Received: 2 March 2022 | Revised: 31 October 2022 | Accepted: 22 January 2024

DOI: 10.1002/ajpa.24908

RESEARCH ARTICLE

AMERICAN JOURNAL OF BIOLOGICAL ANTHROPOLOGY
The Official Journal of the American Association of Biological Anthropologists
WILEY

Sex and ancestry patterning of residual correlations in human dental development: Cooperative genetic interaction and phenotypic plasticity

Valerie Sgheiza

Department of Anthropology, University of Illinois at Urbana-Champaign, Urbana, USA

Correspondence
Valerie Sgheiza, Department of Anthropology, University of Illinois at Urbana-Champaign, Urbana, USA.
Email: sgheiza2@illinois.edu

Abstract

Objectives: Most research in human dental age estimation has focused on point estimates of age, and most research on dental development theories has focused on morphology or eruption. Correlations between developing teeth using ordinal staging have received less attention. The effect of demographic variables on these correlations is unknown. I tested the effect of reference sample demographic variables on the residual correlation matrix using the lens of cooperative genetic interaction (CGI).

Materials and Methods: The sample consisted of Moorrees et al., *Journal of Dental Research*, 1963, 42, 1490–1502, scores of left mandibular permanent teeth from panoramic radiographs of 880 London children 3–22.99 years of age stratified by year of age, sex, and Bangladeshi or European ancestry. A multivariate cumulative probit model was fit to each sex/ancestry group ($n = 220$), each sex or ancestry ($n = 440$), and all individuals ($n = 880$). Residual correlation matrices from nine reference sample configurations were compared using Bartlett's tests of between-sample difference matrices against the identity matrix, hierarchical cluster analysis, and dendrogram cophenetic correlations.

Results: Bartlett's test results were inconclusive. Cluster analysis showed clustering by tooth class, position within class, and developmental timing. Clustering patterns and dendrogram correlations showed similarity by sex but not ancestry.

Discussion: Expectations of CGI were supported for developmental staging. This supports using CGI as a model for explaining patterns of variation within the dentition. Sex was found to produce consistent patterns of dental correlations, whereas ancestry did not. Clustering by timing of development supports phenotypic plasticity in the dentition and suggests shared environment over genetic ancestry to explain population differences.

KEYWORDS
dental development, human variation, plasticity

---

1 | INTRODUCTION

Human variation in dental development is an active area of research in odontometrics, crown traits, and developmental staging (Liversidge, 2011; Stojanowski et al., 2017, 2019). There is limited information, however, regarding factors that influence variation in *correlations* between the developing teeth through the lens of developmental staging. Comparisons of dental covariation have primarily used odontometrics, morphology, and eruption data (Parner et al., 2002; Paul et al., 2020; Stojanowski et al., 2018). As a result, we do not know how sex and ancestry affect residual developmental correlations between teeth (correlations after accounting for the effect of chronological age). Knowledge of how human variation in demographic variables affects developmental timing in the dentition is crucial for understanding the process of dental development in humans. Here I address the effect of sample demography on developmental correlations by comparing correlation matrices constructed from distinct reference samples. I examine the effects of ancestry and sex on dental development by testing correlation matrix findings against expectations that follow from established models of dental development.

Three major models of dental development will be addressed here: field, clone, and cooperative genetic interaction (CGI). According to field theory, tooth classes develop from molecular signaling gradients in the jaw. Concentration thresholds of overlapping signaling gradients in the oral epithelium specify which tooth class should form in each location (Butler, 1939). For example, mutual antagonism between FGF8 and FGF9 with BMP4 defines the presumptive molar and incisor fields, respectively, and changes to these gradients through gene knockouts or addition of exogenous molecules disrupts development (Tucker & Sharpe, 2004).

Clone theory proposes that teeth within a class develop from successive divisions of an individual lineage of neural crest cells (Osborne, 1978). Grafting experiments have shown that transplanted neural crest cells will migrate to the location consistent with their transplant region, but form structures consistent with their pretransplant fate (Noden, 1983). This indicates that neural crest cells are to some extent prepatterned prior to migration. When the neural crest is ablated, local signaling gradients still form and pharyngeal arch formation occurs (Veitch et al., 1999). The field and clone processes are therefore independent from one another, although both are necessary for dental development.

Following these experimental findings, CGI incorporates elements of both field and clone theories. The fate of neural crest cell lineages is determined by homeobox gene patterning (Sharpe, 1995). According to CGI, morphology is also determined by local molecular signaling gradients, which further modify homeobox gene expression (Mitsiadis & Smith, 2006). All three factors—prepatterned neural crest cell lineages, homeobox genes, and local molecular signaling gradients—can be further influenced by epigenetic changes (Townsend et al., 2009, 2012). Many molecular and genetic mechanisms behind CGI have since been tested experimentally (Cobourne & Mitsiadis, 2006; Lan et al., 2014; Mitsiadis & Graf, 2009).

The effect of population affinity on point estimates of age has been assessed through validation research applying existing age estimation methods to global populations (Baghdadi & Pani, 2012; Chaillet et al., 2005; Jayaraman et al., 2013, 2018; Kırzıoğlu & Ceyhan, 2012; Kumaresan et al., 2016; Maia et al., 2010; Mani et al., 2008; Phillips & van Wyk Kotze, 2009; Prasad & Kala, 2019; Tunc & Koyuturk, 2008), but point-estimate-based methods generally do not require or produce a correlation matrix from the reference sample. The effect of population affinity on the correlation matrix is therefore unknown. Morphological correlations between teeth have been thoroughly studied through tooth crown odontometrics (Garn et al., 1966, 1967a, 1967b, 1968, 1981; Garn et al., 1965b; Hemphill, 2013, 2015; Stojanowski et al., 2017). Developmental relationships have also been explored, although this has primarily taken place through eruption studies and not ordinal staging (Brook et al., 2009; Garn et al., 1981; Garn et al., 1965; Garn et al., 1965a; Garn & Smith, 1980a, 1980b; Mihailidis et al., 2009; Parner et al., 2002; Woodroffe et al., 2010).

