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Environmental selection during the last ice age on the mother-to-infant transmission of vitamin D and fatty acids through breast milk

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Abstract: Because of the ubiquitous adaptability of our material culture, some human populations have occupied extreme environments that intensified selection on existing genomic variation. By 32,000 years ago, people were living in Arctic Beringia, and during the Last Glacial Maximum (LGM; 28,000-18,000 y ago), they likely persisted in the Beringian refugium. Such high latitudes provide only very low levels of UV radiation, and can thereby lead to dangerously low levels of biosynthesized vitamin D. The physiological effects of vitamin D deficiency range from reduced dietary absorption of calcium to a compromised immune system and modified adipose tissue function. The ectodysplasin A receptor (EDAR) gene has a range of pleiotropic effects, including sweat gland density, incisor shoveling, and mammary gland ductal branching. The frequency of the human-specific EDAR V370A allele appears to be uniquely elevated in North and East Asian and New World populations due to a bout of positive selection likely to have occurred circa 20,000 y ago. The dental pleiotropic effects of this allele suggest an even higher occurrence among indigenous people in the Western Hemisphere before European colonization. We hypothesize that selection on EDAR V370A occurred in the Beringian refugium because it increases mammary ductal branching, and thereby may amplify the transfer of critical nutrients in vitamin D-deficient conditions to infants via mothers' milk. This hypothesized selective context for EDAR V370A was likely intertwined with selection on the fatty acid desaturase (FADS) gene cluster because it is known to modulate lipid profiles transmitted to milk from a vitamin D-rich diet high in omega-3 fatty acids.

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Environmental selection during the last ice age on the mother-to-infant transmission of vitamin D and fatty acids through breast milk

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Because of the ubiquitous adaptability of our material culture, some human populations have occupied extreme environments that intensified selection on existing genomic variation. By 32,000 years ago, people were living in Arctic Beringia, and during the Last Glacial Maximum (LGM; 28,000–18,000 y ago), they likely persisted in the Beringian refugium. Such high latitudes provide only very low levels of UV radiation, and can thereby lead to dangerously low levels of biosynthesized vitamin D. The physiological effects of vitamin D deficiency range from reduced dietary absorption of calcium to a compromised immune system and modified adipose tissue function. The ectodysplasin A receptor (*EDAR*) gene has a range of pleiotropic effects, including sweat gland density, incisor shoveling, and mammary gland ductal branching. The frequency of the human-specific *EDAR V370A* allele appears to be uniquely elevated in North and East Asian and New World populations due to a bout of positive selection likely to have occurred circa 20,000 y ago. The dental pleiotropic effects of this allele suggest an even higher occurrence among indigenous people in the Western Hemisphere before European colonization. We hypothesize that selection on *EDAR V370A* occurred in the Beringian refugium because it increases mammary ductal branching, and thereby may amplify the transfer of critical nutrients in vitamin D-deficient conditions to infants via mothers' milk. This hypothesized selective context for *EDAR V370A* was likely intertwined with selection on the fatty acid desaturase (*FADS*) gene cluster because it is known to modulate lipid profiles transmitted to milk from a vitamin D-rich diet high in omega-3 fatty acids.

mammary epithelium | dental anthropology | Beringia | adaptation | UV radiation

From Thomas Jefferson's archaeological excavations (1) to modern genomics (2–4), scientists have been fascinated by the first migration of humans into the Americas. A myriad of new evidence reveals that the earliest people in the Western Hemisphere dispersed from a population that lived in genetic isolation for thousands of years on the exposed Beringian platform in the Arctic during the Last Glacial Maximum [LGM; 28,000–18,000 y ago (2–7)]. The Arctic is an extreme environment because of the very low UV radiation (UV) reaching the earth's surface at such high latitude. UV is essential to almost all life forms because it catalyzes biochemical processes, especially the synthesis of vitamin D (8).

Extreme environments can impact genetic variation and provide opportunities to elucidate relationships between genotype and phenotype (9). The classic human example is the range of our physiological adaptations to the hypoxic conditions of high altitude, such as are experienced in the highlands of Ethiopia, the Tibetan Plateau, and the Andean Mountains (10–12). Evidence shows that the populations which have long-occupied these high-elevation regions have an increased frequency of

red blood cell polymorphisms that likely underlie these physiologies (10–12).

