

## The genetic architecture of modern human dental morphology

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Among the most common and well-preserved elements within the hominin fossil record are the teeth which have been intensively used in evolutionary studies. In addition, much of the recent and contemporary human diversity has been assessed using dental morphological traits, including applications in forensic sciences. However, the genetic bases underlying variation in dental morphology continue to be poorly understood. A number of studies have indicated that this variation is highly heritable but very few genes influencing dental morphology have been reliably identified (e.g., *EDAR*). The unprecedented power provided by current genomic technologies offers a great opportunity for a detailed assessment of the genetic basis of modern human dental morphological variation. Here we present a study aimed to identify genes responsible for variation in tooth morphology through multiple genetic tests including genome-wide association studies (GWAS), Wald-test, admixture mapping, etc.

We examined distinct cohorts of unrelated individuals from Latin America of mixed Native American, European and African ancestry (Colombians ~1000 and Chileans ~2000). The Latin American persons have been studied as part of a similar project focused on the genetics of physical appearance (CANDELA consortium) and were genotyped using genome-wide SNP data. We obtained dental plaster casts from the studied individuals and 3D models were acquired through a high-resolution blue light scanner (Artec Space Spider). Distinct dental features such as standard dental measurements and indexes (using manual and automatic approaches), nonmetric traits (with the ASUDAS method) as well as 3D mesh geometric attributes (area, volume, centroid size, etc.) were obtained through the 3D models after automatic segmentation procedures.

Our results reveal that several genes (*PITX2*, *WNT9b*) are associated with the normal dental diversity among living humans including a pervasive and decreasing effect of *EDAR* across the dentition from anterior to posterior teeth. For tooth dimensions, more than 30 traits showed significant associations (P-value <5×10<sup>-8</sup>) with at least one genomic region. Eleven dental nonmetric traits showed genome-wide significant associations with SNPs in at least one genomic region while for mesh attributes 10 genomic regions were significantly associated with at least one trait. According to previous studies, several genetic variants here detected influence a number of oral, craniofacial, and skeletal features including some disorders, syndromes, and dysmorphologies. Interestingly, some of these genes are also associated with both tooth development and eruption as well as with the presence of supernumerary teeth or agenesis, and with normal and abnormal variation in facial/cranial features revealing their pleiotropic effect across the craniofacial complex and the coordinate and modular nature of genetic correlations.

The present study supports previous hypotheses about the strong genetic basis underlying the development of normal dental variation in modern humans, thus warranting the use of tooth features in taxonomic, phylogenetic, and biodistance assessments. The link between genes and tooth features enhances our understanding of the genetic pathways involved in tooth development. Finally, through the identification of specific genes operating across the dentition, the present study possesses wider implications for the investigation of living and extinct hominin evolution and diversity, especially on how genetic mechanisms underlie some of the major events in hominin craniodental evolution. Future work with larger sample sizes and using experimental follow-up analyses to endorse the discovered associations will provide additional insights into the complex relationship between genotype and dental phenotypes.

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