Existing models of dental development each produce a different set of expectations. Field theory predicts increasing variation in development with increasing distance in the jaw from the key tooth within a class (Butler, 1939). This is typically the most mesial (anterior) tooth in permanent classes. According to clone theory, teeth should be more similar within a class than between classes because all teeth within a class are derived from the same cell lineage (Osborne, 1978). According to CGI, since both genetic and epigenetic factors can influence dental development, there should be intergroup differences in dental development. In addition, expectations from both field and clone theory apply under CGI (Mitsiadis & Smith, 2006). Many of these expectations have been met using crown metrics and field theory (Liversidge & Molleson, 1999; Moorrees & Reed, 1964; Stojanowski et al., 2017), tooth morphology and field theory (Stojanowski et al., 2018, 2019), crown metrics and clone theory (Moorrees & Reed, 1964), eruption and clone theory (Parner et al., 2002), and crown metrics and CGI (Brook et al., 2009, 2014).

The purpose of this research is to characterize the magnitude of variability of residual correlations in developmental stages between developing teeth and the axes along which this is expressed. Increasing sample heterogeneity should increase correlations between teeth due to increasing interindividual variation in development that is not accounted for chronological age. This suggests the following set of hypotheses:

> H_{1o}: increased demographic heterogeneity will have no effect on correlations between teeth.
>
> H_{1a}: increased demographic heterogeneity will increase correlations between teeth.
>
> H_{1b}: heterogeneity due to sex will have a larger effect than heterogeneity due to ancestry.

Theories of dental development suggest that teeth should cluster by position within class (field), by class (clone), or both. Furthermore, groups that are more demographically similar should produce more similar tooth clustering patterns (CGI). This translates to the following set of hypotheses:

H_{2o}: clustering from correlation matrices will have no relationship to tooth class membership.

H_{2a}: teeth will cluster by position within class (Field).

H_{2b}: teeth will cluster by class membership (Clone).

H_{3o}: cluster patterns will have no relationship to demographic similarity.

H_{3a}: groups with more demographic variables in common will have more similar dendrograms (CGI).

H_{3b}: same-sex groups will have more similar dendrograms than same-ancestry groups (CGI).

By testing the effect of reference sample demographic composition on the correlation matrix, I address the question of how human variation is expressed in dental developmental correlations.

2 | MATERIALS AND METHODS

The data consist of Moorrees et al. (1963) scores of the left permanent mandibular dentition from 3334 panoramic dental radiographs. Images were taken during normal diagnosis and treatment at Barts and the London School of Medicine and Dentistry, Queen Mary College of London. All scoring was performed by Dr. Helen Liversidge (intraobserver weighted kappa $= 0.952$, $n = 30$ individuals for eight teeth). Missing data on the left side were filled with scores from the right. Scores were recorded on an ordinal scale of 0–15, where 0 denoted an additional crypt stage. Teeth below the cusp initiation stage (recorded as 2) were recorded as stage 1—crypt present if an empty crypt was visible and stage 0—crypt absent if no crypt was visible. The remaining stages numbered 2–15 were defined according to the original 14 stages described by Moorrees et al. (1963).

Criteria for inclusion in the dataset were a clean medical history aside from dental caries and associated oral pathologies. All analyses were conducted in R (R Core Team, 2019). A stratified random sample ($N = 880$) was drawn from the larger dataset using the *sample* function in the *data.table* package (Dowle et al., 2019). Sampling was stratified by sex, ancestry (Bangladeshi or European), and year of age (3–22.99 years) truncated to year. For example, an individual who was 5.68 years old would be in the 5-year-old category for sampling, however, their full decimal age would still be used for modeling. The initial 880-individual sample was repeated five times. Cases were from unique individuals within but not between these samples.

Within the full sample, each tooth was tested for fit to a cumulative probit model with age on a log scale using a Lagrange multiplier goodness of fit test (Bera et al., 1984; Johnson, 1996) and a cutoff *p*-value of 0.1. Univariate models for fit testing were derived using the *polr* function (*method*=*"probit"*) from the *MASS* package (Ripley et al., 2019). First, the tooth was tested for outliers using a second derivative test (Johnson, 1996) and up to 1% of the sample was removed. If the *p*-value of the fit test was below 0.1 after removing outliers, dental stages were collapsed until a fit was found. Outliers were returned to the sample and retested at each round of stage collapsing. See Konigsberg et al. (2016) for details of this stage collapsing procedure.

A total of nine sample structures were used in model fitting: the full sample ($N = 880$), each half of the sample divided by sex ($N = 440$ each), each half of the sample divided by ancestry ($N = 440$ each), and each quarter of the sample divided by both sex and ancestry ($N = 220$ each). Once a good fit was achieved for all eight teeth via stage collapsing in the full sample, a multivariate cumulative probit model was fit to all eight teeth in each of the full, half, and quarter samples using the *mvord* function (with measurement object setting *MMO2*) from the *mvord* package (Hirk et al., 2020) in R. Age was modeled on a log scale. This model is based on a multivariate normal distribution and produces the full residual correlation matrix for all eight teeth.

Each of the nine correlation matrices was averaged across the five runs by taking the Fisher transformation of the lower triangular of each matrix without the diagonal, averaging the Fisher *z*-scores, and then taking the inverse Fisher transformation to convert the *z*-scores back to correlation values. These averaged correlation matrices for each sample split were compared between sample splits by taking the difference between correlation matrices of different splitting levels (full, half, and quarter samples) and testing the difference matrix against the identity matrix using Bartlett's sphericity test from the *psych* package (Revelle, 2018). Negative eigenvalues were dropped, and the difference matrix recalculated to meet the positive semi-definite assumption. Each quarter-sample matrix was compared to its corresponding half-sample matrices (i.e. Bangladeshi girls to both all Bangladeshis and all girls) and each half-sample matrix was compared to the full-sample matrix.

