca mulatta*).

Materials and Methods: The teeth, mandibles, and post-crania of 362 adults from the Cayo Santiago skeletal collection were measured. Humeral and femoral articular surfaces were selected to represent skeletal elements frequently used to reconstruct primate body size. Genetic correlations were estimated in SOLAR. Random skewers analysis was used to compare genetic and phenotypic correlation matrices to each other and to test matrices.

Results: The genetic correlation matrix was most similar to the test matrix of integration by tissue type (tooth and bone) ($r = 0.765$, $p < 0.001$), and nearly as similar to the anatomical region test matrix ($r = 0.714$, $p < 0.001$). Hierarchical clustering of the genetic correlation matrix showed similar separation by tissue type. Phenotypic correlation matrices were significantly similar to the genetic correlation matrix ($r = 0.813$ - 0.846 , $p < 0.001$) and to most of the test matrices.

Conclusions: Post-canine dental traits were highly heritable but were not closely genetically correlated with mandibular or post-cranial dimensions. These findings indicate that scaling relationships between tooth and bone may be maintained in some populations through non-genetic, environmental factors rather than genetic constraints.

Keywords

Quantitative genetics; Dental; Skeletal; Masticatory apparatus; Tooth-body size

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Conflict of Interest: The author has no conflicts of interest to declare.

Ethical Statement: Data were collected for this study from the rhesus macaque skeletal collection at the Caribbean Primate Research Center (CPRC). This study did not involve any observations of or interactions with living animals. The University of Puerto Rico Medical Sciences Campus Institutional Animal Care and Use Committee (IACUC) reviews and monitors all CPRC animal research projects with added supervision from the CPRC Scientific Advisory Board, AAALAC, the Office of Laboratory Animal Welfare (OLAW), and the United States Department of Agriculture (USDA).

Introduction

Covariation is a central concept in the study of morphology and its evolution. When examined at higher taxonomic levels, patterns of covariation and deviations from them can indicate past selection pressures, phylogenetic inertia, and other evolutionary processes (e.g., Halliday & Goswami, 2013; Smaers et al., 2021). Within a population, patterns of covariation can demonstrate the genetic, developmental, and environmental factors (e.g., disease load, malnutrition, social stress) that generate and constrain phenotypes (e.g., Bermúdez de Castro et al., 2021; Guatelli-Steinberg et al., 2022). Analyses of covariation among serially homologous structures, such as teeth, can be especially informative for tracking developmental and genetic contributions to each iteration of the structure. In mammals, for example, the study of covariation among teeth has informed recent hypotheses about tooth formation and associated constraints on dental phenotypes (Evans et al., 2021; Kavanagh, Evans, & Jernvall, 2007; Selig, Khalid, & Silcox, 2021).

Quantitative genetic analyses provide a toolkit for decomposing covariation into its genetic and non-genetic components. This non-genetic component is typically referred to as *environmental*. In a quantitative genetic framework, the variance of a continuous phenotype in a population (phenotypic variance, σ^2_p) is the sum of the genetic variance (σ^2_G) and the environmental variance (σ^2_E) based on the assumption that the number of genetic loci impacting the trait approaches infinity (Falconer & MacKay, 1996). Thus, in the parlance of quantitative genetics, *genetic* variance comprises variation that can be accounted for by relatedness, and *environmental* variance comprises variation that cannot be accounted for by relatedness (Lynch & Walsh, 1998). These variance components can both be subdivided further. For example, σ^2_G has additive genetic, dominance, and epistatic components. The components of σ^2_E are less consistently defined, but many non-genetic factors such as nutrition, disease, injury, and other stresses may contribute to σ^2_E . Broad-sense heritability is the ratio of σ^2_G to σ^2_p , meaning that a population in which different individuals encounter different environmental impacts on a phenotype will typically have a lower heritability for those phenotypes than a population in which a phenotype is impacted by the environment in similar ways across all individuals (Falconer & MacKay, 1996).

Another quantitative genetic parameter, called genetic correlation, estimates the degree to which the same sets of genetic loci influence multiple traits within a population (Lynch & Walsh, 1998). Based on the Breeder's Equation (Lush, 1937), and multivariate extensions thereof (e.g., Lande, 1979; Schluter, 1996), heritability and genetic correlations determine how a trait will respond to direct selection and selection acting on other traits in the population. A higher heritability means a trait will have a greater response to direct selection, and a higher genetic correlation means a trait will have a greater correlated response to selection (Greenfield, 1996; Lande & Arnold, 1983). Genetic correlation is often linked with the concept of morphological integration, coined by Olson and Miller (1958), such that sets of positively genetically correlated traits are described as genetically integrated and genetically independent groups of positively genetically correlated traits are described as genetically modular (e.g., Duckworth & Kruuk, 2009; Hlusko, Sage, & Mahaney, 2011; Koh et al., 2010). Traits may also be organized in variational modules

(Wagner & Altenberg, 1996), meaning they vary together and independently of other such modules, with or without genetic modularity.

Quantitative genetic studies have indicated greater genetic correlations within than between tooth types in cercopithecoid primates (Hardin, 2020; Hlusko & Mahaney, 2009; Hlusko et al., 2011), though studies of humans and brown-mantled tamarins show a greater degree of genetic integration across tooth types (Hardin, 2019b; Hardin et al., 2022; Stojanowski, Paul, Seidel, Duncan, & Guatelli-Steinberg, 2018). Numerous additional studies have estimated genetic correlations in primate crania and mandibles, excluding tooth crown dimensions (Cheverud, 1996; Cheverud, 1995; Joganic et al., 2018; Roseman et al., 2010; Sherwood et al., 2008), and a few have used quantitative genetic methods to estimate genetic correlations between dental and non-dental traits in primates. One such study found that baboon molar crown areas and buccolingual widths, but not mesiodistal lengths, are significantly genetically correlated with trunk length (Hlusko, Lease, & Mahaney, 2006). Another found that human dental dimensions are more closely genetically correlated with dental arch lengths than widths (Hardin et al., 2022).

Although teeth and bones form through distinct cellular processes, dentin and bone are structurally similar and are both of mesenchymal origins. The jaws and dentin are both derived from neural crest ecto-mesenchyme (Svandova et al., 2020). Post-cranial bone is of mesodermal mesenchymal origins and may therefore be less closely embryologically linked with the teeth and bones of the face (Mizoguchi & Ono, 2021). Enamel, on the other hand, is of epithelial derivation, though there is significant epithelial-mesenchymal interaction that influences the teeth and jaws during tooth formation (Jussila & Thesleff, 2012; Miletich & Sharpe, 2004). Given the close association between dentin and enamel morphology (Morita, 2016; Morita et al., 2014) and interactions between tooth and bone tissues in development, dental and skeletal measurements, particularly of the mandible, could be expected to share positive environmental and genetic correlations. Dental tissues are thought to be buffered from environmental effects, including malnutrition and disease, but postnatal bone growth and development may be substantially impacted by these factors (Cardoso, 2007; though see Riga et al., 2014), and this could reduce phenotypic, but not genetic, correlations between these tissues. Although this study does not use quantitative genetic analysis to pinpoint the precise impact of any specific developmental process, one strength of these analyses is that developmental processes that produce similarities between related individuals are included in the genetic components of variance and covariance.

