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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

MINI REVIEW

Evolutionary adaptation highlights the interconnection of fatty acids, sunlight, inflammation and epithelial adhesion

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Abstract

Gene variants that influence human biology today reflect thousands of years of evolution. Genetic effects on infant health are a major point of selective pressure, given that childhood survival is essential to evolutionary success. Knowledge of this evolutionary history can have implications for paediatric research.

Conclusion: An episode of human adaptation to the extremely low ultraviolet radiation environment of the Arctic 20,000 years ago implicates the *Ectodysplasin A Receptor* (*EDAR*) and the *Fatty Acid Desaturases* (*FADS*) in human lactation and epithelial inflammation.

1 | INTRODUCTION

This mini-review uses an episode of human adaptation to the Arctic to reorient perceptions of fatty acid synthesis, the ectodysplasin pathway and inflammation onto their interconnections during the maternal:infant relationship.

2 | FATTY ACIDS AND BREAST MILK

As the name Mammalia implies, lactation is a key innovation in the evolution of life on Earth. Since mammals first arose ~90 million years ago, a tremendous amount of variation in nursing behaviour evolved. For example, brown bears give birth and suckle their young both during hibernation. Fur seals alternate between focused bouts of nursing and 2–3-week foraging trips away from their pups. Orangutans nurse their offspring for 8 years. And eusocial mole-rat "queens" lactate for the whole colony.

In addition to these extreme differences in nursing strategy, there are remarkable differences in milk content. Even though components in milk vary throughout the lactational period, such that the milk of neonates is distinct from that of the weanling, there are consistent differences in the content of the milk produced by the various species of mammals. Among these dissimilarities, few are as striking as the variation in lipid content. For example, the brown lemur (a primate in Madagascar) produces milk with less than 1% lipid content, whereas the hooded seal (a North Atlantic pinniped) produces milk that is as much as 60% milkfat.[1,2]

The main category of fatty acids in milk are the polyunsaturated fatty acids (PUFAs),[3,4] critical for neurological development, response to inflammation and cell membrane function.[5,6] Mammals are unable to internally synthesise the short-chain (SC) PUFAs, linoleic acid (LA) and alpha-linoleic acid (ALA). These must be consumed through diet. While the more biologically active long-chain (LC) PUFAs also come from food, most mammals can convert the SC-PUFAs consumed through their diet into LC-PUFAs using enzymes produced by the *Fatty Acid Desaturase* (*FADS*) gene cluster, among a handful of other genes.[6]

Human genetic variation in *FADS* falls into two major variants that differ in the rate at which they convert the SC-PUFAs into

Abbreviations: ALA, alpha linoleic acid; DHA, docosahexaenoic acid; *EDAR*, *EctodysplasinA Receptor* gene; *FADS*, Fatty *Acid Desaturase* gene cluster; LA, linoleic acid; LC-PUFA, long-chain polyunsaturated fatty acid; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; *PPAR*, *Peroxisomproliferator-activated receptors* genes; PUFA, polyunsaturated fatty acid; SC-PUFA, short-chain polyunsaturated fatty acid; UVR, ultraviolet radiation; *VDR*, *Vitamin D Receptor*gene.

LC-PUFAs (Figure 1). The more efficient variant—that converts SC- to LC-PUFAs more intensely—may have conferred a benefit in populations with reduced access to dietary LC-PUFAs, such as those with subsistence strategies focused primarily on plant products.[7] While the move to agriculture seems like a logical selective pressure favouring the faster conversion *FADS* variant, the evidence for this correlation is not as convincing as originally inferred.[8] In contrast, the variant that leads to a slower rate of SC to LC conversion may have been beneficial in populations with diets high in LC-PUFAs, such as those with subsistence strategies focused on animal products.[9,10] But as with agriculture, selection for the slower rate *FADS* variant in the especially high-fat, high-protein diets of Arctic populations has also been questioned.[11] Despite the uncertain linkage of *FADS* variation with major dietary shifts, scientists have found that this ancestral *FADS* genetic variation has a significant influence on how effective omega-3 supplementation is for adults consuming a western diet.[12]

While public health campaigns in western, wealthy economies aim to educate adults about the health implications of an omega-6 versus an omega-3 biased diet, it is perhaps less known that an adequate level of omega-3 LC-PUFAs is particularly important for infant health. Over evolutionary time, the selective pressures on the FADS variants influencing rates of fatty acid conversion are feasibly related to the omega-3 and omega-6 fatty acids in the diet of infants rather than adults.