Correlation matrices were further analyzed using eigen decomposition, dimensional reduction, and cluster analysis, following methods employed by Hemphill (2015). Cluster analysis provides a visual means of representing relationships between several developing teeth according to their residual correlations. A single residual correlation value provides information only about a pair of teeth and is interpreted as the degree of association between them after accounting for the effect of chronological age. A cluster of teeth indicates that all teeth in the cluster have related growth trajectories. For example, if M1, M2, and M3 were present in a single cluster, this would suggest that delayed or accelerated development of M1 would be associated with the same effect in both M2 and M3. Both spatial proximity along the arcade and temporal proximity in developmental timing are potential confounding factors, so these factors were controlled when comparing clustering patterns. Spatial proximity was defined as the number of teeth separating two teeth of interest. Temporal proximity was treated in three groups: early (incisors and M1), intermediate (canine, premolars, and M2), and late developing (M3).

Eigen decomposition was performed via the base R *eigen* function. At minimum, the first two eigenvalues were retained. For eigenvalues three through eight, the minimum eigenvalue for retention was 1, following the Kaiser–Guttman rule (Kaiser, 1960). None of the remaining eigenvalues met the minimum requirement, so two were

TABLE 1 Bartlett's test for significant difference from identity matrix for difference matrices.

Comparison	Chi-square	*p*-value	df	Mean
All*—Bd	48.7878	0.0088	28	0.0078
All*—Eur	41.7257	0.0460	28	−0.0237
All—M	15.6134	0.9712	28	−0.0185
All—F	21.7938	0.7907	28	−0.0165
Bd*—Bd_M	71.4860	<0.0001	28	−0.0701
Bd*—Bd_F	239.1237	<0.0001	28	−0.0893
Eur—Eur_M	38.2569	0.0936	28	0.0291
Eur—Eur_F	25.7554	0.5865	28	−0.0315
M*—Bd_M	53.4250	0.0026	28	−0.0453
M—Eur_M	29.2154	0.1089	28	0.0271
F—Bd_F	39.1051	0.0792	28	−0.0602
F—Eur_F	31.2845	0.3046	28	−0.0389

Abbreviations: Bd, Bangladeshi; Eur, European; F, female; M, male.
*Significant chi-square value (p < 0.05).

retained in all instances. The remaining vector loadings were used to compute a Euclidean distance matrix for cluster analysis. Optimal number of clusters was determined using ensemble methods from the *NbClust* package with Wards clustering (Charrad et al., 2014) (*NbClust* function with *method*=*"ward.D"*). A 1000-replicate bootstrapped dendrogram was computed using the previously identified optimal number of clusters with the *clusterboot* function (*method*=*"ward.D"* and *clustermethod*=*hclustCBI*) from the *fpc* package, which uses the Jaccard coefficient (Hennig & Imports, 2015). These final dendrograms were compared using cophenetic correlation coefficients via the *cor.dendlist* function (*method*=*"cophenetic"*) from the *dendextend* package (Galili, 2015; Sokal & Rohlf, 1962).

Cophenetic correlations were chosen because this measure of association compares dendrograms rather than the original correlation matrix or distance matrix (Sokal & Rohlf, 1962). Testing hypothesis 3 required considering similarities in dendrograms including their associated branching and clustering. Cophenetic correlation of dendrograms was, therefore, selected over matrix comparison methods such as Box's M test of covariance matrices, Bartlett's test of correlation matrices, or the Dow–Cheverud correlation of distance matrices (Bartlett, 1951; Box, 1949; Dow & Cheverud, 1985).

3 | RESULTS

3.1 | Tests of difference matrices (H_1)

Five Bartlett's tests of difference matrices had significant chi-square values (Table 1). One of the difference matrices had a positive mean (all individuals—all Bangladeshis). The remaining four had negative means (all individuals—all Europeans, all Bangladeshis—Bangladeshi females, all Bangladeshis—Bangladeshi males, and all males—Bangladeshi males). Three of these comparisons involved an increase in heterogeneity by ancestry between sample splits (all individuals—all Europeans, all individuals—all Bangladeshis, and all males—Bangladeshi males), whereas the remaining two comparisons involved an increase in heterogeneity by sex.

3.2 | Analysis of clustering patterns (H_2)

P3 and M1 clustered three times whereas P4 and M2 clustered seven times. This supports an effect of developmental timing in conjunction with field theory because while P3/M1 and P4/M2 are both in the first or second position in their classes respectively, P4 and M2 have more temporally overlapping development. This comparison controls for proximity (both pairs are one tooth apart) and clones. The canine clustered six times with M1 and three times with I2. This supports fields over proximity because while C is adjacent to I2 and two teeth apart from M1, C and M1 hold the first position in their respective classes while I2 holds the second. This comparison controls for timing (both I2 and M1 develop at similar times to each other relative to C) and clones (Figure 1).

P3 clustered three times with M1 and once with I2. P4 clustered seven times with M2 and three times with the canine. Both of these sets of comparisons support field theory while controlling for proximity, timing, and clones. All compared teeth are one tooth apart along the arcade and in separate clones. M1 and I2 develop at similar times to each other relative to P3 and M2, and C develops at similar times to each other relative to P4.

M1 and M2 clustered four times, M1 and M3 clustered three times, and M2 and M3 clustered two times. In contrast, P3 and P4 clustered eight times, and I1 and I2 clustered eight times. This supports an effect from timing in conjunction with clone theory while controlling for proximity (M1/M2 and M2/M3) and fields (M1/M2) (Figure 1).

M1 and M2 clustered four times while M1 and P4 clustered two times. This supports clone theory while controlling for proximity (adjacent teeth), timing (P4 and M2 develop at similar times), and fields (P4 and M2 are second position while M1 is first position). P3 and P4 clustered eight times while P3 and C clustered four times. This supports clones as having a stronger effect than fields while controlling for proximity and timing. P3 and P4 are in the same clone while P3 and C are in the same position. Both comparisons involve adjacent teeth that develop at similar times (Figure 1). M3 clustered five times with I1 and four times with I2. This does not conform with expectations from field theory, clone theory, anatomical proximity, or timing of development.