Here, we investigate whether the population occupying Beringia during the LGM represents another example of human adaptation to an extreme environment, this time adapting to very low UV exposure (Fig. 1). There are two lines of genetic evidence for this: variation in the fatty acid desaturase (*FADS*) gene cluster that modulates the manufacture of polyunsaturated fatty acids and variation in the ectodysplasin A receptor (*EDAR*) gene that influences ectodermally derived structures, such as teeth, hair, and mammary gland ductal branching. A study on selection on the *FADS* gene cluster in the ancestral population of Native Americans has been published previously (13), but, here, we shift the emphasis from phenotypic effects on older adults to focus on those that influence fertility via breast milk. We then present evidence that *EDAR* may have undergone an episode of selection in the same population, likely due to its influence on mammary ductal branching. We hypothesize that the genetically isolated population which occupied Beringia during the LGM experienced selection for an increase in vitamin D in breast milk in response to the low UV environment. Traces of this previously intense selection appear to still be present in the

Significance

The frequency of the human-specific *EDAR V370A* isoform is highly elevated in North and East Asian populations. The gene is known to have several pleiotropic effects, among which are sweat gland density and ductal branching in the mammary gland. The former has led some geneticists to argue that the near-fixation of this allele was caused by selection for modulation of thermoregulatory sweating. We provide an alternative hypothesis, that selection instead acted on the allele's effect of increasing ductal branching in the mammary gland, thereby amplifying the transfer of critical nutrients to infants via mother's milk. This is likely to have occurred during the Last Glacial Maximum when a human population was genetically isolated in the high-latitude environment of the Beringia.

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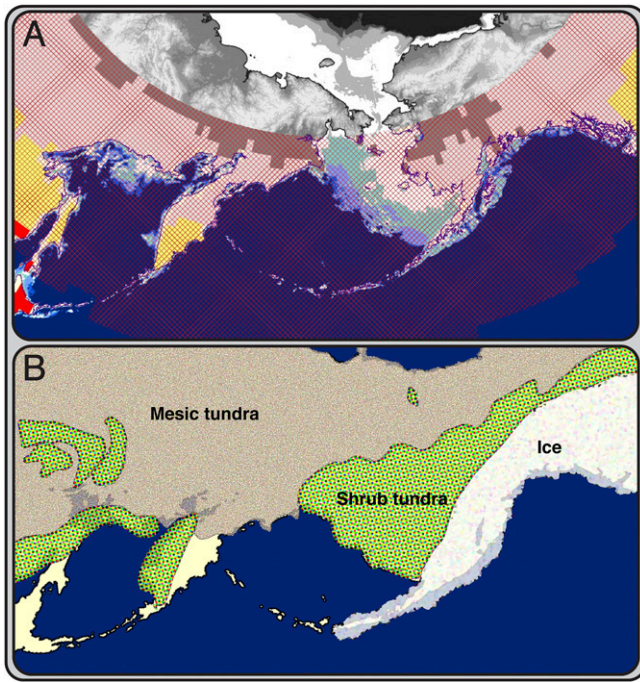


Fig. 1. Geography of Beringia and levels of UV radiation. (A) Map of Beringia today. Cross-hatching indicates the region in which levels of UVMED (defined as the amount of UV radiation that will produce minimal erythema) that reach the Earth's surface are too low to promote cutaneous synthesis of vitamin D in humans on a year-by-year basis, requiring dietary supplementation (modified from ref. 84; projected to show an equal distance map of Beringia). The black and white region marks the Arctic Circle, for which there are no Total Ozone Mapping Satellite Data version 7. Other data show that this region has even less UV-B exposure, as would be expected from the increased latitude. The areas below the Arctic Circle in white and light blue are shallow seas as discerned from modern bathymetry using Etopo2 data, indicating land that would have been exposed during the LGM. (B) Map of Beringia during the LGM showing the exposure of land at 117 m below current sea level and the reconstructed terrestrial environments. The shrub tundra is the only area biologically productive enough to support a human population of the size estimated by molecular data. This population was genetically isolated for ~2,500–9,000 y during the LGM because of the ice to the east and extensive mesic tundra to the west.

genetic variation of Native American and North and East Asian populations today.

