A Morphofunctional Hypothesis for Selection on EDAR V370A and Associated Elements of Sinodonty

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ABSTRACT The phenomenon of Sinodonty refers to a suite of dental characters shared between East Asian and Native American populations, and most prominently to the presence of shoveled incisors. Although this syndrome is a conspicuous aspect of dental differentiation among extant human populations, elements of which have been recent subject of detailed genetic analysis, adaptive consequences of shoveled incisors and related features remain unclear. Here, I hypothesize that many of the associated differences in dentition (along with reduction in mandibular length and increases in salivary gland branching) arose in parallel with the opportunistic consumption of wild rice and millet in central and northern China, respectively, and with their subsequent domestication in the Upper Paleolithic. More efficient mastication and digestion of plant grains (and of other starchy foods obtained via broad-spectrum foraging) would potentially have been enabled by these traits, yielding greater rates of nutritional intake as wild crops were progressively domesticated. This functional hypothesis, although not mutually exclusive relative to other proposed selective factors, matches the estimated timeline in China for both origin and time to fixation of the associated allele (EDAR V370A), and is consistent with chronic energetic gain and fitness benefits independent of any assumptions for concurrent climatic conditions.

Lingually shoveled incisors, an anatomical feature first described by Hrdlička (1920, 1921), are a salient characteristic of the phenomenon now termed Sinodonty, a suite of dental characters common between Native American and East Asian populations, but occurring at much lower frequencies in non-Sinodont populations (Turner, 1971, 1976, 1986, 1990; see also Mizoguchi, 1985; Scott & Turner, 1988; Stojanowski et al., 2013; Scott et al., 2018). This disjunct geographical distribution has historically provided strong indirect support for hypothesized Old World origins of New World human populations (e.g., Turner & Bird, 1981). Anatomically, the condition of Sinodonty refers primarily to the presence of posteriorly shoveled incisors, single-rooted upper premolars, and three-rooted lower molars, and is strongly heritable (Hanihara et al., 1974; Blanco and Chakraborty, 1976), but is also likely to be polygenic in origin. Genetically, presence of the allele EDAR V370A significantly influences the condition of incisor shoveling along with a variety of other ectodermic features, including increased thickness of scalp hairs (see Bryk et al., 2008; Fujimoto et al., 2008; Chang et al., 2009; Kimura et al., 2009). Increased tooth crown size also associates with EDAR V370 (Kimura et al., 2009; Park et al., 2012), and its greater expression in mice furthermore reduces mandibular length (Adhikari et al., 2016). Pleiotropic effects of this allele are thus substantial.

Positive selection on EDAR V370A has been intense in humans, consistent with its very high frequencies in East Asian and Native American populations relative to other groups (see Sabeti et al., 2007; Bryk et al., 2008; Kamberov et al., 2013; Hlusko et al., 2018). Demic modelling based on extant frequencies of EDAR V370A in primarily Asian populations (Kamberov et al., 2013) indicates geographical origins of the allele in central and north China, within a region broadly congruent with the extensive alluvial plains of the Yellow, Huai, and

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Yangtzi (Changjiang) Rivers. This demic model also places time of origination for the allele between ~40,000 and ~13,000 years BP, with a modal value of 35,300 years BP. A parallel approach to allele age using maximum likelihood estimation for data from modern Han Chinese places origination between ~38,000 and ~35,000 years BP (see Kamberov et al., 2013). Finally, the modal value for fixation time of EDAR V370A has been estimated (using haplotype data from 23 individuals of Chinese descent) as 10,740 years BP (Bryk et al., 2008). These estimates for origination and fixation of EDAR V370A within East Asia are recent relative to the age of our species, and are also suggestive of powerful selective forces at play over a short time interval.

Because scalp hair density is increased by EDAR V370A, various authors have suggested that thermoregulatory and water balance would be influenced by this morphological change, particularly in the cooler and drier climates of the Upper Paleolithic (see Yuan et al., 2004; Chang et al., 2009). An alternative hypothesis links increased eccrine (sweat) gland density to greater evaporative heat loss in a humid monsoonal climate (Kamberov, et al., 2013). Mammary duct density also increases in the presence of EDAR V370A, raising the possibility of enhanced maternal milk delivery and associated fitness benefits (Hlusko et al., 2018). Concomitant changes in dentition may thus have derived pleiotropically from selection on other traits.