Skeletal and dental structures can also be more or less functionally integrated (Wagner & Altenberg, 1996). For example, elongated canine teeth can only function if the gape is adequately large (Fricano & Perry, 2019; Hylander, 2013), and gape depends upon the shape and dimensions of the mandibular condyle, ramus, and corpus (Terhune, Hylander, Vinyard, & Taylor, 2015). Phenotypic integration between canine height and mandibular dimensions would be expected to maintain canine functionality. Modular pleiotropy, a pattern of strong genetic integration among functionally integrated structures, can arise in these conditions. This study hypothesizes that traits related to mastication (post-canine tooth dimensions and mandibular dimensions) and traits related to sexual competition (canine-premolar honing complex dimensions and long bone dimensions) are genetically

modular based on this theory. Alternative functional hypotheses, such as the modularity of traits related to mastication and locomotion, could be tested, but these specific postcranial measurements were initially collected for the purposes of estimating body size (Perry, Cooke, Runestad Connour, Burgess, & Ruff, 2018) and may not adequately reflect variation in locomotor traits. For this reason, a functional hypothesis related to overall body size in sexual competition is assessed here.

Metabolic constraints also impact relationships between skeletal and dental structures, as exemplified by the complex scaling relationships between tooth and body size observed across mammals. These relationships can vary based on the exact measurements collected (e.g., body mass or trunk length), the populations studied, and the taxonomic level of analysis (Copes & Schwartz, 2010; Gingerich, Smith, & Rosenberg, 1982). Tooth size, especially post-canine tooth area, typically scales positively with body size, to the extent that some have sought a universal scaling relationship between tooth and body size in mammals (Gould, 1975). Deviations from general scaling relationships can also indicate dietary specializations. In cercopithecoids, for example, different scaling relationships between body mass and post-canine tooth area distinguish folivorous colobines from frugivorous cercopithecines, although facial dimensions scale more consistently with post-canine tooth size across these groups (Scott, 2011). These findings indicate that tooth and body size are not so tightly linked as to prevent evolutionary change in the tooth-body size relationship in primates. However, the degree to which genetic constraints and selection pressures each maintain tooth-jaw-body size scaling relationships within and among primate species is still unclear. An additional aim of this study is to test the hypothesis that anatomical regions, in this case anterior dental, post-canine dental, mandibular, and post-cranial regions, represent independent variational or genetic modules in a primate population.

Hypotheses of tooth-body size and tooth-jaw size scaling are often tested across taxa, leaving a dearth of literature investigating relationships at smaller taxonomic scales. Such studies can inform understanding of microevolutionary processes that contribute to those larger macroevolutionary patterns. In this study, phenotypic and genetic correlations between dental, mandibular, and postcranial dimensions are estimated in a population of free-ranging rhesus macaques (*Macaca mulatta*). Patterns of phenotypic and genetic correlations are described and compared to test matrices to assess whether the traits in question are most strongly genetically and phenotypically correlated by tissue type, function or anatomical region.

Methods

Linear measurements were collected from 362 (179 males, 183 females) skeletonized adult rhesus macaques (*Macaca mulatta*) from the Cayo Santiago population, housed in the skeletal collection of the Caribbean National Primate Research Center at the University of Puerto Rico. A total of 39 measurements (Table 1), including 30 dental measurements and nine skeletal measurements, were collected with nib style Mitutoyo digital calipers (code no. 573-725). Measurements of the skeleton were based on published definitions and illustrations (Buikstra & Ubelaker, 1994) and dental measurements have been previously described (Hardin, 2019a). The geometric mean of four post-cranial measurements (antero-

posterior and medio-lateral dimensions of the distal humerus and distal femur) was calculated to serve as a composite measure of post-cranial body size.

The pedigree for this population includes 9,744 individuals. Of these, 144 are founders with no known dam or sire, 3,902 individuals have known sires and known dams, and 5,698 individuals have known dams but unknown sires. The pedigree has a maximum depth of 11 generations, and a median depth of three generations. A total of 5,698 dummy sires were created for individuals with known dams and unknown sires under the assumption that individuals with the same dam are half-siblings (Hardin, 2019a; Joganic et al., 2012; Konigsberg & Cheverud, 1992). The final pedigree used for analyses therefore contained 15,442 individuals. This pedigree is more complete than the one used in previously published quantitative genetic analyses of these data (Hardin, 2019a, 2020). Pedigree information is based primarily on behavioral observation of the Cayo Santiago rhesus macaque colony, for which maternity data have been collected since the early 1950s (Rawlins & Kessler, 1986), though some paternities have been determined through molecular genetic testing.

Measurement repeatability was assessed using three repeated measurements of ten individuals as the ratio of the repeated measure variance to the overall population variance, subtracted from one to serve as a percentage of overall variance accounted for by variation in measurements. Values over 90% are considered highly repeatable, and measurements with values below 90% should be interpreted with caution.

Genetic correlation estimation

Quantitative genetic analyses were performed using the software package SOLAR (Almasy & Blangero, 1998), a maximum likelihood-based variance decomposition approach designed for use with general pedigrees. Genetic correlation estimation assumes non-zero additive genetic variances for traits included in the bivariate analysis. To ensure this assumption was met, univariate analyses were carried out for all measurements to screen for statistically significant covariates and residual heritability (h^2). Each variable was first adjusted using an inverse Gaussian transformation to ensure multivariate normality. During univariate analysis, the “-screen” function in SOLAR was used to estimate the significance of sex, age, and the interaction of sex-by-age as covariates using likelihood ratio tests. Age was an important covariate to include due to the wide range in ages in the sample (from 3.53 to 31.44 years of age) and the potential for age to correlate with dental wear, which can impact dental dimensions (Hardin, 2019a). Age-by-sex interactions can also be important given the significant sex differences in dental morphology and therefore potential for sex differences in patterns of dental wear with age. Significant covariates ($p < 0.10$) were included in univariate models estimating h^2 .