There are multiple excellent reviews of the effects of *FADS* variation on pregnancy, breast milk and childhood.[3-5] For example, a certain amount of omega-3 LC-PUFA is required for optimal foetal development of the central nervous system and vision, and low levels of omega-3 LC-PUFAs significantly increase the risk of preterm birth.[4] Research has also shown that *FADS* variation is associated with total lipid levels in maternal serum as well as with the relative proportions of omega-3 and omega-6 PUFAs that contribute to the lipid content in breast milk.[6] While maternal diet can influence the fatty acid content in milk by approximately 30%, pregnant and lactating people who carry the slower rate variant of *FADS* have relatively higher concentrations of SC-PUFAs (both the omega-6 linoleic acid and the omega-3 alpha-linoleic acid) and lower concentrations of omega-6 LC-PUFAs (arachidonic acid) in their serum and breast milk.[3,5] This bias in fatty acids starts early. During gestation, the placenta preferentially uptakes omega-3 LC-PUFAs from maternal resources, and the foetus also synthesises LC-PUFAs to some degree in accordance with the foetus' *FADS* genotype.[4] Once born, a nursing infant is entirely dependent on breast milk for essential fatty acids, where maternal *FADS* genotype has a significant influence on the proportionality of omega-3 versus omega-6. The slower rate *FADS* variant correlates with lower LC-PUFAs in breast milk and reduces the dietary influence on DHA levels (an omega-3 LC-PUFA) compared to the faster rate *FADS* variant.[3]

Considering how successful the evolutionary innovation of milk has been and how variable it is across mammals today, we hypothesise that genetic variation influencing milk has very likely been a significant and common target of selective pressures for humans too. Afterall, any benefit that improves infant survival leads to a significant increase in parental evolutionary fitness. Given that the genetic variation observed in human *FADS* genes has an influence on maternal and infant health, we propose that selection on *FADS* is related to mammary gland development, the immune system and vitamin D. This hypothesis intertwines with our previous identification of *EDAR V370A*'s influence on human lactational biology.[13]

Key Notes

- Episodes of evolutionary adaptation provide insight to the physiological mechanisms critical to early childhood survival.
- A bout of intense selective pressure on a human population living in the Arctic during the last ice age highlights the important interplay of ectodysplasin, fatty acids, vitamin D, inflammation and ultraviolet radiation on maternal:infant health.
- This evolutionary perspective presents novel hypotheses for research into human lactational biology and infant health.

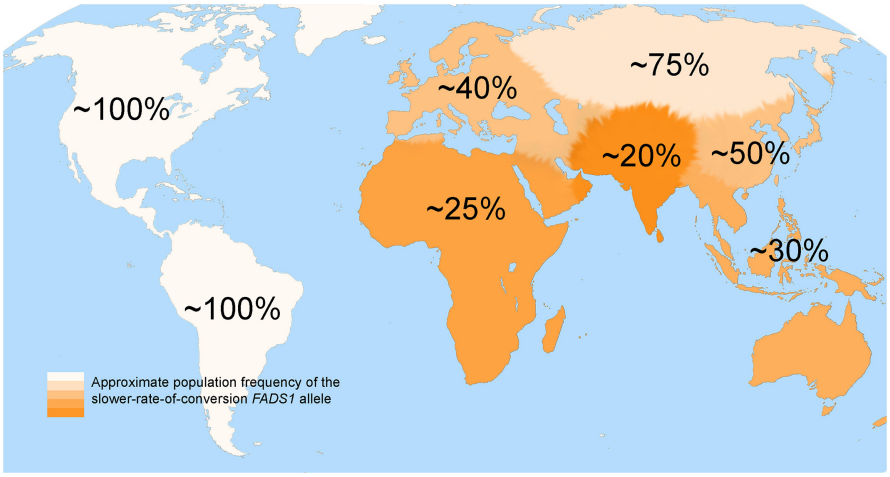

FIGURE 1 Map showing worldwide occurrence of the slower rate-of-conversion *FADS* variant. The population-level frequencies reported here are estimated from Mathieson and Mathieson (2018)[8]

