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Was the Last Ice Age dusty climate instrumental in spreading of the three "Celtic" diseases (hemochromatosis, cystic fibrosis and palmar fibromatosis)?

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A B S T R A C T

Cystic fibrosis, hereditary hemochromatosis and palmar fibromatosis are often described as "Celtic", based on their contemporary prevalence. The former two are among genetically defined disorders that seem to provide survival advantages to heterozygote individuals, while severe health problems happen in homozygote mutation carriers. Although palmar fibromatosis has no defined mutations, its prevalence has been linked to the prevalence of Y-Chromosome Haplogroup I that expanded after the Last Ice Age, thus making th distribution of all three "Celtic" diseases dependent on the global climate from 40 to 8 Kya. During the Last Ice Age, the global climate was dry and dark due to dust-laden atmosphere (20–25 times more than today). It has been postulated that skin pigmentation was related to insolation, UV protection and skin synthesis of vitamin D, so when our ancestors moved to Eurasia, individuals with pale skin became advantageous.

Deficiency of vitamin D has several health consequences and some of them have been proposed by other authors as important for the spreading of cystic fibrosis mutations: rickets/osteomalacia; susceptibility to diarrheal diseases and tuberculosis and salt induced arterial hypertension.

The here proposed link is between vitamin D deficiency and the anaemia of chronic disease that might have facilitated spreading of the hemochromatosis mutation. It seems plausible that the risk of health problems in the offspring of close relatives might have resulted in social taboos of consanguinity in Eurasian protosocieties. Ancient steam bath rituals seem linked to lower incidences of cystic fibrosis in several European populations, thus suggesting health protection in an arid, dusty climate of the last glaciation, that made CFTR mutations in heterozygote carriers less advantageous.

Introduction

Three medical conditions are often described as "Celtic" or sometimes as "Viking", namely cystic fibrosis, caused by CFTR mutations [1,2], hereditary hemochromatosis, caused by HFE mutations [3,4] and palmar fibromatosis [5,6], still without clear genetic explanation.

Cystic fibrosis and hemochromatosis are among disorders that seem to provide survival advantages to heterozygote individuals, while severe health problems happen in homozygote mutation carriers. Otherwise, mutated genes would not have been so successfully spread in various populations.

A possible link between these seemingly unrelated "Celtic" conditions might be their time of occurrence and spreading among our Eurasian ancestors (shown also in Table 1):

The emergence of a mutated cystic fibrosis gene is estimated to be early in the Last Ice Age [7]. The main mutation, delta F508, seems to be older than 52 Ky and its spreading over Europe has happened some 40 Kya.

The most prevalent hemochromatosis mutation has occurred much later, estimated to be older than 6 Ky [3,4], so we might expect that it happened during and after the Eurasian deglaciation, some 10 Kya.

Palmar fibromatosis has no defined mutations, but its contemporary prevalence resembles the prevalence of Y-Chromosome Haplogroup I (Hg I) [8,9], also linked to the period of inhabiting Europe, soon after the Last Ice Age (some 10 Kya).

Background

Human evolution and atmospheric dust

Nina G. Jablonski and George Chaplin have proposed that during human evolution, skin pigmentation was related to insolation, UV protection and skin synthesis of vitamin D [10]. Skin became dark after our African ancestors have lost their body hair. Darker skin indviduals were better protected against UV rays, able to destroy the circulating folate. When our ancestors moved to Eurasia, individuals with less dark skin became advantageous, since the reduced sun exposure in northern latitudes compromised their vitamin D synthesis. Deficiency of vitamin D impaired bone growth and locomotion, particularly in young individuals.

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Table 1
The simplified time scale and climate change in Eurasia from 100 to 10 Kya. Cold, arid and a dusty climate during the last Ice Age resulted in vitamin D deficiency, impaired mobility and dust exposure. These unfavorable conditions might have been important in spreading of genes for pale skin, heterozygote settings for hemochromatosis or cystic fibrosis and also predisposition for palmar fibromatosis.