The *FADS* Gene Cluster

Allelic variation in the *FADS* gene complex corresponds strongly to geographic ancestry (14, 15), and is the most pronounced allele frequency difference between the Greenlandic Inuit and other human populations (16). Because modern Western cultures place much attention on the cardiovascular disease risks associated with diets rich in omega-6 versus omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) (17, 18), the high frequencies of these alleles in the Inuit have been primarily interpreted as an adaptation to their traditionally meat-rich (and omega-3-rich) diet (16, 19). However, and surprisingly, 95% of native Central and South Americans also show evidence of selection on the same *FADS* polymorphisms, yet these cultural groups do not traditionally consume diets nearly as rich in omega-3 fatty acids as do the Inuit, suggesting that their common ancestral population is characterized by one which did (13).

From an evolutionary perspective, the possibility that the selective force favoring these *FADS* alleles was a healthier ratio of omega-3 to omega-6 fatty acids in adults would indicate that the effect must have been very strong, as selective pressure is rela-

tively low on genetic variation that influences later and post-reproductive years of life (20). In contrast, even very small positive effects on fertility and childhood survival have far greater selective power (20). Considering this, the selective benefits of these *FADS* polymorphisms are more likely connected to their significant role in modulating the relative levels of omega-3 and omega-6 fatty acids during gestation and postnatal growth of infants.

To elaborate, the fatty acids arachidonic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are essential to cognitive and visual development (21). Maternal polymorphisms in the *FADS* gene cluster have strong effects on the levels of EPA and DHA in breast milk [in humans (22–27) and in other mammals (27, 28)]. This suggests that lipid levels in a mother's diet are optimized by specific polymorphisms in her *FADS* gene cluster during milk synthesis (Fig. 2A). These polymorphisms are therefore a potentially strong target of selection because fetuses and infants have a very limited ability to synthesize LC-PUFAs on their own and are dependent on their mother's genotype to modulate their relative proportions (22–27). We propose that the phenotypic effects of *FADS* polymorphisms on the LC-PUFA content of breast milk was the primary target of selection in past human populations that consumed diets with compromised proportions of omega-3 and omega-6 fatty acids, such as is seen in the traditional diets of people living in the Arctic.

EDAR. The human *EDAR V370A* variant encodes a change in amino acid sequence in the highly conserved death domain of *EDAR* (29–32). *EDAR* functions as a protein receptor on a cell's surface that activates the transcription factor NF- κ B in the ectodysplasin pathway (29). Comparative studies show this pathway is functionally conserved across virtually all vertebrates, playing essential roles in the development of ectodermal structures from bird feathers to fish scales (33, 34).

EDAR is one of four genes implicated in hypohidrotic ectodermal dysplasia (HED), a set of ~150 syndromes characterized by mild to severe defects in ectodermally derived structures, such as hair, teeth, breasts, and sweat glands (33, 35–37). In contrast to HED, the *EDAR V370A* allele has the opposite effect. Genome-wide association studies (GWASs) of multiple Asian populations show that *EDAR V370A* is correlated with hair shaft caliber (38, 39), earlobe and chin shape (40), and a suite of morphological variants on teeth (40–43). Knock-in mouse studies reveal that the *V370A* allele leads to a twofold increase in NF- κ B activation (30, 31, 44). Just like humans, the *EDAR V370A* mouse has thicker hair shafts, an increase in the branching density of mammary gland ducts, and (inconsistently) an increase in the number of eccrine glands on the footpads (30, 31).

Several studies conclude that *EDAR V370A* experienced a bout of intense positive selection ~20,000 y ago in northern China (29, 31, 45). Previous interpretations as to why this selection occurred focused on the associated increase in eccrine sweat gland density on the fingertips, concluding that the selection was for improved thermoregulatory sweating during a warm spell during the LGM (31) or that the increase in sebaceous glands would offer protection from the cold, dry air of the LGM (30). These interpretations rely primarily on the current distribution of the allele in living populations (Fig. 3A), which shows high frequencies of *EDAR V370A* in North and East Asian and Native American populations but virtual absence in other populations around the world (29–31, 45).

The post-LGM diaspora into the Americas and the subsequent centuries of European colonization (and genetic admixture) have dramatically overwritten the allelic variation of ~20,000 y ago when *EDAR V370A* experienced a bout of selective pressure. To best interpret the evolutionary history of *EDAR V370A*, we need information on past allele frequencies. This task is difficult from a genome sequence approach because of the paucity of ancient

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