3 | INTENSE SELECTION ON *EDAR* ABOUT 20,000 YEARS AGO

The evidence for ectodysplasin's influence on human mammary glands begins with evolutionary genomics. Analyses of human genomic variation revealed an episode of intense selection about 20,000 years ago for the *V370A* variant of the *Ectodysplasin A Receptor* (*EDAR*) gene.[14] Unlike many other episodes of selection on genetic variation that confirmed our prior knowledge of adaptation—such lactase persistence and malarial resistance, for example—this discovery was initially unexpected and rather puzzling. *EDAR V370A* leads to an increase in the activity of the ectodysplasin pathway, which in turn leads to a decrease in the adhesive strength that holds epithelial cells together.[15] Phenotypic variation associated with *EDAR V370A* includes thicker and straighter hair, an increase in the number of sweat glands, maxillary incisors that are shovel-shaped on the tongue side (Figure 2), and an increase in the ductal branching of the mammary glands, among other effects.[13] The modern-day occurrence and frequency of the *V370A* variant suggested that the selective event was in northern China.[14] Ideas for what the targeted anatomical feature might have been range from sweat glands to sebaceous glands, or, somehow, to the ability to eat rice that would not be domesticated for another 10,000 years.[14,16,17] A closer look at the function of *EDAR* provides more insight.

4 | THE *ECTODYSPLASIN A RECEPTOR* (*EDAR*) GENE

*EDAR*is one of the death receptors in the tumour necrosis factor receptor superfamily that evolved 350–450 million years ago.[18] Not all of the death receptors are involved in programmed cell death. Some have evolved over many millions of years to utilise the same signalling pathways for other roles. For example, the ectodysplasin pathway includes NF-κB signalling to regulate gene expression involved in the development of ectodermally derived epithelial structures.[18] This co-option is fascinating because the main role of NF-κB signalling is to regulate pro-inflammatory responses and support innate immune cells and inflammatory T cells.[19] As the *V370A* variant increases the activity of the ectodysplasin pathway leading to a reduction in the adhesive strength between epithelial cells (that results in increased mammary gland ductal branching, shovel-shaped incisors and thicker hair shafts), it also increases the activity of NF-κB signalling by perhaps as much as 100%.[14] The broader physiological implications of this increased *EDAR*-induced NF-κB signalling have not yet been explored. However, we know that too much NF- κB signalling in epithelial cells leads to chronic inflammation and disease, while too little NF-κB signalling also leads to inflammation and disease, suggesting that there is an optimal range for NF-κB activity.[20] This window of ideal NF-κB signalling may be a constraint on the range of viable *EDAR* expression.

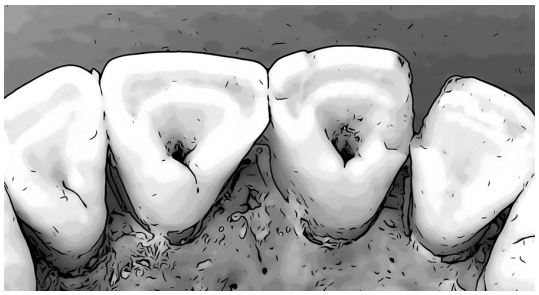

FIGURE 2 Illustration of the lingual view of human maxillary central incisors with a high degree of incisor shovelling. Among humans, this topography varies from flat to the highly curved configuration seen here. Illustration based on image courtesy G. Richard Scott

5 | WHERE DID THE SELECTION FOR *EDAR V370A* OCCUR?

