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Hypothesis: Possible respiratory advantages for heterozygote carriers of cystic fibrosis linked mutations during dusty climate of last glaciation

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HIGHLIGHTS

- Airway fluid is lost through evaporation, particularly when breathing cold and arid air.
- Fluid reabsorption depends on active CFTRs that allow ENaCs to absorb salt and water.
- The cystic fibrosis (CF) mutation is common in north Europe and probably near 52 ky old.
- Between 50 and 10 kya, the European climate was arid, cold, with a dust-laden atmosphere.
- Individuals with one CF mutation due to slower fluid reabsorption might have better clearance of inhailed dust.

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ABSTRACT

This paper puts forward a new hypothesis to interpret the high carrier frequency of CFTR mutations in individuals of European descent. The proposed heterozygote advantage factor is related to the specific climate conditions in Europe during the last 50 ky that might have heavily compromised the respiratory function of our ancestors in Eurasia. A large part of the last 50 ky was cold, and the coldest period was the Last Glacial Maximum (LGM) (26.5 to 19 kya). The global climate was dry with a dust-laden atmosphere (20 to 25 times more dust than the present level). High levels of atmospheric dust started more than 40 kya and ended less than 10 kya.

Secretion of airway fluid is usually related to the submucosal tissue hydration, while salt reabsorption relies on activation of CFTRs that allow ENaCs to absorb salt and water. The water loss by evaporation depends on the air humidity and flow rate. Salt accumulation in the mucus is normally prevented by reabsorption of Na^+ and Cl^- by epithelial cells if the presence of functional CFTRs is normal.

If one gene for CFTR is mutated, the number of functional CFTRs is reduced and this limits the capacity of salt reabsorption by epithelial cells. This means that evaporation makes the airway fluid more hypertonic, and osmotic forces bring more water from the interstitial space, thus leading to a new balance in mucosal fluid traffic. Increased osmolarity and volume of airway fluid can be more moveable in cases when evaporation and dust exposure is increased.

If both CFTR genes are mutated, low number of functional CFTRs diminishes salt resorption of epithelial cells. Salt accumulated in the mucous fluid within respiratory ducts, as previously described. The hypertonic ductal content forces more water and some electrolytes to enter the airway fluid from the interstitial fluid, and evaporation leads to further concentration of thick immobile mucus.

The proposed interpretation is that CFTR mutations have spread among our ancestors that roamed the central Eurasia after the LGM. The heterozygote individuals might have benefitted from the limited water resorption in their respiratory mucosa that allowed improved airway cleansing.

1. Introduction

A puzzling question is what makes the prevalence of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) mutations

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so common among Europeans, particularly in people from northern Europe (estimated mutation incidences are 1:200 in northern Sweden, 1:143 in Lithuanians, and 1:38 in Denmark (Wennberg and Kucinskas, 1994)). Besides that, the highest disease incidence was reported in Italy, France, Switzerland, British Isles, Germany and Greece (Bobadilla et al., 2002). It is puzzling that Saamis and Finnish have the lowest rates in Europe (Wennberg and Kucinskas, 1994), while the highest incidences have been found in some disparate locations such as Ireland, Romania, Slovakia and Bulgaria (Farrell, 2008).

Although the geographical distribution of the disease is key to judge the suitability of any hypothesis aiming to explain its etiology, in the described setting of CFTR mutations, the overall information is blurred by continuous human migrations during the last 50 ky. The situation became even more complex during the Neolithic period when improved climates opened new routes for animal migration (Pinhasi et al., 2012) thus forcing hunter-gatherers to cover new and longer distances that helped gene spreading.

An early interpretation of high prevalence of CFTR mutations in Caucasian population was that it had resulted from a fertility advantage in CF carriers. Despite early small supportive studies, this hypothesis was not supported by data of 143 grandparent couples of Utah CF patients compared with 20 replicate sets of matched control couples from the Utah Genealogical Database (Jorde and Lathrop, 1988). More recently, the same idea of increased fertility was tested in the Hutterites of South Dakota, a genetic isolate with a relatively high CF carrier frequency (M1101K and F508 mutations) (Gallego Romero and Ober, 2008). Again, with no evidence of nonrandom transmission of mutations, skewed sex ratios in children of carrier parents or of altered overall fertility of carriers. These data clearly suggest that other, fertility unrelated mechanisms are more likely to be responsible for the prevalence of CF related genes.

Other possible advantages of being a CFTR mutation carrier include improved resistance to cholera toxin and other diarrhea disorders, including lactose intolerance (Modiano et al., 2007). Besides that, the heterozygotes seem to have better resistance to typhoid fever (Pier et al., 1998).