Bivariate analyses were performed in SOLAR to estimate genetic correlations between pairs of variables with significant univariate h^2 estimates ($p < 0.05$). Covariates were included in bivariate analyses for traits for which the p-value was less than 0.10; 0.10 is the default alpha for covariate testing in the SOLAR software package. These bivariate analyses model

environmental and genetic correlations (ρ_E and ρ_G , respectively) as contributors to the phenotypic correlation (ρ_P), such that:

$$\rho_P = \rho_G(\sqrt{h_{xr}^2}\sqrt{h_{yr}^2}) + \rho_E(\sqrt{1-h_{xr}^2}\sqrt{1-h_{yr}^2})$$

where h_{xr}^2 is the residual heritability of trait x and h_{yr}^2 is the residual heritability of trait y (Almasy & Blangero, 1998).

Significance testing of ρ_G estimates was performed in SOLAR using likelihood ratio tests, comparing models in which ρ_G was estimated to models in which ρ_G was restricted to equal 0.00 or 1.00 (or -1.00 if ρ_G was negative). Each ρ_G estimate therefore has two p-values: one describing the probability that it is equal to 0.00 and another describing the probability that it is equal to ± 1.00 .

Phenotypic correlation estimation

Two methods were employed to estimate phenotypic correlation matrices. In both cases, only variables included in the final genetic correlation matrix were used (i.e., those with statistically significant h^2). In the first method, carried out in R version 4.2.2 (R Core Team, 2013), data were separated by sex and then residuals from a linear regression on age were estimated for all variables and all individuals. These age-corrected data were then used to estimate Pearson correlation coefficients for each pair of variables using the `cor()` function, including all individuals with data for both variables. This method was used to estimate separate phenotypic correlation matrices for males and females. In the second method, phenotypic correlation estimation was performed in SOLAR during bivariate genetic correlation estimation. Phenotypic correlations estimated in SOLAR exclude variance related to kinship and statistically significant covariates (sex, age, and sex-by-age interaction), and male and female data were used in their estimation. The resulting phenotypic correlation matrix therefore accounts for the non-independence of closely related individuals in this population of rhesus macaques.

Comparison of correlation matrices

Statistical comparison of the genetic, phenotypic, male phenotypic, and female phenotypic correlation matrices was performed using random skewers analyses (Cheverud, 1996) in the R package `phytools`, using 5000 simulations and the “unifcorrmat” method to reduce the risk of type I error (Revell, 2012). Random skewers analysis was selected to assess the similarity of correlation matrices (following Cheverud, 1996) because it is less conservative than other methods such as common principal components analysis (Cheverud & Marroig, 2007) and can be used to assess correlation and covariance matrices.

The four estimated matrices were also compared to test matrices using random skewers analyses with the same parameters (5000 simulations and “unifcorrmat” method). Test matrices were designed to assess hypotheses for correlation matrix structure and were structured as correlation matrices with entries of 0.00 or 1.00 off the diagonal and entries of 1.00 on the diagonal. The following hypotheses were tested (Figure 1):

- 1) Independence: A matrix of values of 0.00 with values of 1.00 on the diagonal (Figure 1A)
- 2) Integration: A matrix of 1.00s (Figure 1B)
- 3) Tissue type: A matrix with values of 1.00 on the diagonal, between dental traits and between skeletal traits, and values of 0.00 for any dental-skeletal trait correlations (Figure 1C)
- 4) Anatomical region: A matrix with values of 1.00 on the diagonal, between canine-premolar honing complex traits (C^1 , C_1 and P_3 dimensions), between post-canine traits (non- P_3 premolar and molar dimensions), between post-cranial traits, and between mandibular traits, and values of 0.00 for any across-region correlations (Figure 1D)

In addition, a functional text matrix was constructed to test the hypothesis that genetic and/or phenotypic correlations would be more positive between structures with shared primary functions. Two functions were selected, specifically to separate canine size and body size, which are hypothesized to be under sexual selection in most anthropoid primates, from those without hypothesized competitive function. Those traits hypothesized to be under sexual selection, referred to hereafter as competition-related traits, were dimensions of the canine-premolar honing complex and long bones (Galbany, Tung, Altmann, & Alberts, 2015; Leutenegger & Kelly, 1977; though see Blomquist & Turnquist, 2011; Kimock, Brent, Dubuc, & Higham, 2022; Kimock, Dubuc, Brent, & Higham, 2019). All remaining traits (mandibular dimensions and dental dimensions outside the canine-premolar honing complex) were deemed mastication-related traits. So the following hypothesis was tested:

- 5) Function: A matrix with values of 1.00 on the diagonal, values of 1.00 between competition-related traits and between mastication-related traits, and values of 0.00 for any competition-mastication trait correlations (Figure 1E).

Patterns of correlation were visualized and described using complete-linkage hierarchical clustering of correlation matrices with the R package corplot (Wei et al., 2021). Eigenvalues and eigenvectors of all matrices were estimated (following Rohlf, 2017) using the eigen function in R.

Results

Measurement reliabilities

Measurement repeatabilities ranged from 69.2% (P_4MD) to 99.9% (mandibular ramus depth) (Table 1), and repeatabilities for all but four measurements were greater than 90%. All measurements were retained for additional analyses to ensure that all regions of the tooth row were represented, but findings for low-repeatability measurements (P^3MD , P^4MD , P_4MD , and M^1BL) should be interpreted cautiously. The measurement data from this study are provided (Supplementary Table 4).

Heritability estimates

Univariate quantitative genetic parameter estimation in SOLAR produced residual heritability estimates (h^2_r) for all 40 traits (Table 1, Supplementary Table 1). Of the 40 traits, 26 had estimates significantly different from zero ($p < 0.05$). Estimates of h^2_r ranged from 0.00 (C^1 height, C_1 height) to 1.00 (P_4 height), with a mean value of 0.479. Sex was a significant ($p < 0.1$) covariate for all traits. Age was a significant covariate for 26 traits in total, and for 17 of the 26 traits with significant h^2_r . Sex-by-age was a significant covariate for 11 traits in total, and for 6 of the 26 traits with significant h^2_r . Variance accounted for by covariates ranged from 0.073 (P_4 breadth) to 0.697 (geometric mean of post-cranial measurements). Kurtosis values for these analyses ranged from 0.005 to 3.875.

By tissue type, h^2_r ranges and means were similar; for non-dental traits the mean h^2_r value was 0.455 (range: 0.111 – 0.859) and for dental traits the mean h^2_r value was 0.487 (range: 0.00-1.00). By function, masticatory traits had higher average h^2_r values; for competition-related traits the mean h^2_r value was 0.339 (range: 0.00-0.790) and for mastication-related traits the mean h^2_r value was 0.555 (range: 0.249-1.00). By anatomical region, post-canine traits had the greatest h^2_r values; for canine-premolar honing complex traits the mean h^2_r value was 0.322 (range 0.00-0.790), for post-cranial traits the mean h^2_r value was 0.369 (range: 0.111-0.636), for mandibular traits the mean h^2_r value was 0.541 (range: 0.274-0.859), and for post-canine traits the mean h^2_r value was 0.558 (range: 0.249-1.00). The fourteen traits with non-significant h^2_r were excluded from all following analyses.