3.3 | Comparison of groupings (H_3)

Only dendrograms with nonoverlapping samples were considered in the analysis of dendrogram correlations. This was to ensure that observed similarities between dendrograms were due to similarities in development rather than resampling of the same

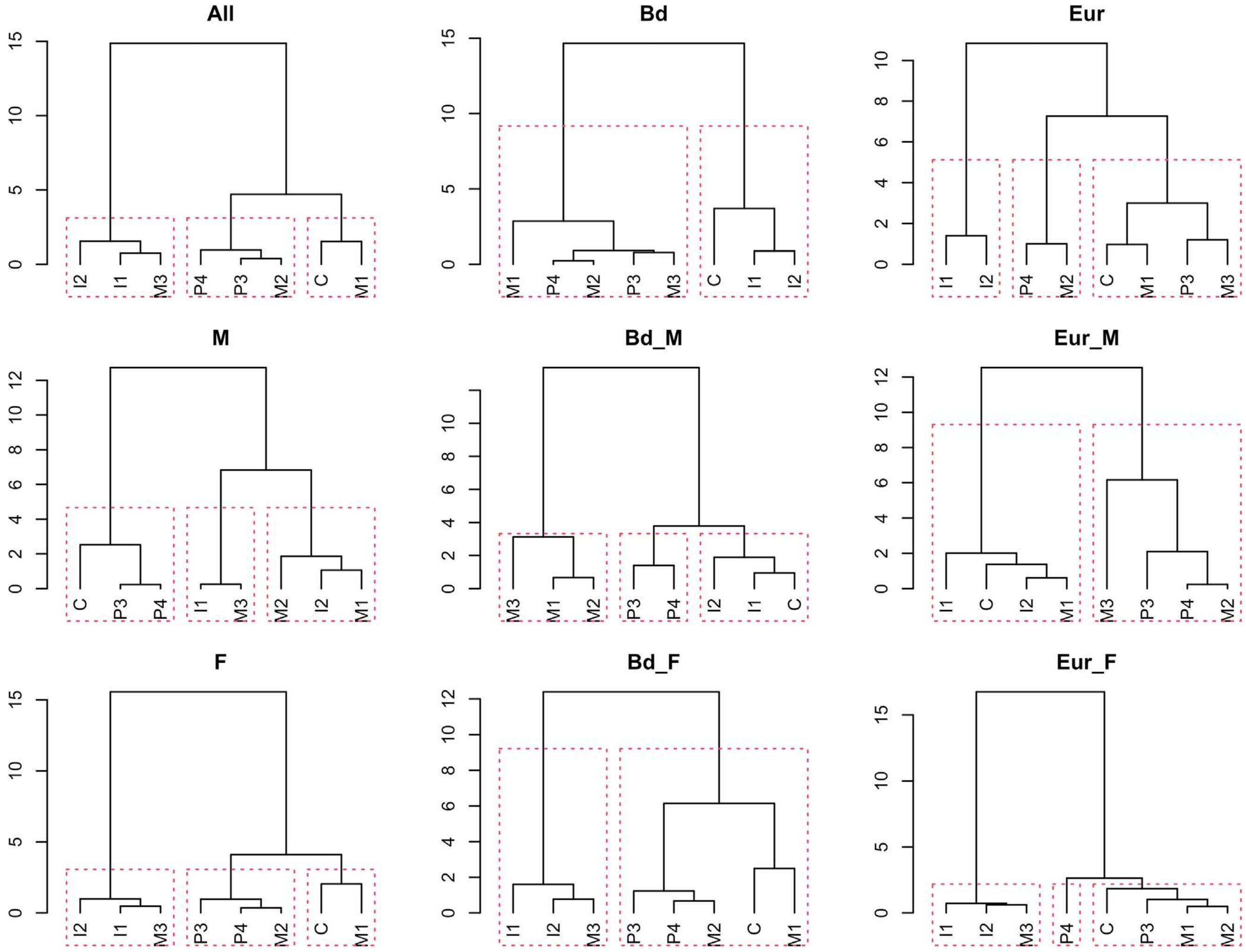

FIGURE 1 Bootstrapped dendrograms from cluster analysis of residual correlation matrices for all reference samples. Dashed boxes indicate optimized clusters.

TABLE 2 Dendrogram-combined sample sizes (upper triangular) and cophenetic correlations (lower triangular).

	All	Bd	Eur	M	F	Bd_M	Bd_F	Eur_M	Eur_F
All	1	1320	1320	1320	1320	1100	1100	1100	1100
Bd	0.1803	1	**880**	880	880	660	660	**660**	**660**
Eur	0.3877	**0.4326**	1	880	880	**660**	**660**	660	660
M	0.2228	−0.1699	−0.1629	1	**880**	660	**660**	660	**660**
F	0.9986	0.1777	0.3894	**0.2301**	1	**660**	660	**660**	660
Bd_M	−0.1434	0.1839	**−0.1164**	0.1523	**−0.1358**	1	**440**	**440**	**440**
Bd_F	0.9866	0.1957	**0.3685**	**0.2145**	0.9809	**−0.1540**	1	**440**	**440**
Eur_M	0.1061	**0.4499**	0.1841	−0.0746	**0.0799**	**−0.0160**	**0.1767**	1	**440**
Eur_F	0.9791	**0.1529**	0.3871	**0.2326**	0.9857	**−0.1179**	**0.9383**	**−0.0104**	1

Note: Values for comparisons with nonoverlapping samples are in bold.
Abbreviations: Bd, Bangladeshi; Eur, European; F, female; M, male.

individuals. Under this criterion, the most similar dendrograms by cophenetic correlation (branching pattern and branching length) were Bangladeshi females to European females (rho = 0.9383). The least similar were Bangladeshi males to Bangladeshi females (−0.154) and Bangladeshi males to all females (−0.1358) (Table 2).

Sex had a stronger effect on similarity than did ancestry. The correlation between both ancestry groups of mixed sex (0.4326) was larger than the correlation between both sex groups of mixed ancestry (0.2301). Three of the four quarter sample groups had higher correlations with all individuals of the other ancestry than with all individuals of the other sex. For three of the four quarter sample groups, the next most similar quarter sample group was that of the same sex, while none of the quarter sample groups were most similar to the quarter sample of the same ancestry. Three of the four quarter sample groups were least similar to a quarter sample of the other sex while two of the four were least similar to a quarter sample of the other ancestry. This supports H_{3b} and follows most expectations of CGI, although support for H_{3a} is mixed because ancestry had no consistent effect.