Another interesting proposition is that the distribution of CF genes results from the development of the cattle pastoralism in the recent Neolithic period (Alfonso-Sánchez et al., 2010). These combined seasonal migrations of men and their cattle helped spreading of infectious disease that imposed a new survival pressure favoring certain traits, possibly even the CF related genes in heterozygote individuals. These authors propose that an increased resistance to the diseases caused by pathogens transmitted by dairy cattle would have constituted a definite selective advantage. A single copy of mutated CFTR gene might provide additional resistance to chloride secreting diarrheas. This attractive interpretation is based on similar distributions of the lactase persistence and of the most common CF mutation (Delta F508).

An even more complex physiological interpretation of CFTR spreading, is proposed by Lubinsky (2012) and, involves the question of resistance to tuberculosis (Poolman and Galvani, 2007; Williams, 2006). The core idea is that complex interaction between climate, pathogens and human physiology can explain the CFTR mutation carrier distribution. The climate factors that are considered are temperature, latitude and altitude, the probable pathogen is tuberculosis while the physiological mechanisms involve vitamin D availability and arterial hypertension. The basic idea is that altered Cl^- transport suppresses tuberculosis and alleviates the risk of hypertension caused by salt ingestion. On the other hand, low vitamin D availability, due to scarce sun exposure, increases the chances for tuberculosis and hypertension. This vitamin D and CFTR mutation link is based on the distribution of CF mutations with a high incidence among people from northern latitudes with low vitamin D food levels and low insolation, except among Inuits on the vitamin D reach sea food diet. On the other hand, cold climate, high altitude and vitamin D deficiency can all increase risk of arterial hypertension that becomes a very strong selective pressure during pregnancy. Thus, the heterozygote individuals for the CF mutation might have been more resistant to hypertension in this setting due to increased salt losses.

This complex interpretation seems plausible and in concordance with a large part of epidemiological data. The idea that CFTR mutations have something to do with seemingly unrelated physiological mechanisms (vitamin D deficiency, hypertension etc.) is in several ways related to interpretation presented here that spreading of CFTR mutations might have been an adaptation to survival pressures in continental Eurasia.

The other important piece of evidence is the estimate that the most common CF linked mutation is possibly no more than 52 ky old (Wiuf, 2001), clearly suggesting that any paleophysiological explanation of this rapid spreading of CFTR mutations needs to be focused on the last 50 ky of European climate and its impact on human health.

2. The climate setting in Europe during last 50 ky

A large part of the last 50 ky was much colder in Europe than the present climate (Spielhagen et al., 2004). The coldest period was the Last Glacial Maximum (LGM) (26.5 to 19 kya), when the global climate was cold and dry with a dust-laden atmosphere. Reported levels of dust in ice cores were 20 to 25 times greater than the present dust levels (Lambert et al., 2012; Kohfeld and Harrison, 2001; Claquin et al., 2003). This increased dust exposure started more than 40 kya and ended less than 10 kya. Probable causes for this long lasting dustiness include glacial erosion, scarce vegetation, aridity with little precipitation and strong winds. This heavy dust exposure lasting for thousands of years has formed the European loess ridges aligned with the prevailing winds during the last glacial period (Haase et al., 2007; Frechen et al., 2003). Estimated periods of atmospheric dust lasted from 360 to 340 kya, 270 to 255 kya, 170 to 130 kya, 80 to 60 and finally 40 to 10 kya. Some of them coincide with migrations of the Neanderthals and H. sapiens out of Africa, suggesting that the harsh climate with reduced daily light might have been important for in making our ancestors migrate.

The most convincing link between human locomotion, sun exposure, pregnancy and nakedness of our ancestors was proposed by Jablonski and Chaplin (2000, 2010). They have postulated that skin pigmentation possibly increased after our African ancestors have lost their body hair. This new dark skin protected folate in the blood stream from harmful African UV exposure that was particularly important during pregnancy. Pale skin was then interpreted as a later adaptation to reduced sun exposure when our ancestors moved to continental Eurasia. Insufficient vitamin D formation in the skin due to northern latitudes might compromise bone growth and locomotion of young adults.

Noting that sustained exposure to atmospheric dust might have been the decisive factor in adapting both skin pigmentation and respiratory function to this harsh climate is important. During long periods of drought, drinkable water sources were scarce and the lack of water might have forced our ancestors to follow animals from the Eurasian coast to the central continent, near the south edge of the belt of glaciers. The lack of sea food and exposure to dim light in dusty atmosphere might have resulted in a strong pressure toward lighter skin pigmentation, eventually leading to the Caucasian phenotype.

This possible link between sun exposure and hominid evolution is supported by new evidences that skin pigmentation genes in our genome came from the Neanderthals (Sankararaman et al.,