Genetic and phenotypic correlation estimates

Bivariate quantitative genetic parameter estimation in SOLAR produced 325 genetic correlation estimates (ρ_g) for the 26 traits with significant h^2_r estimates. Estimates of ρ_g ranged from -0.404 to 1.00, with a mean of 0.418. Of the 325 ρ_g estimates, 49 values were significantly different from 0.00 and ± 1.00 , 68 values were significantly different from 0.00 but not from 1.00, and 183 values were significantly different from ± 1.00 but not from 0.00 (Supplementary Table 2). 25 values were not significantly different from 0.00 or ± 1.00 and were therefore inconclusive. No negative ρ_g estimates were significantly different from zero. Eight ρ_g estimates were equal to 1.00.

Pooled phenotypic correlations, estimated in SOLAR, ranged from -0.139 to 0.808 with a mean of 0.288. Male-specific phenotypic correlations, estimated in R, ranged from -0.138 to 0.858 with a mean of 0.333. Female-specific phenotypic correlations, also estimated in R, ranged from -0.219 to 0.797 with a mean of 0.264.

Matrix comparisons

Random skewers analyses of the estimated matrices found significant similarity among all four matrices ($p < 0.001$). The greatest r-value from these comparisons was between the male-specific phenotypic correlation matrix and the phenotypic correlation matrix estimated

in SOLAR ($r = 0.956$). The genetic correlation matrix had the greatest r -value with the male-specific phenotypic correlation matrix ($r = 0.846$) and the smallest r -value with the female-specific phenotypic correlation matrix ($r = 0.813$). Across all comparisons, r -values were greater between phenotypic correlation matrices than between genetic and phenotypic correlation matrices (Table 2). The estimated matrices were all more similar to each other, based on random skewers analyses, than they were to any of the test matrices.

Despite these similarities, not all of the estimated matrices were equally similar to the test matrices. Random skewers analyses between estimated matrices and test matrices yielded r -values ranging from 0.374 to 0.809 (Table 3). All four estimated matrices were significantly ($p < 0.05$) similar to the test matrices for integration (Figure 1B), tissue type (Figure 1C), and anatomical region (Figure 1D). Each estimated matrix was most similar to the tissue type test matrix, although the male-specific phenotypic correlation was nearly equally similar to the tissue type and anatomical region test matrices ($r = 0.809$ and 0.807 , respectively). All phenotypic correlation matrices were significantly similar to the function test matrix (Figure 1E), but the genetic correlations matrix was not. Only the female-specific phenotypic correlation matrix was significantly similar to the independence test matrix (Figure 1A; $r = 0.581$). Eigenvalues and eigenvectors for all nine matrices are also provided (Supplementary Table 3).

Hierarchical clustering

In all estimated correlation matrices except the phenotypic correlation matrix estimated in SOLAR, post-cranial and mandibular traits clustered together and separately from any dental traits (Figure 2). The order of dental trait clustering was slightly different for each of these matrices. Tooth mesiodistal lengths clustered separately from buccolingual breadths in the female- (Figure 2C) and male-specific (Figure 2D) phenotypic correlation matrices, with C_1 length somewhat separate. There was no clear organization to dental trait clustering in the genetic correlation matrix (Figure 2A). In the phenotypic correlation matrix estimated in SOLAR (Figure 2B), all molar mesio-distal lengths except M^3 length clustered with all post-cranial and mandibular traits, as did P_3 height.

Discussion

This study of genetic and phenotypic correlations among dental, mandibular, and post-cranial dimensions in rhesus macaques is focused on determining how anatomical region, function, and tissue type relate to patterns of genetic and phenotypic covariation. Heritability estimates ranged widely within tissue types and anatomical regions, but were greatest on average in post-canine dental dimensions. Most genetic correlation estimates were positive, and random skewers analyses supported the hypothesis of integration (Hypothesis 2) over the hypothesis of independence (Hypothesis 1) for genetic and phenotypic correlation matrices. Genetic and phenotypic correlation matrices were significantly similar to each other, and all correlation matrices were most similar to the test matrix organized by tissue type (Hypothesis 3), though the matrices were nearly as similar to the anatomical region test matrix (Hypothesis 4). Overall, there is evidence that the genetic and phenotypic correlation matrices are organized by both tissue type and anatomical region. Male- and

female-specific correlation matrices also differed in ways that could reflect environmental or genetic patterns contributing to sexual dimorphism. Together, these findings demonstrate low genetic covariation between tooth and bone, such that functional integration between the jaws and teeth might be maintained by forces other than genetic constraints. The findings also indicate that considerable morphological differences can be associated with subtle differences in correlation matrices (i.e., male and female rhesus macaques).

Heritabilities are moderately high in the mandible and post-canine dentition

Skeletal traits are generally expected to demonstrate greater environmental variance and therefore lower heritability than dental traits due to lifelong remodeling of bone (Raggatt & Partridge, 2010), yet heritabilities were not simply greater in dental traits than in skeletal traits in this study. Post-canine dental h^2 estimates were greatest on average (mean $h^2 = 0.56$), followed closely by mandibular skeletal h^2 estimates (mean $h^2 = 0.54$). Post-cranial skeletal h^2 estimates were lower on average (mean $h^2 = 0.37$) as were canine-premolar honing complex dental h^2 estimates (mean $h^2 = 0.32$). The low heritability of canine-premolar honing complex traits is partially explained by the inclusion of tooth crown heights, which tend to be more severely impacted by tooth wear than tooth breadths or lengths and had smaller sample sizes with inconclusive heritability estimates ($h^2 = 0$). Estimates of h^2 were higher for mandibular traits in this study than in a previous study of mandibular distances in baboons (Willmore, Roseman, Rogers, Cheverud, & Richtsmeier, 2009), but were similar to previously estimated heritabilities of craniofacial traits in baboons (Roseman et al., 2010). The greater h^2 of mandibular traits than post-cranial traits indicates that variation in mandibular dimensions is more strongly genetically influenced than is variation in non-mandibular skeletal measurements in this population. This trend may be unique to this population, but it could reflect a broader tendency in *Macaca*, papionins, or even cercopithecoids.