While reference sample demographic heterogeneity had an effect on residual correlations, this effect was not consistent in either direction or magnitude by sex versus ancestry. H_{1a} (increased correlations due to increased heterogeneity) was not supported. As a result, H_{1b} (larger effect from sex than ancestry) was also not supported. Teeth clustered by both class and position within class when controlling for timing of development and proximity along the arcade, supporting both H_{2a} (clustering by position) and H_{2b} (clustering by class). In dendrogram correlations, H_{3a} (more demographic variables in common leads to similar dendrograms) was supported for sex but not for ancestry, while H_{3b} was supported. Sex increased dendrogram correlations but ancestry did not.

4 | DISCUSSION

This paper presents an analysis of the effects of demographic heterogeneity on the residual developmental correlation matrix, providing a test of expectations of theories of dental development on dental staging data from a mixed-ancestry sample. Results largely conform to expectations of CGI, although sex had a larger effect than ancestry, which showed little to no effect. In addition, cluster analysis showed an effect from similar timing of development. These results are consistent with prior findings of odontometric, morphological, and eruption research, which follow expectations of CGI (Moorrees & Reed, 1964; Parner et al., 2002; Stojanowski et al., 2017, 2018).

Correlation matrix difference analysis showed significant but inconsistent effects from degree of reference sample heterogeneity by sex and ancestry. Hierarchical clustering proved more informative than whole-matrix comparison. Cluster analysis showed some support for both field (H_{2a}) and clone theories (H_{2b}), which is consistent with expectations of CGI. Dendrogram correlation results follow most expectations of CGI, other than increased correlations due to ancestry (H_{3a}). Cluster analysis showed that of the patterns of development that exist in the dentition, some are conserved across most reference samples while others are shared between some groups but not others. These patterns are obscured in whole-matrix comparison.

The expectations of CGI have been met in studies of crown morphology and eruption (Brook et al., 2009; Moorrees & Reed, 1964; Parner et al., 2002; Stojanowski et al., 2017, 2018). Here these expectations are also met for developmental stages. CGI is supported over field, clone, or homeobox explanations alone, because evidence supporting all of these components of CGI is observed. For example, teeth clustered by both class and position within class and showed moderate patterning by sex. Consistent differences in human dental development by sex are established in the literature for developmental timing (Demirjian & Levesque, 1980; Garn et al., 1958; Moorrees et al., 1963). Similar findings are reported here, with some clustering and branching patterns conserved by sex. This demonstrates that sex affects not just the raw chronological timing of development of individual teeth but also the patterns in which groups of teeth may cluster and develop as a unit. For example, the canine tended to cluster with anterior teeth in male quarter samples and posterior teeth in female quarter samples.

Ancestry findings are not consistent with the literature. Many studies of dental developmental age estimation report consistent differences in method performance by population affinity (Jayaraman et al., 2018; Kırzıoğlu & Ceyhan, 2012). Ancestry effects here were inconsistent or not observed. There are a few possible reasons for these observed differences. First, there are several studies of population affinity and dental development that find no significant effect (Braga et al., 2005; Liversidge, 2011; Thevissen et al., 2010). These studies share many structural similarities to this one, such as large samples, uniform age distributions, and reverse regression (stage regressed on age). It is therefore possible that some intergroup differences observed in other studies are in fact sampling or methodological effects (Corron et al., 2018; Rodriguez et al., 2021). Second, differences in developmental timing by ancestry were tested and not found in this particular dataset (Liversidge, 2011).

Third, most studies that find effects from population affinity are based on point estimates and do not produce a correlation matrix. This study examines the correlation matrix, but not developmental timing. It is possible that even if ancestry affects developmental timing, the residual correlations between teeth are conserved due to underlying biological processes such as those described by CGI. Finally, both ancestry groups were from the same geographic area (London). It is possible that population differences in dental developmental phenotypes are more driven by environment than by genetics.

Support for CGI is consistent with genetic control of dental development, however persistent effects of developmental timing were also observed. This supports phenotypic plasticity in dental development because teeth that are developing at the same time experience the same whole-organism environmental effects. Such plasticity would explain the lack of ancestry patterning since all individuals developed in the same geographic environment of East London. Evidence of phenotypic plasticity in developmental timing has been found previously for environmental factors such as socioeconomic status (Caldas & Cardoso, 2021; Cardoso, 2007; Carneiro et al., 2017). Plasticity also offers an explanation for the relationship between the third molar and the incisors. These teeth are distant spatially and temporally and do not belong to the same clone or share a class position. Their relationship suggests instead that factors that affect the development of the incisors may also have delayed effects on M3. Low birthweight, for example, is correlated with both delayed incisor development and third molar agenesis (Keene, 1971; Seow, 1997).

It is not possible for the results presented here to distinguish whether environmental effects shift developmental timing of several teeth, causing them to cluster together, or whether environment affects the relationships between teeth, causing them to develop along similar trajectories. Clarifying this cause and effect relationship would require more detailed knowledge of individual histories such as illness that was not available here.

The findings presented here are limited to a single dataset derived from a single geographic location; therefore, it is important to not overgeneralize these results to other contexts. Nevertheless, these results suggest that population effects may be more related to location-based factors rather than genetic ancestry. Correlations follow patterns predicted by established theories of dental development and are largely conserved across ancestry groups. This indicates that further studies of these correlations across additional groups should be undertaken. In particular, it would be useful to compare population model parameters from multiple geographic locations and of known socioeconomic status.

The findings are also limited to the left mandibular dentition. It would be worthwhile to examine whether the observed patterns are retained when the right side and maxillary dentition are included. Patterns of asymmetry of developmental stages between arcades are an additional means of approaching CGI through dental development, as has been studied for tooth morphology, dental metrics, and eruption (Garn et al., 1967a; Mihailidis et al., 2009; Paul et al., 2021). Furthermore, while anatomical proximity was controlled for in analyses, the construction of the dataset meant that it was not possible to address whether there was an effect from proximity. Filling of missing left side data with right side scores negated the meaning of any observed patterns related to anatomical proximity.