Human occupation around the world has changed quite a lot over the intervening 20,000 years. For example, there was the migration into and throughout the Americas that started around 15,000 years ago, and then the European colonisation of these continents 500 years ago. These major migratory events remind us that the pattern of allelic distribution observed in populations today is only a very rough proxy for the past. Fortunately, teeth (yes, teeth) provide a window into the occurrence of *EDAR V370A* over this time period. As mentioned previously, *EDAR V370A* has pleiotropic effects on a variety of epithelial traits and these effects are additive. People with one or two copies of *V370A* have incisors that are slightly to strongly shovel-shaped, reflecting either one or two copies of the *V370A* allele.[21]

Hlusko and colleagues observed the pattern of incisor-shovelling variation in 5,333 people from over 54 archaeological populations across Eurasia and the Americas that all predate European colonisation (Figure 3).[13] The dental data from archaeological populations revealed that incisor shovelling rose to very high frequency in a population that took refuge in Beringia during the last ice age 28,000 to 18,000 years ago. Because of the association between the degree of incisor shovelling and the *EDAR* genotype,[21] we inferred that people with shovel-shaped incisors carried one or two copies of this gene variant. The timing of this dramatic increase in incisor shovelling matches the timing of selection on *EDAR V370A*, indicating that our use of dental variation as a proxy for *EDAR* genotype was appropriate. The pattern of incisor shovelling across archaeological populations revealed that the selective event for *EDAR V370A* occurred in the region of Beringia, an area that is now mostly covered by the rise in sea level that began with the end of the last ice age. Knowing the geographic region of the selective event, we then identified the most likely selective pressure: the extremely low level of sunlight in the Arctic that leads to dangerously low levels of vitamin D.

The next step in solving this evolutionary puzzle was to figure out, of all the anatomical structures mentioned previously that are influenced by *EDAR*, which could confer an advantage under low ultraviolet radiation (UVR) conditions? Mammary glands are the most closely

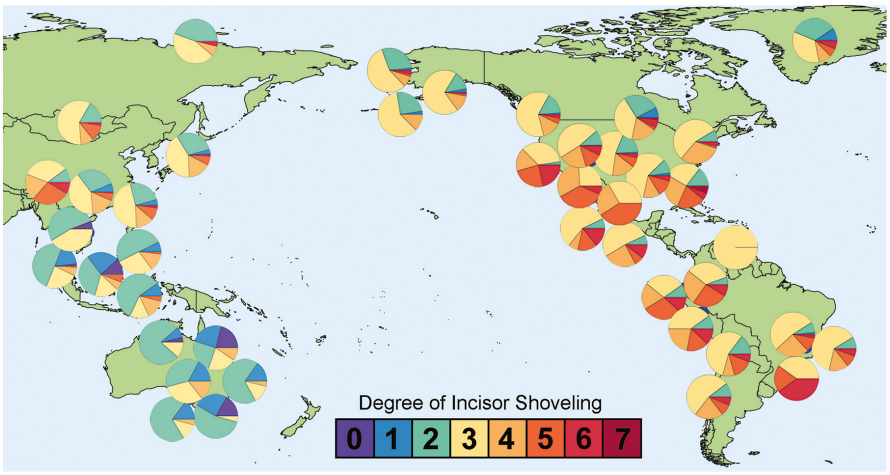

FIGURE 3 Pie charts showing the degree of incisor shovelling observed for dozens of human populations across East Asia and the Western Hemisphere. The color-coded scale at the bottom of the image reports the degree of shovelling expression, from a smooth lingual crown surface with a score of zero (dark blue), to fully expressed shovelling with a score of seven (dark red). The central incisors illustrated in Figure 2 have a score of seven. Map is modified from Hlusko et al. (2018)[13]

related to a particularly fragile time during a person's life (infancy) in a particularly challenging environment (the vitamin D-poor Arctic). Infants are solely reliant on mother's milk for their vitamin D because their skin cannot synthesise it in such a low UV environment and they cannot yet eat vitamin D-rich foods as adults do. Piecing together other evidence about milk production, Hlusko and colleagues hypothesised that the increase in mammary gland ductal branching associated with *EDAR V370A* likely conferred an advantage in the transmission of vitamin D and other nutrients between mother and infant through breast milk in this high latitude population.[13] While incisor shovelling was the key to figuring out this episode of selection, the primary phenotypic effect of interest is mammary gland ductal branching.