Stress, disease, and nutrition can all impact skeletal growth and remodeling to increase environmental variance and thereby reduce heritability in skeletal traits. The Cayo Santiago rhesus macaques are somewhat shielded from these sources of variance because of dietary provisioning, yet studies of linear enamel hypoplasia do indicate rank-related impacts on individuals' nutrition and stress in this population (Benderlioglu & Guatelli-Steinberg, 2019). The familial aspects of rank may bias heritability estimates (Bourret & Garant, 2017), though the sample includes multiple social groups and matrilineal lines that may help to offset that potential bias. Many individuals included in the sample for this study were also born prior to 1956 when consistent provisioning began on Cayo Santiago (Guatelli-Steinberg & Benderlioglu, 2006). It is therefore difficult to estimate the relative impacts of rank and provisioning on the heritability of dental and skeletal traits in this population. Studies of the same traits in closely related provisioned and non-provisioned pedigreed populations would be necessary to test the hypothesis that features of the masticatory apparatus are highly heritable even in a population with greater individual variation in dietary quality. Comparing heritabilities across populations is also fraught due to the potentially weighty impacts of unaccounted for genetic and non-genetic differences (Falconer & MacKay, 1996).

Genetic correlations are modular by tissue type and anatomical region

Genetic correlations were positive or near zero across most measurements, and genetic correlations tended to be greater within dental, mandibular, and post-cranial traits than across these trait categories (Figure 2). Previous studies have estimated genetic correlations between mandibular and craniofacial distances in baboons and humans (Joganic et al., 2018, 2012; Sherwood et al., 2008; Willmore et al., 2009), but have not estimated genetic correlations across dental, mandibular, and post-cranial traits. One study of a human population estimated genetic correlations across tooth areas and arch measurements and found strong positive genetic correlations between post-canine tooth areas and arch length (Hardin et al., 2022). In the present study, mandibular corpus length was highly genetically correlated with post-cranial dimensions and M² breadth, but the relationships between post-canine tooth sizes and mandibular corpus length were not as pronounced in this macaque population as in the aforementioned human study.

A study of genetic correlations between body size and molar size in baboons estimated statistically significant positive ρ_G estimates between body size and molar buccolingual breadths, but not between body size and molar mesiodistal lengths (Hlusko et al., 2006). That same pattern was not observed in this population of rhesus macaques. In fact, mesiodistal lengths clustered more closely with post-cranial dimensions than did buccolingual breadths based on hierarchical clustering. The only dental traits with statistically significant positive ρ_G estimates with post-cranial measurements were P₃ height, P₃ length, and M₃ length. The mean ρ_G between molar mesiodistal lengths and the post-cranial geometric mean was 0.309 (range: -0.108 – 0.509), slightly greater than the mean ρ_G of 0.305 (range: 0.109 – 0.421) for molar buccolingual breadths and the post-cranial geometric mean. A few important differences between this study and that of Hlusko et al. (2006) may explain these differences in the findings. Hlusko et al. (2006) had a larger sample of 630 baboons, used body mass and trunk length collected from living individuals, and screened body mass and trunk length as covariates during quantitative genetic analyses. This sample was smaller at 362 macaques and femoral and humeral joint dimensions served as measures of body size in the present study. Body size was also not included as a covariate in this study because this inclusion could potentially bias heritability and genetic correlation estimates by removing informative covariation. One challenge of comparisons across populations is that so few populations have the large sample sizes and pedigrees necessary for quantitative genetic parameter estimation, and those that do may differ in the availability of skeletal or morphological data. Hlusko et al. (2006) studied a population of living baboons and did not have access to skeletal data that are available from the Cayo Santiago macaques, but this study of the Cayo Santiago macaques likewise did not have access to body mass and trunk length data that can be gathered from a population of living individuals.

Genetic correlations were not especially high between post-cranial measurements and post-canine tooth dimensions. Dental traits are frequently used to estimate overall body size in fossil assemblages (Gingerich et al., 1982; Gould, 1975; Hopkins, 2018; Millien & Bovy, 2010), yet previous research has shown that covariation between tooth and body size is not especially strong within mammal populations (Copes & Schwartz, 2010). The weak

genetic correlations estimated here are consistent with the hypothesis that tooth-body size relationships are maintained through selection on metabolism and body scaling, rather than through pleiotropy. The dental traits most closely genetically correlated with post-cranial size (P^3 length, P_3 height, and M_3 length) are among those that complete eruption in the fifth year or later, though fourth premolars and canines are also late-erupting teeth in this population (Wang, Turnquist, & Kessler, 2016). Additional study of the quantitative genetics of developmental parameters would contribute to the understanding of relationships among these late-developing traits.

Random skewers analyses were used to compare the estimated genetic and phenotypic correlation matrices to five test matrices representing the following five hypotheses: 1) complete independence across all traits, 2) complete integration across all traits, 3) complete integration within tissue types (tooth and bone), 4) complete integration within anatomical regions (canine-premolar honing complex, post-canine, post-cranial, and mandibular), and 5) complete integration within functional groups (competition and mastication). The genetic correlation matrix and all three phenotypic correlation matrices were most similar to the tissue type test matrix (Hypothesis 3). The genetic correlation matrix was least similar to the test matrix reflecting complete independence (Hypothesis 1). These findings indicate that traits are genetically and phenotypically correlated in this population, especially within tissue types, but that genetic correlations cannot be assumed to maintain scaling relationships between tooth and bone. The weakly positive genetic and phenotypic correlations estimated here between dental and skeletal traits may be sufficient to maintain efficient mastication, and if they are not, that indicates that there may be a limit to the degree of genetic correlation that is possible between different tissue types, due either to the existing genetic and developmental pathways upon which they are founded or to potential evolutionary costs of their integration (e.g., Evans et al., 2017; Schluter, 1996; Wagner & Altenberg, 1996).

The genetic correlation matrix was very similar to all three phenotypic correlation matrices, providing support for the conjecture that phenotypic correlation matrices may serve as useful approximations of the genetic correlation matrix when it cannot be estimated (Cheverud, 1988). The similarities indicate that environmental effects are contributing to covariation in the same direction as genetic effects for most traits. There were, however, several important differences between the genetic and phenotypic correlation matrices, including instances of negative environmental correlations in traits with significantly positive genetic correlations. These negative environmental correlations were typically reducing highly positive genetic correlations, resulting in near-zero phenotypic correlations (e.g., C_1 length and M_1 length, M_3 length and M_3 breadth, geometric mean and corpus depth). Taking the correlation between the geometric mean of post-cranial measurements and mandibular corpus depth as an example, the results demonstrate pleiotropy between the two traits, indicating that some alleles that would increase post-cranial size would also increase mandibular corpus depth. The negative environmental correlation indicates that some combination of non-genetic effects that would increase post-cranial size would also decrease mandibular corpus depth. When negative environmental correlations occur (e.g., an experimental manipulation on one trait that could reduce its correlations with other traits), the phenotypic correlation matrix will be dissimilar to the genetic correlation matrix and substitution is not recommended.

