Letter to the Editor

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What is the evolutionary disadvantage of migraine?

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A recent article published in *Cephalalgia* has reinforced the concept of migraine as a dysevolutionary disorder, proposing that certain traits associated with migraine may have conferred advantages in the past but have become maladaptive in modern times.[1] This idea was first notably introduced by Elizabeth Loder in her seminal paper *What is the evolutionary advantage of migraine?*, which suggested that physiological features of the migraine brain may have provided adaptive benefits to early humans.[2]

One key aspect of migraine is the genetically determined hypersensitivity to sensory stimuli, which is well-documented in individuals with this condition.[3] From an evolutionary perspective, heightened sensory perception may have been advantageous in ancestral environments. For example, an enhanced sense of sight or hearing could have improved survival by aiding in predator detection or hunting. A more acute sense of smell could have facilitated the identification of toxins in food and water or played a role in mate selection. Under the principles of natural selection, advantageous traits tend to persist in populations, while detrimental ones are progressively eliminated. This may help explain the high prevalence of migraine in modern humans because the genetic traits underlying migraine might have once conferred survival benefits.[2]

However, the modern environment has drastically altered the selective pressures acting on these traits. The same heightened sensory responsiveness that may have been beneficial in natural settings now renders individuals susceptible to sensory overload, potentially leading to recurrent activation of the brain's alarm system, namely the trigeminovascular system, a hallmark of migraine attacks. Additionally, the impact of migraine appears to be greater during menstruation, yet menstrual cycles were less frequent in our ancestors due to shorter lifespans, prolonged lactation, and frequent pregnancies, all of which are protective against migraine.

If migraine-associated genes are truly shaped by natural selection, we would expect them to have proliferated historically due to past advantages and to be gradually declining due to present day disadvantages. The extent to which natural selection still influences migraine prevalence (i.e. a measure of this decline) can be quantified using the Biological State Index (I_{bs}), a metric that estimates the strength of selective pressure on a population.[4,5]

Testing natural selection's effect on migraine prevalence

To evaluate whether migraine prevalence is influenced by natural selection, we examined its correlation with the BSI across different populations. The I_{bs} is defined as:

$$I_{bs} = 1 - \sum_{x}(d_x \cdot s_x)$$

where d_x represents the frequency of deaths at age x, and s_x represents the probability of not having completed fertility at age x. A higher I_{bs} indicates stronger selective pressure, while a lower I_{bs} reflects a relaxation of natural selection.[4,5]

We collected migraine prevalence estimates from 38 countries and compared them with each country's I_{bs}. The mean ± SD global migraine prevalence was 13.23 ± 6.46%, and we found a significant negative correlation between migraine prevalence and I_{bs} ($r = -0.49$, $R^2 = 0.24$, $p = 0.002$) (Figure 1). This suggests that in populations where natural selection remains stronger, migraine prevalence tends to be lower.

These findings indicate that migraine may indeed be subject to ongoing evolutionary pressures. Beyond affecting the overall prevalence of migraine, selective forces may shape its genetic profile and phenotypic expression across populations. This aligns with recent research showing geographical variation in the distribution of

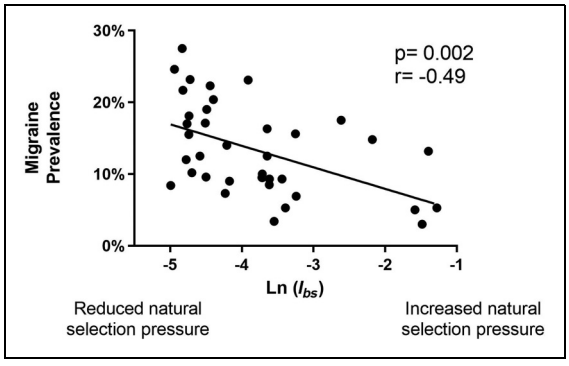

Figure 1. Relationship between the Biological State Index (I_{bs}) (ln-transformed) and migraine prevalence. Lower I_{bs} values (indicating diminished evolutionary pressure) are associated with higher migraine prevalence, whereas higher I_{bs} values (indicating increased natural selection pressure) correspond to lower migraine prevalence rates.

migraine-associated genes,[6] as well as our previous findings on how physiological responses in migraine patients vary with climatic factors.[7]

Given the substantial heterogeneity of migraine across individuals and populations, we propose that its evolutionary history should be integrated into future research. Understanding the selective forces that shaped migraine susceptibility in the past may provide crucial insights into its persistence and variability in present day populations.

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References

1. Pensato U, Cevoli S and Pierangeli G, et al. The evolutionary meaning of migraine. Cephalalgia 2023; 43: 3331024231209303.
2. Loder E. What is the evolutionary advantage of migraine? *Cephalalgia* 2002; 22: 624–632.
3. Lisicki M, Ruiz-Romagnoli E, D'Ostilio K, et al. Familial history of migraine influences habituation of visual evoked potentials. *Cephalalgia* 2017; 37: 1082–1087.
4. Henneberg M and Piontek J. Biological state index of human groups. *Przeglad Antropologiczny* 1975; 41: 191–201.
5. You W and Henneberg M. Relaxed natural selection contributes to global obesity increase more in males than in females due to more environmental modifications in female body mass. *PLoS One* 2018; 13: e0199594.
6. Key FM, Abdul-Aziz MA, Mundry R, et al. Human local adaptation of the TRPM8 cold receptor along a latitudinal cline. *bioRxiv* 2018; 14: 1–30.
7. Lisicki M, D'Ostilio K, Erpicum M, et al. Sunlight irradiance and habituation of visual evoked potentials in migraine: the environment makes its mark. *Cephalalgia* 2018; 38: 1351–1360.

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