Meeting the expectations of CGI using developmental staging data confirms that this model is an effective representation of dental development, as found through other avenues such as morphology and eruption. It also implies that there are consistent, predictable relationships within the developing dentition that may be conserved across other axes of human variation, such as ancestry, for example the strong correlations between the incisors and between the premolars. These findings could be further expanded by examining model means and variances fit to the individual teeth.

Cluster analysis and dendrogram correlations have shown here that there are consistent differences in correlation patterns by sex. Cluster and branching patterns are typically more similar between samples of the same sex than between samples of the opposite sex, and dendrogram correlations are typically higher between same-sex samples. This demonstrates that teeth associate in sex-specific developmental patterns. It would be worthwhile to explore whether the patterns observed here are conserved across other axes of variation, such as geographic location. Temporal proximity of development also shows persistent effects, indicating that while dental development is controlled genetically, correlations are also responsive to environmental effects. Inconsistent effects or lack of effects from ancestry imply two possibilities. Broadly, genetic ancestry may not affect dental development. More conservatively, ancestry may affect developmental timing, but not residual correlations between teeth.

5 | CONCLUSIONS

In this analysis, it is shown that CGI is an appropriate model for dental development, including dental staging. Teeth cluster by both class and position and show strong patterning by sex. This supports the field, clone, and genetic components of CGI. Results suggest that the developmental residual correlation matrix may be robust to effects from ancestry. Ancestry had no consistent effect on either clustering patterns or dendrogram correlations. Cluster analysis supports phenotypic plasticity as a major factor in dental residual correlations, meaning that shared environment may be more important than genetic ancestry for explaining dental development.

AUTHOR CONTRIBUTIONS

Valerie Sgheiza: Conceptualization (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); software (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead).

ACKNOWLEDGMENTS

I am grateful to my advisor Lyle Konigsberg and committee members Cris Hughes, Laura Shackelford, and Kyra Stull for their advice and continued support of this project. I also thank Helen Liversidge for giving me access to her data and intra-observer error statistics.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study may be available from Helen Liversidge upon request at h.m.liversidge@qmul.ac.uk. Privacy and ethical restrictions apply to the availability of these data.

ORCID

Valerie Sgheiza https://orcid.org/0000-0002-9896-9252

REFERENCES

Baghdadi, Z. D., & Pani, S. C. (2012). Accuracy of population-specific Demirjian curves in the estimation of dental age of Saudi children. *International Journal of Paediatric Dentistry*, *22*(2), 125–131.

Bartlett, M. S. (1951). The effect of standardization on a χ^2 approximation in factor analysis. *Biometrika*, *38*(3/4), 337–344.

Bera, A. K., Jarque, C. M., & Lee, L.-F. (1984). Testing the normality assumption in limited dependent variable models. *International Economic Review*, *25*, 563–578.

Box, G. E. (1949). A general distribution theory for a class of likelihood criteria. *Biometrika*, *36*(3/4), 317–346.

Braga, J., Heuze, Y., Chabadel, O., Sonan, N. K., & Gueramy, A. (2005). Non-adult dental age assessment: Correspondence analysis and linear regression versus Bayesian predictions. *International Journal of Legal Medicine*, *119*(5), 260–274.

Brook, A. H., Griffin, R. C., Townsend, G., Levisianos, Y., Russell, J., & Smith, R. N. (2009). Variability and patterning in permanent tooth size of four human ethnic groups. *Archives of Oral Biology*, *54*, S79–S85.

Brook, A. H., Jernvall, J., Smith, R. N., Hughes, T. E., & Townsend, G. C. (2014). The dentition: The outcomes of morphogenesis leading to variations of tooth number, size and shape. *Australian Dental Journal*, *59*, 131–142.

Butler, P. M. (1939). Studies of the mammalian dentition—Differentiation of the post-canine dentition. *Proceedings of the Zoological Society of London*, *109*(1), 1–36.

Caldas, I. M., & Cardoso, H. F. (2021). Socioeconomic differences in permanent teeth mineralization of Portuguese girls and boys from Porto, Portugal. *Anthropologischer Anzeiger*, *78*, 267–277.

Cardoso, H. F. (2007). Environmental effects on skeletal versus dental development: Using a documented subadult skeletal sample to test a basic assumption in human osteological research. *American Journal of Physical Anthropology*, *132*(2), 223–233.

Carneiro, J. L., Caldas, I. M., Afonso, A., & Cardoso, H. F. V. (2017). Examining the socioeconomic effects on third molar maturation in a Portuguese sample of children, adolescents and young adults. *International Journal of Legal Medicine*, *131*(1), 235–242.

Chaillet, N., Nyström, M., & Demirjian, A. (2005). Comparison of dental maturity in children of different ethnic origins: International maturity curves for clinicians. *Journal of Forensic Science*, *50*(5), 1164–1174.

Charrad, M., Ghazzali, N., Boiteau, V., & Niknafs, A. (2014). NbClust: An R package for determining the relevant number of clusters in a data set. *Journal of Statistical Software*, *61*, 1–36.

Cobourne, M. T., & Mitsiadis, T. (2006). Neural crest cells and patterning of the mammalian dentition. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, *306*(3), 251–260.

Corron, L., Marchal, F., Condemi, S., & Adalian, P. (2018). A critical review of sub-adult age estimation in biological anthropology: Do methods comply with published recommendations? *Forensic Science International*, *288*, 328.e1–328.e9.

Demirjian, A., & Levesque, G.-Y. (1980). Sexual differences in dental development and prediction of emergence. *Journal of Dental Research*, *59*(7), 1110–1122.

Dow, M. M., & Cheverud, J. M. (1985). Comparison of distance matrices in studies of population structure and genetic microdifferentiation: Quadratic assignment. *American Journal of Physical Anthropology*, *68*(3), 367–373.

Dowle, M., Srinivasan, A., Gorecki, J., Chirico, M., Stetsenko, P., Short, T., Lianoglou, S., Antonyan, E., Bonsch, M., & Parsonage, H. (2019). *Package data.table: Extension of "data.frame"* (1.12.8) [R]. https://r-datatable.com

Galili, T. (2015). dendextend: An R package for visualizing, adjusting and comparing trees of hierarchical clustering. *Bioinformatics*, *31*(22), 3718–3720.