<table>
<tr><th rowspan="2">Time (in Kya)</th><th rowspan="2">Trait spreading</th><th rowspan="2">Atmospheric dust</th><th rowspan="2">Insolation</th><th colspan="3">Eurasia</th></tr>
<tr><th>South</th><th>Central</th><th>North</th></tr>
<tr><td>100 to 30 Increasing glaciation</td><td rowspan="2">delta F508 occurrence (>52Kya) & spreading (40Kya)</td><td>Increasing due to arid erosion by glaciers</td><td>Low</td><td rowspan="2">Mammoth steppe, from Spain to Alaska, south of permafrost and ice sheets</td><td>permafrost</td><td rowspan="2">Ice sheets</td></tr>
<tr><td>30 to 20 Last Glacial Maximum</td><td>High</td><td>Minimal</td><td>ice sheets</td></tr>
<tr><td>20 to 12 Slow deglaciation</td><td rowspan="2">Spreading of Hg I & palmar fibromatosis (~10Kya) Hemochromatosis (>6Kya)</td><td>High, slowly decreasing</td><td>Low Slowly increasing</td><td>receding permafrost</td><td>receding ice sheets</td></tr>
<tr><td>12 to 10 Rapid deglaciation</td><td colspan="2">Rapid dust precipitation and increases insolation, changes toward modern humid climate</td><td colspan="3">Defrosted areas spread toward north</td></tr>
</table>

Indirect supportive evidence can be found in reports that the levels of vitamin D vary among ethnic groups [11], suggesting adaptations to different insolation levels among their ancestors. The other supportive evidence is the report that human genes for pigmentation came from the Neanderthals [12] who have lived longer than 400 Ky years in Eurasia, surviving several ice periods with high atmospheric dust and reduced insolation.

We must keep in mind that during the Last Ice Age (more than 100 Kya till less than 10 Kya), the global climate was dry and with reduced insolation due to the dust-laden atmosphere (20 to 25 times more atmospheric dust than the modern day level) [13], as shown in Table 1.

Here it is important to note that disadvantages of low vitamin D production have probably become more important during migrations into north Eurasian territories, at the end of the Last Ice Age, when ice was melting with abundance of fresh water, thus allowing emergence of new living areas further north. So, as the dust slowly settled down due to more atmospheric humidity, people started migrating to higher latitudes. They already were pale skinned, used heavy clothing to protect from cold, so there was no simple way for them to further improve their vitamin D production in skin. Only those who have reached north seas were saved by high dietary availability of vitamin D from seafood.

Diverse health issues caused by vitamin D deficiency

Beside the already proposed link of vitamin D deficiency with tuberculosis and hypertension [14], another important vitamin D action is in iron homeostasis, regulated by hepcidin. This is a liver synthesized peptide hormone that regulates all aspects of systemic iron homeostasis, including iron tissue distribution and inhibiting intestinal iron absorption [15]. Synthesis of hepcidin is increased by iron ingestion, during infections and inflammation, by liver cells exposure to HFE protein [16] and also by deficit of vitamin D [17]. High hepcidin levels cause the anaemia of chronic disease.

The proposed hypothesis

The here proposed hypothesis is that in many of our ancestors who roamed through continental areas of Eurasia, deficient skin production of vitamin D has become the limiting factor of their stamina due to these reasons:

compromised bone growth and strength limit locomotion abilities of affected individuals [10]
increased hepcidin levels result in chronic anemia due to altered iron homeostasis, even in hunters on a meat rich diet [17]
Increased susceptibility to diarrheal diseases, tuberculosis and also to arterial hypertension caused by high salt ingestion [14].

This opens the possibility that a certain interplay between regulatory mechanisms of the calcium and of the iron metabolism can result in a united survival challenge that weakens otherwise normal individuals when migrating to a physically challenging environment with insufficient insolation and low dietary vitamin D. Although this complex environmental setting can seem quite unlikely today, at the end of the Last Ice Age, large areas of central and northern Eurasia were probably just like that.

Altered iron metabolism

Based on the assumption that vitamin D deficiency and the consequent hepcidin dependent anemia were common among our ancestors in Eurasia after the last Ice Age, some 10 to 6 Kya, sporadic mutations of the HFE gene have probably become important for survival. The heterozygote carriers of one mutated HFE gene had lower levels of HFE protein that subsequently reduced hepcidin synthesis in liver, despite the vitamin D deficiency.

So, if migration toward north compromised the muscle strength of our ancestors, due to anemia of chronic disease, individuals with lower HFE protein levels were less anemic and thus more durable.

The heterozygote condition for HFE mutations might become important for survival even at low latitudes and after the agrarian revolution, while the other two “Celtic” traits have probably lost their survival advantages some 6 Kya. Using mainly cultured plants in diet significantly reduced iron ingestion, so less HFE might help avoid anemia in individuals living on plant food. On the other hand, iron poor diet reduced risk of severe hemochromatosis in homozygote individuals and this also helped spreading of mutated HFE genes all over Eurasia.

