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Did Going North Give Us Migraine? An Evolutionary Approach on Understanding Latitudinal Differences in Migraine Epidemiology

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This commentary discusses a recent publication by evolutionary biologists with strong implications for migraine experts. The Authors showed that a gene polymorphism associated with migraine gave our ancestors an evolutionary advantage when colonizing northern, and thus colder, territories. They then highlight that the prevalence of migraine may differ among countries because of climatic adaptation. These results may prove useful in planning both epidemiological and physiological studies in the field of migraine.

Key words: migraine, TRPM8, latitude, cold adaptation, migraine epidemiology, evolutionary biology

Abbreviations: SNP single-nucleotide polymorphism, TRPM8 transient receptor potential cationic channel subfamily M member 8

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Migraine is a complex neurological disabling disorder that is unfortunately very common. Its worldwide prevalence is higher than any other disorder, except tension-type headache and dental cavities.[1] It has a wide global distribution: it can be found in all continents, but with a prevalence that varies across geographic regions, higher in North, South America and Europe, intermediate in Asia, and lowest in Africa.[2] In general, within each continent, migraine is more prevalent in high-latitude regions (both northbound and southbound).

The causes of such differences are still unknown: they appear to be partially linked to socioeconomic and educational status, but there are possible methodological

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biases associated, and those factors still fail to fully explain the observed distribution.[3] Moreover, recent studies weakened this hypothesis as headache distribution does not fit sociodemographic development.[2]

We still cannot exclude the effects of confounders, since some countries still lack epidemiological data about migraine (analyses principally focus on Western countries), available studies span temporally over decades and it is hard to compare results from old and new publications (see Ref. 2 for a discussion of this topic).

Recently, serum level of vitamin D (strictly dependent on latitude) has been advocated to explain this difference, but to date it seems to influence the prevalence of tension-type headache rather than migraine.[4,5]

From a genetic point of view, single-nucleotide polymorphisms (SNPs) associated with common forms of migraine (both with and without aura) have been found in a dozen genes.[6] Among them there is the TRPM8 gene, encoding for the receptor with the same name, which is the only known receptor for cold and plays an important role in cold sensation and physiological thermoregulation.[7,8] It appears to be regulated by the SNP rs10166942, one of the polymorphisms most reliably associated with migraine. This SNP is present in humans in 2 variants: C, ancestral and protective against migraine, and T, which appeared after a mutation (=derived) and is associated with increased risk of migraine.[9]

A recent article[9] investigated the distribution of the rs10166942-T allele focusing on its role in cold adaptation. They analyzed 20 populations from Africa, Asia, and Europe from the 1000 Genomes project[10] and 220 genomes from the Simons Genome Diversity project.[11] The frequencies of the T variant varies a lot among geographic regions, being much more common in people living at high latitude than in those closer to the equator (88% in Finland vs 5% in Nigeria), and it significantly correlates with both latitude and temperature.[9]

So, why and how did the T mutation of the rs10166942 SNP reach such high frequencies in some populations, especially given the fact that it is associated with a painful and potentially invalidating condition such as migraine?

The authors performed a large set of analyses and computer simulations. Comparing a null model where the T variant spread following the demographic history of the human population in its expansion from Africa to the rest of the world,[12] with one where the same variant gave an advantage to those who carried it when living in cold regions, the second model appeared much more likely than the first one. This means that the distribution of the T variant is most likely the result of adaptation to cold environments.

What about migraine? The story seems to be the following one: when humans reached northern latitudes and colder regions (Europe and Northern Asia), the (likely) few individuals carrying the rs10166942-T variant had more migraine than people carrying the C variant, but were also better adapted to the cold, and had a better chance of surviving and have children (they were "positively selected," in evolutionary terms). For this reason, the T variant increased in frequency in colder regions of the globe, while migraine became a sort of price-to-pay in order to be able to survive better in those areas with challenging climatic conditions. This study has the advantage that the implications about migraine distribution are the result of analyses on two sets of genetic data independently collected[10,11] without considering diagnostic information (which may be influenced by methodological choices). The study aimed at investigating climatic adaptation based on allele frequencies of a genetic variant associated with cold perception that by chance appears to play a role in migraine. In fact, somehow, the results obtained on migraine are a "side effect," and, so, appear more reliable, as the frequency found for the rs10166942-T allele nicely matches the known prevalence of the disease obtained with other methods.

On the other hand, it is important to remember that the association between variation at the rs10166942 locus and migraine prevalence is high but not complete, and (as already suggested) other factors may play a significant role in shaping the prevalence of the disease.

Even considering these limitations, this is the first study trying to link the geographical distribution of migraine with natural selection and typical evolutionary mechanisms, and in our opinion it represents a new and powerful way to investigate migraine, especially considering that recent epidemiological studies found no clear correlation between migraine prevalence and usual known determinants (eg, socioeconomic status).[2]

Given the results presented in Key et al[9] and the very high worldwide prevalence of migraine, it is indeed possible that common forms of migraine, as

migraine with or without aura, traditionally considered as single entities, may actually include multiple subtypes characterized by distinct genetic and possibly pathophysiological aspects. This interpretation is reinforced by the fact that genome-wide studies found a large number of genetic variants implicated in several functions associated with migraine.[3] Under this scenario, the geographical distribution of some subtypes may depend on the evolutionary forces shaping the spread of the associated SNPs across the continents.

As a conclusion, we would like to encourage integrating an evolutionary approach in the analysis of migraine and other genetically determined disease, together with a closer collaboration between clinical and evolutionary researchers. Such collaborations has proven very valuable for the medical practice (eg, when antigenic cartography has been used to better plan influenza vaccines).[13]

We are aware that such an effort for interdisciplinarity may be difficult for many reasons, but it has the power not only to increase understanding of the epidemiology of such diseases but may also be of great utility for planning both epidemiological and physiological studies.

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