Male and female phenotypic matrices are similar despite canine and body size dimorphism

The genetic correlation matrix was most similar to the male-specific phenotypic correlation matrix based on random skewers analyses. These two matrices also tended to have greater correlation estimates than the other estimated matrices. High phenotypic correlations do not necessarily indicate greater genetic correlations in males than in females, because greater environmental correlations could also increase phenotypic correlations. The differences in phenotypic correlations between males and females is likely due to differences in the overall degree of integration between the sexes, and not due to differences in the sample sizes since a similar number of males and females were included. Unfortunately, the sample size for this population is not yet sufficient to estimate sex-specific quantitative genetic parameters. The female phenotypic correlation matrix was very similar to the male phenotypic correlation matrix, but it was characterized by a greater degree of independence between dental mesio-distal lengths and bucco-lingual breadths.

Differences in male and female dental and skeletal development could contribute to sex differences in environmental and genetic correlations. Post-cranial epiphyses fuse earlier in females than in males (Cheverud, 1981; Turnquist & Kessler, 1989) and adult body mass is achieved at 5.5 to 6.5 years of age in females and at 6.77 to 7.78 years of age in males (Turcotte et al., 2022). Males reach a greater adult body size than females through both prolongation of growth and a faster growth rate for body mass (Turcotte et al., 2022). Male rhesus macaques experience more rapid growth of the craniofacial skeleton from 2 to 8 years of age, while females experience a longer period of growth from 8 to 15 years of age (Wang, Dechow, & Hens, 2007). Timing of dental eruption is generally similar in males and females although canines erupt later in males than females (Cheverud, 1981). These developmental differences likely contribute to sex-specific patterns of environmental correlations. Environmental conditions during a period of especially rapid growth (i.e., a sensitive developmental window; McPherson, 2022; Fawcett & Frankenhuis, 2015) in males could increase environmental correlations among traits actively growing during that spurt. Those same traits may be subject to a longer, more variable period of growth in females and would therefore exhibit weak or even negative environmental correlations. For example, an environmental stressor like a hurricane (e.g., Testard et al., 2024) during a sensitive developmental window for a male individual could reduce the growth of the mandible, long bones, and teeth and result in a positive phenotypic correlation among these traits even in the absence of a positive genetic correlation. A female experiencing the same stressor could exhibit reduced growth of the long bones alone, if growth of the teeth and mandible had ceased, and would therefore have lower phenotypic correlations across these traits than the male. Growth and development is also closely associated with evolutionary tradeoffs for males and females, leading to the evolution of sex-specific patterns of growth and development (Altmann & Alberts, 2005). These differences in growth could explain the overall greater correlations in the male phenotypic correlation matrix relative to the female correlation matrix.

The similarity between male and female phenotypic correlation matrices is potentially surprising given the substantial morphological differences between male and female rhesus macaques. It is possible that the phenotypic correlation matrices are more similar to each

other than are the underlying genetic correlation matrices. Sex differences in patterns of genetic correlation would indicate reduced between-sex genetic correlations. Most traits are assumed to have high between-sex genetic correlations because male and female genomes are almost identical (Poissant, Wilson, & Coltman, 2010). When between-sex genetic correlations are high, the same alleles contribute to the same traits in the same direction in males and females. In cases of sexually antagonistic selection, in which an allele is beneficial in one sex but detrimental in the other sex, sex-specific patterns of gene expression are expected to evolve. These patterns would reduce between-sex genetic correlations and allow traits to evolve somewhat independently in males and females (Lande, 1980). This has been observed in primary reproductive structures and fitness components, and between-sex genetic correlations tend to decrease as sexual dimorphism increases (Poissant et al., 2010). This is a potentially informative area of future study in this population as the skeletal collection and its pedigree grow.

Evolutionary implications

Investigations of scaling relationships between body and tooth size have demonstrated that individual variation within species and populations does not adhere closely to scaling relationships apparent at higher taxonomic levels (Copes & Schwartz, 2010). The results of this study illustrate how genetic correlations in a single species relate to those scaling relationships, first within dental traits and then between dental and post-cranial traits. The tendency for strong genetic correlations across dental, especially post-canine, measurements in this species is consistent with the identification of consistent molar proportion scaling relationships at many taxonomic levels (Bermúdez de Castro, Modesto-Mata, Martín-Francés, et al., 2021; Billet & Bardin, 2021; Halliday & Goswami, 2013). If these relationships are maintained genetically via pleiotropy, they are observable phenotypically at all taxonomic levels because very few individuals develop without the influence of this highly conserved genetic architecture.

On the other hand, there are weak genetic correlations between most dental measurements and most skeletal measurements despite the important functional and developmental relationships between the skeleton and dentition. Scaling relationships tend to be apparent at higher taxonomic levels in primates despite these low genetic correlations (Copes and Schwartz, 2010). Differences in the genetic expression of dental and non-dental tissues may preclude the establishment of close genetic correlations. Necessary functional relationships between dental and non-dental tissues would therefore be maintained primarily through selection rather than pleiotropy. This would be consistent with the tendency for body and tooth size to be closely correlated at higher taxonomic levels when individual variation is averaged out of the analyses. The individual variation that is possible because of lower genetic correlations between dental and skeletal tissues would also allow natural selection to act rapidly on tooth-body size relationships.

The weak genetic correlations between dental and skeletal traits may initially seem discouraging for those interested in estimating body size from dental remains, but phenotypic correlations between skeletal dimensions and molar lengths are quite high and the phenotype is typically the goal of body size estimation. These results do,

however, demonstrate the value of distinguishing between interspecific and intrapopulation relationships when estimating body size from dental dimensions, especially when examining small samples as is often the case for fossil primates.

Conclusions

This study compares phenotypic and genetic correlation matrices to assess patterns of integration by tissue type, anatomical region, and function in a population of rhesus macaques. The findings demonstrate a general pattern of genetic independence between dental and skeletal traits. The lack of genetic integration across these tissues indicates that selection may be maintaining phenotypic covariation, even in structures with close spatial and functional relationships such as the mandible and dentition. Future studies of tooth-jaw-body size relationships and their evolution should examine whether these traits are genetically independent in other populations, and work to account for patterns of genetic and phenotypic correlation and how they may evolve over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

The data that supports the findings of this study are available in the supplementary material of this article. These data were collected at the Caribbean Primate Research Center which is supported by grant number P40 OD012217 from the Office of Research Infrastructure Programs (ORIP) of the National Institutes of Health.