However, Sinodonty by definition refers to tooth anatomy, which broadly reflects diet in mammals (Ungar, 2010; Pineda-Munoz et al., 2017). It is therefore parsimonious to consider dietary shifts concurrent with the rise of EDAR V370A and associated elements of Sinodonty that may have been the target of natural selection. In particular, the timeline for fixation of this allele, along with its inferred geographical region of origin, correspond well to archaeological data that indicate foraging of wild rice and millet in China, along with their subsequent domestication. The origins of prominent features of Sinodonty, in other words, correlate temporally with a major dietary shift associated with the emergence of cultivated crops in East Asia. I hypothesize that this specialized human dentition, along with other related phenotypic effects of EDAR V370A, were advantageous for the mastication and subsequent digestion of sympatric wild grains, and thus yielded energetic advantage during the extended process of crop domestication.

Timeline for rice and millet domestication in China

Domesticated rice in East Asia refers to a single subspecies (*Oryza rufipogon* ssp. *japonica*) derived from a wild ancestor, whereas millet refers to two species domesticated from different grass genera (broomcorn millet: *Panicum miliaceum*; foxtail millet: *Setaria italica*). Phylogenetic reconstruction places rice domestication in China at ~13,500–8200 BP (Molina et al., 2011), a range congruent with corroborative archeological evidence (see Liu et al., 2007; Gross & Zhao, 2014). Similarly, archeological finds are consistent with the domestication and cultivation of millet nearly 10,000 years ago (Lu et al., 2009; Yang et al., 2012; Bestel et al., 2014).

Foraging on wild grains would have necessarily preceded their domestication. For example, processing with grinding stones of wild grass seeds (including possibly ancestral millets) occurred as early as ~24,000 years BP (see Liu et al., 2013; Liu et al. 2018). The oldest known sites for pottery in China date to ~20,000–10,000 years BP, possibly marking the emergence of agriculture (see Wang & Sebillaud, 2019). Starchy foods more generally became increasingly prevalent through the Upper Paleolithic in China, as suggested by increased usage of nuts, beans, and tubers (see Liu et al., 2013). Archeological records cannot capture in detail the spectrum of foraging and cultivation behaviors carried out over millennia, and across a geographical mosiac, during the process of crop domestication (see Fuller et al., 2014; Larson et al., 2014). Nonetheless, the overlap between estimated timelines for the origin and fixation of EDAR V370A, and for the domestication of rice and millet, is substantial (Figure 1).

Functional consequences of Sinodonty

Shoveled incisors and related features of Sinodonty may influence chewing dynamics and masticatory efficiency. It has long been suggested that shoveling increases tooth strength and resistance to bending (see Hrdlička, 1921; Dahlberg, 1963). Specific effects of incisor shoveling and changes in premolar and molar root numbers are unknown for mastication, which is associated with diverse features of jaw kinematics (see Ross et al., 2012). Also relevant is the substantial reduction in mandibular length associated with expression of the EDAR allele (by 5–10% in mice; see Adhikari et al., 2016). In human agriculturalists, mandible dimensions are reduced relative to non-agricultural populations, consistent with relaxation of masticatory demand (see von Cramon-Taubadel, 2011; Noback &

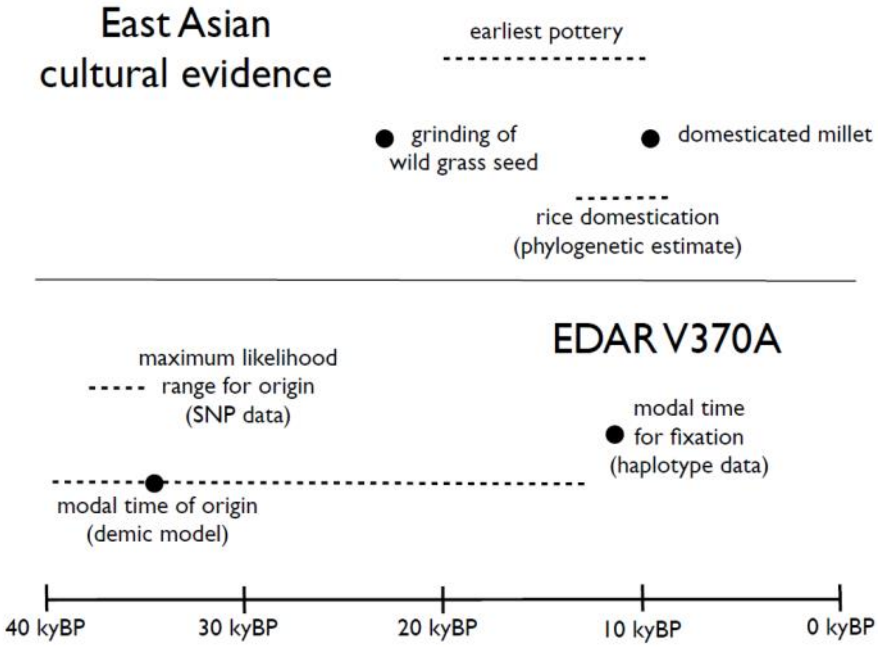

Figure 1. Timelines for estimated origin and fixation of EDAR V370A, and for relevant archaeological data and estimates of crop domestication. Dashed lines indicate approximate temporal ranges; see text for details and relevant citations.