Bears provide an interesting comparison for this discussion. Brown and black bears are found in temperate to sub-Arctic regions. Polar bears reside only in the Arctic. Milk lipid content is 19–22% for brown bears, 23–30% for black bears and 27–35% for polar bears.[22,23] The dangers of lipid and vitamin D deficiency in early life are best exemplified by a study on captive polar bears. These polar bear cubs developed rickets after being fed with a fortified formula based on cow's milk that was far lower in both lipid and vitamin D than polar bear milk.[23] It turns out that polar bear milk contains 675 IU/l of vitamin D (compared with 400 IU/l in cow's milk) to compensate for the inability of polar bear cubs to biosynthesise vitamin D, a problem not attributed to brown or black bears.[23]

6 | VITAMIN D AND LATITUDE

Another example of human adaptation to variation in ultraviolet radiation (UVR) is skin pigmentation.[24,25] The penetration of UVR through skin initiates the biosynthesis of vitamin D in the body. Vitamin D (specifically $1,25(OH)_2$ D_3) regulates the transcription of genes by binding to the *Vitamin D Receptor* (*VDR*) gene, which in turn modulates hundreds of genes in a wide variety of cell types and tissues.[26] In equatorial regions, humans are exposed to so much UVR that vitamin D synthesis is never a concern; the physiological challenge comes from the damaging effects of UVR exposure. Therefore, in low latitudes selection favours darkly pigmented skin as protection against the harmful effects of UVR. As humans expanded into higher latitudes they were exposed to significantly less UVR. The ability to biosynthesise vitamin D became more problematical for survival than UVR's damaging effects. Genetic variants that reduce levels of skin pigmentation were positively selected for, repeatedly, because they facilitate the body's ability to absorb UVR under conditions of low exposure, and thereby enable the biosynthesis of adequate levels of vitamin D. Reduced levels of skin pigmentation have been selected for at least three different times in recent humans.[25]

However, as people moved to higher and higher latitudes, they eventually reached a point where the levels of UVR exposure were so low that no degree of skin depigmentation could compensate (~46 degrees latitude).[24] Cultural innovations were necessary to overcome this biological boundary, such as a heavy reliance on marine resources and other foodstuffs rich in vitamin D, as seen in traditional Arctic cultures today. These are the high-fat, high-protein diets that may have led to selection for the slow-conversion *FADS* variant that reduces levels of LC-PUFAs mentioned earlier.[9,10]

7 | THE IMPLICATIONS FOR INFLAMMATION

Variation in the structure of fatty acids leads to different physiological effects in the body. We previously mentioned the pro-inflammatory effects of omega-6 and the anti-inflammatory effects of omega-3 fatty acids, noting that the LC-PUFAs are the more bioactive. Keep in mind that the major *FADS* variants influence the rate of synthesis of the LC-PUFAs. The inflammatory effects of omega-3 and omega-6 play out through antagonistic signalling of the NF-κB pathway and *Peroxisom proliferator-activated receptors* (*PPAR*).

PPAR receptors act as co-activators and corepressors for genes involved in metabolism and inflammation.[3,27] The PPAR-gamma isotype is expressed in adipose tissue, mammary epithelial cells and placenta.[27,28] PPAR-gamma's role in the inflammatory and anti-inflammatory effects of fatty acids is particularly important to our discussion because of its ability to inhibit the NF-κB pathway. An increase in the activity of PPAR-gamma leads to a decrease in the

activity of the NF-κB pathway, and therefore, a decrease in its pro-inflammatory effect. To summarise, an increase in PPAR-gamma signalling and an increase in ectodysplasin signalling have opposite effects on NF-κB signalling in epithelial cells.[27,28]