Possible survival advantages for a single CFTR mutation carriers

Among the already proposed advantages of being a CFTR mutation heterozygote carrier, several of them are based on the local climate in

Eurasia at that time:

Improved resistance to cholera toxin and other diarrheal disorders, including lactose intolerance [18], typhoid fever [19], possibly related to the cattle pastoralism and migratory routes [20].
Limited water resorption in respiratory mucosa of heterozygotes might allow improved airway cleansing [21] during dusty atmosphere of the Last Ice Age.
Altered Cl^- transport suppresses tuberculosis and alleviates the risk of hypertension caused by salt ingestion [14,22], since low vitamin D availability increases the chances for tuberculosis and hypertension.

The last proposition links consequences of vitamin D deficiency with altered chloride transport on mucous membranes. Here again, the proposed mechanism can ameliorate the consequence of the reduced vitamin D availability, caused by low insolation. The mutated gene alters the overall setting by introducing a mild counteracting disorder to the already present health deteriorating vitamin D deficiency. Unfortunately, in homozygote individuals, alterations of both genes cause severe health problems.

Possible survival advantages of the palmar fibromatosis predisposition

If the climate of the Last Glacial Period was so cold, dark and arid that the survival of our ancestors depended heavily on their physical stamina and skills, anatomical adaptations that would improve hill climbing were highly favorable, particularly to hunters and gatherers living in high northern latitudes whose health was already compromised due to low vitamin D availability that might lead to rickets, anaemia, respiratory and diarrheal infections or arterial hypertension.

When a predisposition for palmar fibromatosis, due to change of collagen type in palmar fascia, from type I to type III, has emerged among our ancestors, this complex trait has spread easily. Individuals with this predisposition were more physically able in their young age, so they survived longer and produced more children. Few of them would have lived long enough to suffer from palmar contractures.

Even in modern times, palmar fibromatosis seems to be of a high incidence among climbers. It was reported that 19.5% of male climbers had developed Dupuytren's disease and at an earlier age of onset than in the general population [23], possibly suggesting that individuals with this predisposition are somehow also predisposed for climbing as a recreational activity.

Evaluation of the proposed hypothesis

Here proposed idea is that heterozygote carriers of mutations linked to cystic fibrosis, or of HFE mutations or individuals predisposed for palmar fibromatosis, all had a survival edge in the continental Eurasia during and after the last glaciation.

The proposed central role of vitamin D deficiency in spreading of some of these traits among our ancestors is shown in Table 2. Two phenotype features are not directly linked to vitamin D, these are palmar fibromatosis and improved cleansing of airways, so they are listed in the last two columns of this table.

Nevertheless, it has been proposed that there is a link between vitamin D and palmar fibromatosis, via Transforming growth factor-ß1 (TGF-ß1) and its downstream Smad signaling pathway [24,25]. TGF-ß1 mediates fibrosis and myofibroblast differentiation through the increase in mitochondrial ROS production, particularly during vitamin D deficiency. The same mechanism seems applicable to fibrosis of lungs and other organs [26].

If certain traits have proved advantageous only in the climate of the last Ice Age, the above mentioned probable relation between low vitamin D and increased fibrosis can be interpreted as an additional unfavorable condition, forcing selection of traits might seem unrelated to the vitamin D availability:

For instance, if vitamin D protects from airway inflammation [27], our ancestors were probably more prone to pulmonary fibrosis due to vitamin D deficiency. In this setting, improved airway cleansing in heterozygote carriers of the CFTR mutation might have been even more important in that dusty atmosphere.
If disabling locomotor fibrosis was more common than today, also due to vitamin D deficiency, only a few individuals with improved climbing skills might have been advantageous. This selection might have resulted in widespread predisposition for palmar fibromatosis as the winning phenotype variant.

In these two examples, vitamin D deficiency makes individuals more prone to develop disabling conditions and spreading of CFTR mutation or of predisposition for palmar fibromatosis might have reduced risks of developing health problems in heterozygote carriers.

The steam bath question

Possibly another example of counteracting the individual chances of having respiratory problems due to the atmospheric dust, might be the practice of steam bath rituals in various populations around the globe (reviewed in [29]). IA Lopatin has defined the steam bath as “the water vapor bath”, very common among Russians, Swedes, Norwegians, people of Finland, the Esthonians and the Latvians and among almost all the American Indian tribes in North America and some South American tribes. He points out from this geographical distribution, that the steam bath of the Sauna type is typical of northwestern Europe and of Americas only, and that it occurs neither in Asia nor on the other continents.