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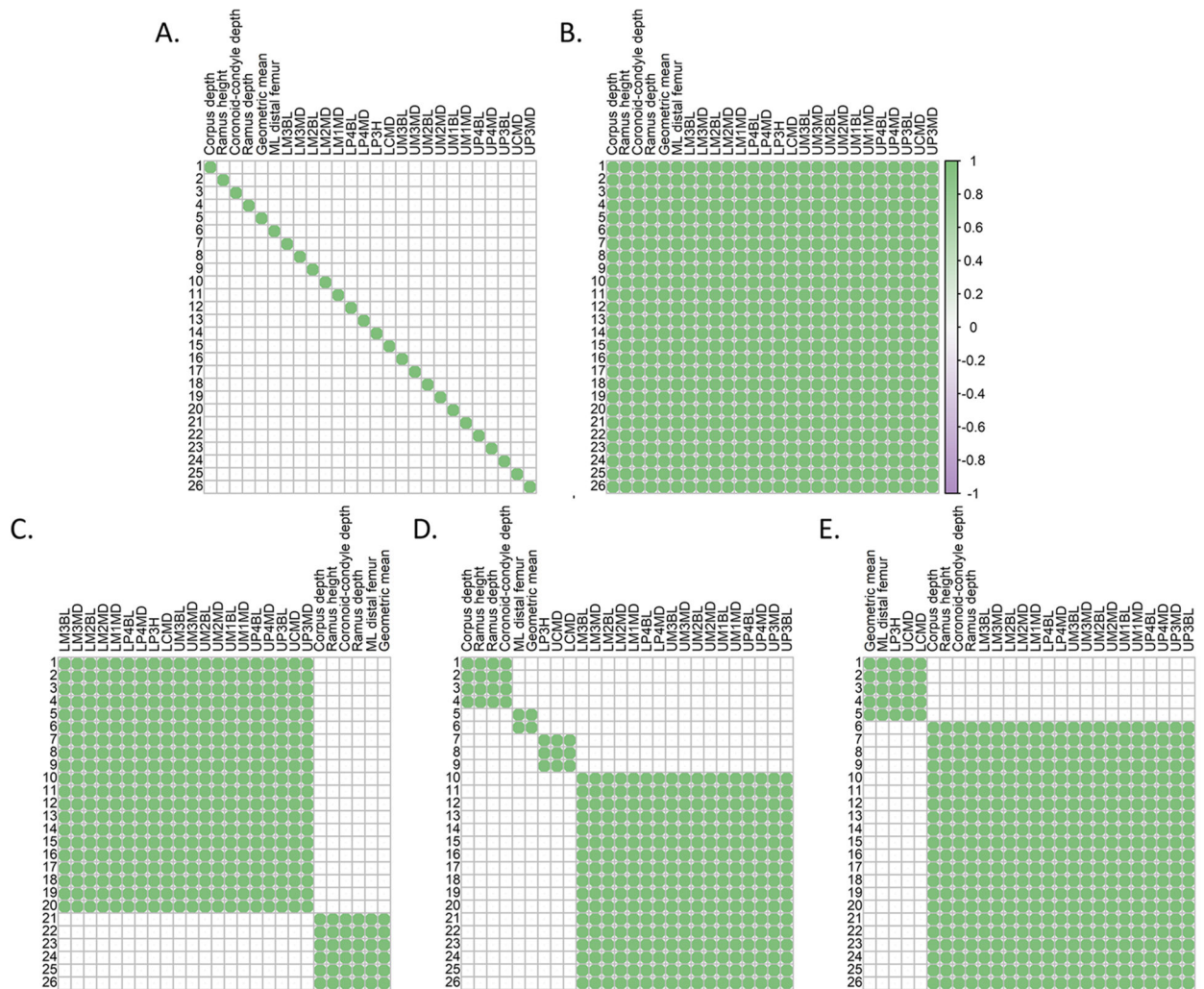


Figure 1. Structure of test matrices used in random skewers analyses. A) Independence hypothesis, B) Integration hypothesis, C) Tissue type hypothesis, D) Anatomical region hypothesis, E) Function hypothesis.

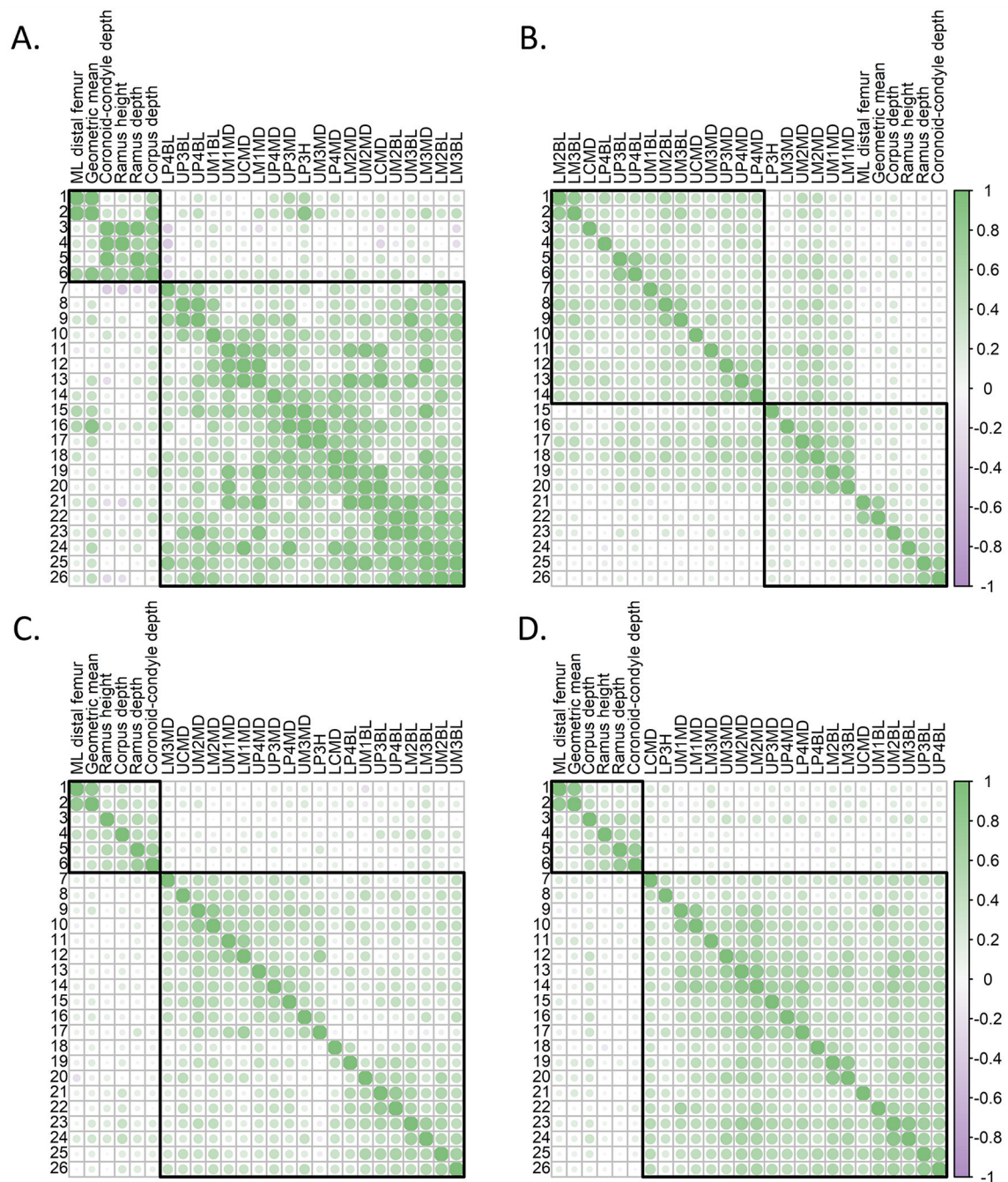


Figure 2.