Garn, S. M., Lewis, A. B., & Blizzard, R. M. (1965). Endocrine factors in dental development. *Journal of Dental Research*, *44*(1), 243–258.

Garn, S. M., Lewis, A. B., & Kerewsky, R. S. (1965a). Genetic, nutritional, and maturational correlates of dental development. *Journal of Dental Research*, *44*(1), 228–242.

Garn, S. M., Lewis, A. B., & Kerewsky, R. S. (1965b). Size interrelationships of the mesial and distal teeth. *Journal of Dental Research*, *44*(2), 350–354.

Garn, S. M., Lewis, A. B., & Kerewsky, R. S. (1966). The meaning of bilateral asymmetry in the permanent dentition. *The Angle Orthodontist*, *36*(1), 55–62.

Garn, S. M., Lewis, A. B., & Kerewsky, R. S. (1967a). Buccolingual size asymmetry and its developmental meaning. *The Angle Orthodontist*, *37*(3), 186–193.

Garn, S. M., Lewis, A. B., & Kerewsky, R. S. (1967b). Shape similarities throughout the dentition. *Journal of Dental Research*, *46*(6), 1481.

Garn, S. M., Lewis, A. B., & Kerewsky, R. S. (1968). Relationship between buccolingual and mesiodistal tooth diameters. *Journal of Dental Research*, *47*(3), 495.

Garn, S. M., Lewis, A. B., Koski, K., & Polacheck, D. L. (1958). The sex difference in tooth calcification. *Journal of Dental Research*, *37*(3), 561–567.

Garn, S. M., & Smith, B. H. (1980a). Developmental communalities in tooth emergence timing. *Journal of Dental Research*, *59*(7), 1178.

Garn, S. M., & Smith, B. H. (1980b). Patterned asymmetry in tooth emergence timing. *Journal of Dental Research*, *59*(9), 1526–1527.

Garn, S. M., Smith, B. H., & Moyers, R. E. (1981). Structured (patterned) dimensional and developmental dental asymmetry. *Proceedings of the Finnish Dental Society*, *77*, 33–36.

Hemphill, B. E. (2013). A fool's mission? A test of three common assumptions in dental metric analyses. *Dental Anthropology Journal*, *26*(3), 16–30.

Hemphill, B. E. (2015). Measurement of tooth size (odontometrics). In *A companion to dental anthropology*, John Wiley & Sons, Inc. (pp. 287–310).

Hennig, C., & Imports, M. (2015). Package fpc. Retrieved July 08, 2017, from http://Cran.r-Project.Org/Web/Packages/Fpc/Fpc.Pdf

Hirk, R., Hornik, K., & Vana, L. (2020). mvord: An R package for fitting multivariate ordinal regression models. *Journal of Statistical Software*, *93*(4), 1–41.

Jayaraman, J., Roberts, G. J., Wong, H. M., & King, N. M. (2018). Dental age estimation in southern Chinese population using panoramic radiographs: Validation of three population specific reference datasets. *BMC Medical Imaging*, *18*(1), 1–8.

Jayaraman, J., Wong, H. M., King, N. M., & Roberts, G. J. (2013). The French–Canadian data set of Demirjian for dental age estimation: A systematic review and meta-analysis. *Journal of Forensic and Legal Medicine*, *20*(5), 373–381.

Johnson, P. A. (1996). A test of the normality assumption in the ordered probit model. *Metron*, *54*, 213–221.

Kaiser, H. (1960). The application of electronic computers to factor analysis. *Educational and Psychological Measurement*, *20*(1), 141–151.

Keene, H. J. (1971). Birth weight and congenital absence of teeth in twins. *Acta Geneticae Medicae Et Gemellologiae: Twin Research*, *20*(1), 23–42.

Kırzıoğlu, Z., & Ceyhan, D. (2012). Accuracy of different dental age estimation methods on Turkish children. *Forensic Science International*, *216*(1–3), 61–67.

Konigsberg, L. W., Frankenberg, S. R., & Liversidge, H. M. (2016). Optimal trait scoring for age estimation. *American Journal of Physical Anthropology*, *159*(4), 557–576.

Kumaresan, R., Cugati, N., Chandrasekaran, B., & Karthikeyan, P. (2016). Reliability and validity of five radiographic dental-age estimation methods in a population of Malaysian children. *Journal of Investigative and Clinical Dentistry*, *7*(1), 102–109.

Lan, Y., Jia, S., & Jiang, R. (2014). Molecular patterning of the mammalian dentition. *Seminars in Cell & Developmental Biology*, *25*, 61–70.

Liversidge, H. M. (2011). Similarity in dental maturation in two ethnic groups of London children. *Annals of Human Biology*, *38*(6), 702–715.

Liversidge, H. M., & Molleson, T. I. (1999). Deciduous tooth size and morphogenetic fields in children from Christ Church, Spitalfields. *Archives of Oral Biology*, *44*(1), 7–13.

Maia, M. C. G., da Gloria Almeida Martins, M., Germano, F. A., Neto, J. B., & Da Silva, C. A. B. (2010). Demirjian's system for estimating the dental age of northeastern Brazilian children. *Forensic Science International*, *200*(1–3), 177.e1–177.e4.

Mani, S. A., Naing, L. I. N., John, J., & Samsudin, A. R. (2008). Comparison of two methods of dental age estimation in 7–15-year-old Malays. *International Journal of Paediatric Dentistry*, *18*(5), 380–388.

Mihailidis, S., Woodroffe, S. N., Hughes, T. E., Bockmann, M. R., & Townsend, G. C. (2009). Patterns of asymmetry in primary tooth emergence of Australian twins. In *Comparative dental morphology* (Vol. 13, pp. 110–115). Karger Publishers.

Mitsiadis, T. A., & Graf, D. (2009). Cell fate determination during tooth development and regeneration. *Birth Defects Research Part C: Embryo Today: Reviews*, *87*(3), 199–211.