This puzzle regarding discontinuous distribution of steam bath rituals only among the “pale” skin populations (northern Europe/west Asia, both Americas), might be related to the reported genome of a juvenile individual (MA-1) from the Mal'ta Upper Palaeolithic site in south-central Siberia, near Lake Baikal, who lived 24.4–23.9 Kya [28]. The findings suggest that his mitochondrial genome is related to Upper Palaeolithic and Mesolithic European hunter-gatherers, while some autosomal genes and the Y chromosome are related to modern western Eurasians and most Native American lineages, while no close affinity to east Asians was found.

A possible interpretation is that this juvenile individual belonged to a small population of the Mal'ta–Buret' culture whose members tried to spread along the Mammoth steppe to more habitable areas, during and after the Last Glacial Maximum (some 26.5 Kya). Some of them went to the west Asia and Europe, while the rest of them moved over the Bering land bridge into Alaska, to become the first Paleoamericans. Since they have probably left very few descendants in the east Asia, modern Asian populations are genetically remote from them.

These possible ancestors of both modern Europeans and of Native Americans might have already developed steam bath rituals, before splitting and leaving the Baikal region. Although the steam bath rituals were probably of spiritual importance, they obviously helped our ancestors in cleansing of dust from skin and respiratory organs.

This question becomes more interesting if we compare Lopatin’s distribution of steam bath rituals [29] with the reported incidences of cystic fibrosis [30–32]. European populations with the lowest rates of cystic fibrosis [30–32] are also populations with a long steam bath tradition [29]: Finland (1:25000 births); Sweden (1:7300); Russia (1:4900); Denmark (1:4700); Norway (1:4500); Estonia (1:4500). Populations with highest risks of cystic fibrosis in Europe are also populations that lack tradition of steam baths (Slovenia, Belgium, Czech Republic, United Kingdom, Bulgaria, Italy, France, Romania, Switzerland, Scotland, Slovakia and Ireland with the risk of 1:1353 births).

A possible interpretation is that during the last glaciation, regular steam bath cleansing of respiratory organs was so beneficial to the

Table 2
The overall view on survival challenges in Eurasia during the last Ice Age that might have been important in spreading of genes for pale skin, heterozygote settings for hemochromatosis or cystic fibrosis and also of the predisposition for palmar fibromatosis (previously proposed relations in light gray, here proposed relations in gray).

Possible survival related settings	Survival advantage against health challenges due to atmospheric dust in Eurasia during and after the Last Ice Age (100-8 Kya)							
	Vitamin D deficiency due to low insolation						Climbing dependent survival	Cleansing of dust from respiratory organs
	Rickets/ Osteomalacia	Anaemia of chronic disease (16, 17)	Diarrheal diseases & tuberculosis (14)	Salt induced arterial hypertension (14)	Induction of fibrosis via TGF-β1 (24-27)			
					pulmonary	plantar		
Pale skin	Proposed (10)	Proposed (here)	NOT expected					
Seafood rich in vitamin D			Proposed (14)		EXPECTED		NOT expected	
Cystic fibrosis mutation	NOT expected				NOT expected		NOT expected	Proposed (21)
Hemochromatosis mutation	NOT expected	Proposed (here)	NOT expected					
Predisposition for palmar fibromatosis	NOT expected					disadvantage in the older age	Proposed (9)	NOT expected

survival that in these populations already present CFTR mutations were of marginal survival advantage and thus their incidence remained lower than in populations that lacked the steam bath practice. If this proposition is plausible, the steam bath rituals might be the oldest surviving human folklore, older than 20 Ky.

Modern epidemiological data and ancient migrations

It seems important here to recognize that the modern data on epidemiology of all these traits probably still contain information regarding Eurasian migrations during the last 20 Ky. Spreading of Celts and Vikings should then be considered only as the most recent migrations. Differences between populations in traits' incidences and also in activities that might be related to the dust exposure might thus reflect their survival challenges during and after the last glaciation.

By using this approach, we might expect that populations with an increased incidence of cystic fibrosis might have dwelled during the Last Ice Age in dusty, loess forming Eurasian areas. Dust exposure of their respiratory organs might have increased survival of heterozygous carriers of CFTR mutation, until the risk of homozygote health problems has become so evident to force them to address consanguinity. It seems possibly that the awareness of consanguinity-related health risks (occurrence of cystic fibrosis or of homozygote thalassemia) might have resulted in social taboos of consanguinity and thus changed Eurasian proto societies toward larger and more open communities.

Likewise, after the last Ice Age, populations with high prevalence of HFE mutations might have lived further north than the other groups without this mutation.

Based on the same line of thinking, European populations with high chances of developing palmar fibromatosis might have lived in regions with steep mountains during the Last Ice Age and then migrated in a pattern similar to the carriers of Y-Chromosome Haplogroup I [8,21].

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