Hierarchical clustering of the genetic correlation matrix (A), phenotypic correlation matrix estimated in SOLAR (B), female-specific phenotypic correlation matrix (C), male-specific phenotypic correlation matrix (D) demonstrates greater overall genetic correlations but similarities across the genetic and sex-specific phenotypic correlation matrices.

Table 1.

Measurements with descriptions, measurement reliability percentages, and significance of univariate estimates of heritability (h^2 , $p < 0.05$) and covariates ($p < 0.10$): sex (S), age (A), and sex-by-age interaction (S*A).

	Measurement	Description	Reliability	h^2	$p < 0.10$		
					S	A	S*A
Dental	C ¹ H	Maxillary canine height	99.70%		X		X
	C ¹ MD	Maxillary canine maximum length	96.50%	X	X		
	C ¹ BL	Maxillary canine breadth, perpendicular to C ¹ MD	98.80%		X	X	X
	P ³ H	Maxillary third premolar height	94.00%		X		
	P ³ MD	Maxillary third premolar length	83.30%	X	X		X
	P ³ BL	Maxillary third premolar breadth	97.40%	X	X		
	P ⁴ H	Maxillary fourth premolar height	92.90%		X	X	
	P ⁴ MD	Maxillary fourth premolar length	84.80%	X	X		
	P ⁴ BL	Maxillary fourth premolar breadth	94.70%	X	X	X	X
	M ¹ MD	Maxillary first molar length	93.30%	X	X	X	
	M ¹ BL	Maxillary first molar breadth	88.30%	X	X		
	M ² MD	Maxillary second molar length	95.10%	X	X		
	M ² BL	Maxillary second molar breadth	91.10%	X	X	X	X
	M ³ MD	Maxillary third molar length	97.10%	X	X	X	X
	M ³ BL	Maxillary third molar breadth	97.00%	X	X	X	X
	C ₁ H	Mandibular canine height	99.80%		X	X	X
	C ₁ MD	Mandibular canine maximum length	96.90%	X	X	X	
	C ₁ BL	Mandibular canine breadth, perpendicular to C ₁ MD	99.40%		X	X	
	P ₃ H	Mandibular third premolar height	98.10%	X	X	X	
	P ₃ MD	Mandibular third premolar length	92.50%		X	X	X
	P ₃ BL	Mandibular third premolar breadth	95.50%		X		
	P ₄ H	Mandibular fourth premolar height	97.10%		X		
	P ₄ MD	Mandibular fourth premolar length	69.20%	X	X	X	X
	P ₄ BL	Mandibular fourth premolar breadth	90.90%	X	X		
	M ₁ MD	Mandibular first molar length	95.30%	X	X	X	
	M ₁ BL	Mandibular first molar breadth	93.50%		X		
	M ₂ MD	Mandibular second molar length	96.20%	X	X		
	M ₂ BL	Mandibular second molar breadth	90.50%	X	X	X	
	M ₃ MD	Mandibular third molar length	98.00%	X	X		
	M ₃ BL	Mandibular third molar breadth	94.20%	X	X	X	
Mandibular	Corpus height	Height of corpus at C ₁	99.60%		X	X	
	Ramus depth	Antero-posterior depth of ramus at occlusal plane	99.90%	X	X	X	

	Coronoid-condyle depth	Antero-posterior depth from condyle to coronoid process	99.30%	X	X	X	
	Ramus height	Height from gonial angle to condyle	98.20%	X	X	X	
	Corpus depth	Antero-posterior depth from gonial angle to inferior-most point of mandibular symphysis	98.40%	X	X	X	
Post-cranial	AP distal humerus	Antero-posterior dimension of humeral condyle	96.20%		X	X	
	ML distal humerus	Medio-lateral dimension of humeral condyle	99.00%		X	X	
	AP distal femur	Antero-posterior dimension of femoral condyle	95.80%		X	X	X
	ML distal femur	Medio-lateral dimension of femoral condyle	98.90%	X	X	X	
	Geometric mean	Geometric mean of four post-cranial measurements	-	X	X	X	

Table 2.

Results of random skewers analyses between age-corrected male-specific and female-specific phenotypic correlation matrices, age- and sex-corrected phenotypic correlation matrix estimated in SOLAR, and genetic correlation matrix. Parameters: nsim = 5000, method = unifcorrmat.

	Phenotypic SOLAR	Female-specific	Male-specific
Genetic	r = 0.819	r = 0.813	r = 0.846
	p < 0.001	p < 0.001	p < 0.001
Phenotypic SOLAR		r = 0.942	r = 0.956
		p < 0.001	p < 0.001
Female-specific			r = 0.909
			p < 0.001

Table 3.

Results of random skewers analyses between estimated matrices (age-corrected male and female phenotypic correlation matrices, age- and sex-corrected phenotypic correlation matrix, and genetic correlation matrix) and five test matrices. Bolded values are significantly similar ($p < 0.05$). Parameters: nsim = 5000, method = unifcorrmat.

Test matrix	Genetic	Phenotypic SOLAR	Female-specific	Male-specific
Independence (all zeroes)	$r = 0.374$	$r = 0.572$	$r = 0.581$	$r = 0.537$
	$p = 1.00$	$p = 0.074$	$p = 0.032$	$p = 0.413$
Integration (all ones)	$r = 0.614$	$r = 0.619$	$r = 0.603$	$r = 0.651$
	$p = 0.002$	$p < 0.001$	$p = 0.005$	$p < 0.001$
Tissue type (dental + bone)	$r = 0.765$	$r = 0.774$	$r = 0.733$	$r = 0.809$
	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Function (competition + mastication)	$r = 0.574$	$r = 0.632$	$r = 0.600$	$r = 0.664$
	$p = 0.065$	$p < 0.001$	$p = 0.006$	$p < 0.001$
Region (canine-premolar honing complex, postcanine, postcranial, mandibular)	$r = 0.714$	$r = 0.764$	$r = 0.710$	$r = 0.807$
	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$