Mitsiadis, T. A., & Smith, M. M. (2006). How do genes make teeth to order through development? *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, *306*(3), 177–182.

Moorrees, C. F., Fanning, E. A., & Hunt, E. E., Jr. (1963). Age variation of formation stages for ten permanent teeth. *Journal of Dental Research*, *42*(6), 1490–1502.

Moorrees, C. F., & Reed, R. B. (1964). Correlations among crown diameters of human teeth. *Archives of Oral Biology*, *9*(6), 685–697.

Noden, D. M. (1983). The role of the neural crest in patterning of avian cranial skeletal, connective, and muscle tissues. *Developmental Biology*, *96*(1), 144–165.

Osborne, J. W. (1978). Morphogenetic gradients: Fields versus clones. In *Development, function and evolution of teeth*, Academic Press, (pp. 171–201).

Parner, E. T., Heidmann, J. M., Kjaer, I., Vaeth, M., & Poulsen, S. (2002). Biological interpretation of the correlation of emergence times of permanent teeth. *Journal of Dental Research*, *81*(7), 451–454.

Paul, K. S., Stojanowski, C. M., Hughes, T., Brook, A., & Townsend, G. C. (2021). The genetic architecture of anterior tooth morphology in a longitudinal sample of Australian twins and families. *Archives of Oral Biology*, *129*, 105168.

Paul, K. S., Stojanowski, C. M., Hughes, T. E., Brook, A. H., & Townsend, G. C. (2020). Patterns of heritability across the human diphyodont dental complex: Crown morphology of Australian twins and families. *American Journal of Physical Anthropology*, *172*(3), 447–461.

Phillips, V. M., & van Wyk Kotze, T. J. (2009). Testing standard methods of dental age estimation by Moorrees, Fanning and Hunt and Demirjian, Goldstein and Tanner on three South African children samples. *The Journal of Forensic Odonto-Stomatology*, *27*(2), 20–28.

Prasad, H., & Kala, N. (2019). Accuracy of two dental age estimation methods in the Indian population—A meta-analysis of published studies. *The Journal of Forensic Odonto-Stomatology*, *37*(3), 2–11.

R Core Team. (2019). *R: A language and environment for statistical computing* (3.6.1). R Foundation for Statistical Computing. http://www.R-project.org/

Revelle, W. (2018). *psych: Procedures for personality and psychological research* (1.8.12). Northwestern University. https://CRAN.R-project.org/package=psych

Ripley, B., Venables, B., Bates, D. M., Hornik, K., Gebhardt, A., Firth, D., & Ripley, M. B. (2019). *MASS: Support functions and datasets for Venables and Ripley's MASS* (7.3-51.5) [R].

Rodriguez, B., Cucina, A., Vega, E., Hoyos, R., & Cardoso, H. F. V. (2021). A critical test of twelve methods for estimating age using radiographic staging of developing teeth on a sample of 6-to 15-year-old children from Mérida, Yucatán (México). *International Journal of Legal Medicine*, *135*, 1–11.

Seow, W. K. (1997). Effect of preterm birth on oral growth and development. *Australian Dental Journal*, *42*(2), 85–91.

Sharpe, P. T. (1995). Homeobox genes and orofacial development. *Connective Tissue Research*, *32*(1–4), 17–25.

Sokal, R. R., & Rohlf, F. J. (1962). The comparison of dendrograms by objective methods. *Taxon*, *11*, 33–40.

Stojanowski, C. M., Paul, K. S., Seidel, A. C., Duncan, W. N., & Guatelli-Steinberg, D. (2017). Heritability and genetic integration of tooth size in the South Carolina Gullah. *American Journal of Physical Anthropology*, *164*(3), 505–521.

Stojanowski, C. M., Paul, K. S., Seidel, A. C., Duncan, W. N., & Guatelli-Steinberg, D. (2018). Heritability and genetic integration of anterior tooth crown variants in the South Carolina Gullah. *American Journal of Physical Anthropology*, *167*(1), 124–143.

Stojanowski, C. M., Paul, K. S., Seidel, A. C., Duncan, W. N., & Guatelli-Steinberg, D. (2019). Quantitative genetic analyses of postcanine morphological crown variation. *American Journal of Physical Anthropology*, *168*(3), 606–631.

Thevissen, P. W., Alqerban, A., Asaumi, J., Kahveci, F., Kaur, J., Kim, Y. K., Pittayapat, P., Van Vlierberghe, M., Zhang, Y., & Fieuws, S. (2010). Human dental age estimation using third molar developmental stages: Accuracy of age predictions not using country specific information. *Forensic Science International*, *201*(1–3), 106–111.

Townsend, G., Bockmann, M., Hughes, T., & Brook, A. (2012). Genetic, environmental and epigenetic influences on variation in human tooth number, size and shape. *Odontology*, *100*(1), 1–9.

Townsend, G., Harris, E. F., Lesot, H., Clauss, F., & Brook, A. (2009). Morphogenetic fields within the human dentition: A new, clinically relevant synthesis of an old concept. *Archives of Oral Biology*, *54*, S34–S44.

Tucker, A., & Sharpe, P. (2004). The cutting-edge of mammalian development; how the embryo makes teeth. *Nature Reviews Genetics*, *5*(7), 499–508.

Tunc, E. S., & Koyuturk, A. E. (2008). Dental age assessment using Demirjian's method on northern Turkish children. *Forensic Science International*, *175*(1), 23–26.

Veitch, E., Begbie, J., Schilling, T. F., Smith, M. M., & Graham, A. (1999). Pharyngeal arch patterning in the absence of neural crest. *Current Biology*, *9*(24), 1481–1484.

Woodroffe, S., Mihailidis, S., Hughes, T., Bockmann, M., Seow, W. K., Gotjamanos, T., & Townsend, G. (2010). Primary tooth emergence in Australian children: Timing, sequence and patterns of asymmetry. *Australian Dental Journal*, *55*(3), 245–251.

How to cite this article: Sgheiza, V. (2024). Sex and ancestry patterning of residual correlations in human dental development: Cooperative genetic interaction and phenotypic plasticity. *American Journal of Biological Anthropology*, e24908. https://doi.org/10.1002/ajpa.24908