Now let us consider the role that PUFAs play in all of this. Omega-6 fatty acids bind to PPAR-gamma, diminishing its ability to suppress NF-κB activity. This is why diets high in omega-6 fatty acids are associated with an increase in inflammation; PPAR is preoccupied by these fatty acids and therefore does not suppress NF-κB activity to the same degree as it would in the presence of lower levels of omega-6 fatty acids. In contrast, omega-3 fatty acids activate PPAR-gamma, increasing its ability to inhibit the NF-κB pathway.[27]

Once we include LC-PUFAs into our consideration of inflammation, we see that an increase in the activity of the ectodysplasin pathway (such as is caused by the *V370A* variant of *EDAR*) and very high levels of long-chain omega-3 PUFAs have opposite effects on NF-κB signalling.

Today, western cultures strive to increase the amount of omega-3 PUFAs in their diets to counterbalance foods that are highly biased towards omega-6 fatty acids. Omega-3-rich foods are seen as very healthy. But can there be too much of a good thing? Research indicates yes. Consuming too much omega-3 LC-PUFAs is associated with dampened immunity, especially in the face of acute infection and tumour surveillance.[29]

In traditional Arctic cultures, people consume a marine diet rich in omega-3 fatty acids which increases PPAR-gamma's suppression of NF-κB signalling. We can surmise that the ancient Beringians 20,000 years ago also consumed high levels of dietary omega-3 that suppressed NF-κB signalling. This ancient Beringian population also had a high occurrence (and perhaps selection for) the slower-rate variant of *FADS* that reduces the effects of fatty acids by lowering the overall level of the more bio-active LC-PUFAs and suppressing the uptake of dietary omega-3 LC-PUFAs into breast milk. Simultaneously, the ancient Beringians experienced intense selection on a variant of *EDAR* that increased the activity of NF-κB signalling.

Could the selection for *EDAR V370A* and the presumed selection for the slower rate *FADS* variant be the result of the need to balance the effects of NF-κB signalling on the immune system in the extreme environment of the Arctic? Keep in mind that higher levels of oestrogen and progesterone, as is associated with pregnancy, induce the synthesis of LC-PUFAs, presumably to better support the developing fetus.[6] This increase in omega-3 LC-PUFAs would theoretically bring with it even further suppression of NF-κB signalling.

8 | VITAMIN D AND THE IMMUNE SYSTEM

We have raised two possibilities for how *EDAR V370A* may have conferred an advantage to maternal-infant health in the Beringian population 20,000 years ago:

- The very low levels of UVR in the Arctic present an extreme environmental selective pressure on vitamin D. Increased ductal branching may have facilitated nutrient transfer from mother to infant, although exactly how this mechanism works is not yet known.
- Alternatively, the increased activity of the ectodysplasin pathway may have been selected for because of its effects on the NF-κB pathway, increasing the activity of this pro-inflammatory pathway in the face of a diet high in anti-inflammatory fatty acids.

These two scenarios may not be mutually exclusive. Vitamin D, working through expression of *VDR*, is intricately involved in immunity.[30] Vitamin D and *VDR* are also essential for optimal metabolic function of adipose tissue, including the pink adipocytes of the mammary glands.[26] Vitamin D reduces adipose tissue inflammation through the inhibition of NF-κB signalling, like PPAR-gamma.[26] The similarities between the activities of vitamin D/*VDR* and PPAR-gamma have been outlined in detail.[30] Given that these two receptors are highly expressed during the early stages of metabolic disease and cancer, they may be working together to counterbalance those harmful effects.[30]

9 | CONCLUSION

Evolutionary biologists have long recognised that adaptation to extreme environments can provide a window to physiological processes that are otherwise difficult to discern. These "natural experiments" provided by evolution offer unique perspectives on biology. The mini-review presented here suggests that adaptation to life in the Arctic may prove to be key in elucidating the interconnections between fatty acids, vitamin D and ectodysplasin's effects on maternal-infant health.

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CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

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