Harvati, 2015; Katz et al., 2017). Paleontological data are not available to document the tempo of mandibular reduction across the rice and millet domestication sequence in East Asia, but a causal link with EDAR V370A cannot be excluded.

Interestingly, another consequence of enhanced EDAR expression in mice is to increase branching of adult salivary glands (by ~25%; Chang et al., 2009), which may in turn increase rates of saliva production and thereby facilitate starch digestion in the mouth (Valdez & Fox, 1991). This mechanism would provide a direct linkage between anatomical changes associated with EDAR V370A expression in humans, and advantageous physiological outcome as starchy crops were domesticated. An analogous argument was advanced by Hlusko et al. (2018) relative to increases in mammary duct density and lactation; such effects on gland density could moreover be complementary in some contexts (e.g., greater energy uptake would enable increased milk production), and would pertain independently of any specific climatic conditions. Pleiotropic changes in teeth, mandibular bone, and salivary gland density resulting from EDAR V370A can therefore influence human nutritional physiology in diverse ways.

Discussion and Conclusions

Various alleles alternative to EDAR V370A may contribute to tooth shoveling and other features characteristic of Sinodonty, and do not necessarily correspond to specific dietary adaptations. Prominent incisor shoveling in Neanderthals, for example, well precedes the origin of EDAR V370A, and does not associate with increased masticatory stresses (Clement et al., 2012). Similarly, a 3-rooted lower second molar has been described from a Denisovan mandible from western China, dated at ~160,000 BP (Bailey et al., 2019), although identification of this tooth has been challenged (see Scott et al., 2020; Bailey et al., 2020). The age of this specimen nonetheless well precedes the 38,000–35,000 BP estimated origination time for EDAR V370A (see Kamberov et al., 2013), and its features presumably derive from different genetic origins. Incisor shoveling in Native Americans likely derives genetically from their Eurasian source populations in northeastern Siberia (see Flegontov et al., 2019; Mathieson, 2020), but the oldest known human dentition from this latter region (~31,000 BP) is unfortunately incomplete with unknown occurrence of Sinodonty (see Sikora et al., 2019). The increased incidence of shoveling in Down syndrome (see Cohen et al., 1970) is not yet characterized at the allelic level. Finally, an additional EDAR variant is found in south China and southeast Asia, but has not apparently been the target of positive selection (Riddell et al., 2020).

A pressing empirical need to evaluate any functional hypothesis relating to Sinodonty and to effects of EDAR V370A is to obtain a quantitative assessment of tooth and mandibular variation through time in East Asia. Changes in dentition and mandibular dimensions across the Paleolithic in China are not currently available, although there was a substantial reduction in mandibular dimensions from the Neolithic through the Bronze Age (Li et al., 2012). Incisor shoveling incidence in western European populations (which is low relative to that found in East Asia) has declined since the Neolithic (Brabant, 1971), a trend which may derive from genetic drift. Quantitative measurements of tooth morphology (e.g., Carayon et al., 2018) would enable better characterization of the shoveling phenotype and associated variation through time and among human populations, along with finite-element modeling of tooth bending mechanics. Similarly, consequences of changes in mandibular geometry can be inferred from mechanical modeling, although functional outcomes can be complex and not necessarily predictable from linear data (Sella-Tunis et al., 2018), to which end three-dimensional structural modelling using finite-element analysis would be appropriate (see Morales-García et al., 2019).

Multiple hypotheses pertain to the possible selective advantages of EDAR V370A, and none of these are mutually exclusive. Recognition of the temporal correlation between allele age and the timelines for wild grain consumption and domestication in East Asia, however, provides a linkage between diet and nutritional gain during the transition to agriculture. Worldwide, this transition has been associated with diverse changes in human behavior and morphological features, and is suggestive of powerful selective forces at play. For example, an allele for a highly active form of alcohol dehydrogenase originated in central China in parallel with rice domestication, prompting speculation as to increased dietary exposure to ethanol derived from carbohydrate fermentation (Peng et al., 2010). The pleiotropic effects of EDAR V370A are multifaceted, and unifactorial explanations for associated selective forces are likely to be incomplete. Nonetheless, chronic energetic benefits concurrent with grain domestication in East Asia have not previously been envisioned for this allele, and may have been of considerable advantage.

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