The variation of the activity of Xenobiotic metabolizing enzymes with latitude as a potential factor in determining the course of history.

Shireesh Prakash Apte* **and Kyle Hoffman**

Harmony Science Academy, Euless, TX 76040

Received: May 5, 2014; *Accepted:* May 25, 2014

Opinion and Commentary Paper

KEY WORDS: Alkaloidal food ingredients, latitudinal diversity gradient, xenobiotic metabolizing enzymes, culinary evolution, empire size, cytochrome P450, secondary metabolites, world history

Levin argued that the incidence of alkaloid-bearing plants was dependent upon their habitat and ecogeographical distribution (1). His data demonstrated that the incidence of alkaloids among tropical floras was nearly twice that of temperate floras, and a latitudinal cline was evident. Plant families primarily distributed in the tropics had a higher percentage of alkaloid-bearing species than those of temperate regions. He explained this latitudinal gradient using the co-evolutionary theory (see below) and suggested that ecogeographic patterns may have been the result of differences in pest pressure, the alkaloids playing a defensive role in plants as secondary metabolites.

The evolution of plant secondary metabolites occurred because plants need animals for their reproductive cycles but must also maintain defence systems for survival. Consequently, there was an 'explosion' of new animal cytochrome P450 genes in the CYP2 family (2) with an evidence of > 50 gene duplication events starting ~ 400 million years ago when animals first came onto land and began ravaging stationary terrestrial plant forms. Presumably, plants had to defend themselves by evolving new genes (and thus new metabolites) to make them less palatable or more toxic, and animals responded by evolving new xenobiotic metabolizing enzyme (XME) genes in order to adapt to the constantly changing plants (3).

The most striking, large scale pattern in biological diversity is the dramatic increase in the number of species and higher taxa from the poles to the tropics. This taxonomic trend is commonly called the latitudinal diversity gradient (LDG) (4). Invoking the co-evolution theory to explain the presence of XME in animals implies that there must be an LDG for XME as well.

Investigations of the frequencies of CYP2D6 in different populations revealed 30% in Ethiopians, 10% in Spaniards and 10% of the populations in Italy and Turkey, whereas ultra metabolizers (UM) were uncommon (1-2%) in Northern Europe (5). A similar gradient was

* Corresponding author: Shireesh Prakash Apte, Harmony Science Academy, Euless, TX 76040, sapte@harmonytx.org, shireeshpapte@msn.com, Tel: 817 5012984

seen for metabolizers of CYP2C19 and CYP2D6; with ultra metabolizers (UM) and poor metabolizers (PM) seen at higher frequencies in southern and northern Europe respectively (6). The frequency of the CYP3A5*3 allele was shown to increase with the distance from the equator (7). A selection of alleles carrying multiple active CYP2D6 genes has been proposed to occur in North East Africa, the basis of which would be the capability of the CYP2D6 enzyme to detoxify alkaloids, thereby increasing the availability of potential food among carriers of multiple CYP2D6 gene copies. This would be very beneficial for the survival in geographic regions (near the equator) where there occurs a profusion of plant secondary metabolites (alkaloids) that, in turn, are expressed as protection from the greater biodiversity of animal predators.

Because XME have been shown to exist in the human brain at levels that can modulate the levels of neurotransmitters or are involved in the metabolism of endogenous substances important for central nervous system function (8), it has been proposed that specific XME isoforms in the brain can potentially be associated with specific personality traits (9). Specifically, because CYP2D6 has been shown to regenerate serotonin from 5-methoxy tryptamine, as well as, facilitate the hydroxylation of tyramine to dopamine, low CYP2D6 activity has been linked to personality characteristics of social cognitive anxiety. This may bear some resemblance to milder forms of psychotic-like symptoms (10). PM have been shown to be more anxiety-prone, more impulsive and less successfully socialized than extensive metabolizers (EM) (11). PM also had significantly lower scores on the Karolinska psychasthenia scale and had a higher frequency of extreme responses than EM (12). PM have also been shown to be less tolerant to pain, in part due to the decreased formation of morphine via CYP2D6 (13).

Because there is a demonstrated inverse correlation in the active alleles of XME isoforms with increasing distance from the equator and a demonstrated negative correlation between XME active isoforms in the brain with psychosis like personality disorders, it is not unreasonable to assume that the more anxiety prone, more impulsive and less successfully socialized phenotype probably assumes increasing frequency with increasing distance from the equator. Interestingly, previous surveys have found a tendency for schizophrenia prevalence to increase with latitude (14), part of which could potentially be attributed to the decreased frequency of active XME alleles in the brain.

Overwhelming evidence that demonstrates the presence of an LDG suggests that the early hunting and gathering tribes and even the early civilizations of the pre-common era that flourished at relatively higher latitudinal clines, such as those in Egypt (New Kingdom), the Arabian Peninsula (Persian empire) and even Anatolia (Macedonian empire), would have been less exposed to alkaloid containing plant and animal matter in their diet. A consequent decreased expression of XME alleles could help to explain some of the aggressive nature of these civilizations as they started to expand their territories and conquer other lands. The one commonality that these empires would have had was the fact that they fell within the same (relatively higher) latitudinal cline and therefore would have had similar diets and access to the same biodiversity found in this tropic zone.

Because the socially maladapted, psychotic phenotype is likely to be more aggressive (15) interestingly in part due to decreased levels of serotonin which is entirely consistent with this hypothesis, an increased frequency of this phenotype with increasing latitude may be interpreted to imply, among other factors, that there is an increased probability for forced acquisition (of land, wealth and goods) at higher latitudes. Because such activity is

extremely difficult to quantify, it is consequently not encountered in recorded history, although anecdotal evidence is plentiful. A surrogate for such activity may reasonably be assumed to be the size of empires. Figure 1 presents the variation of the size of empire with latitude. A positive slope for the line of best fit is indicative of the fact that, while a coincidental relationship between the two variables cannot be entirely excluded, this quantifiable surrogate model is in agreement with the hypothesis presented in this manuscript, namely, that the distance from the equator determines the levels of the active alleles of XME in the brain, which in turn determine the levels of personality influencing endogenous neurotransmitters, which, in their turn, determine the level of predatory behavior or aggression and hence, the size of empires surrogate.

Table 1 Correlation of Empire area with latitude (data from reference 16).

EMPIRE	LATITUDE	AREA (Mm2)	APPROXIMATE TIME PERIOD
Egypt (new kingdom)	27°N	1	1550-1064 BCE
Inca	13°S	2	1438-1533 C.E
Mali	12.3°N	1.1	1100-1591 C.E
Rome	41°N	5	270-476 C.E
Huns	47°N	4	370-453 C.E
Srivijaya	2°S	1.2	671-1400 C.E
Khmer	12°N	1	802-1600 C.E
Mauryan	25°N	5	323-185 BCE
Achaemenid Persian	48°N	5.5	550-330 BCE
Hellenic (Alexander)	41°N	5.2	336-323 BCE
Merovingian	50.7°N	3.24	481-814 C.E
Ottoman	40.96°N	5.2	1300-1923 C.E
Mughal	28.4°N	4	1504-1876 C.E
Mongol	47°N	24	1300-1400 C.E
Russia	56.4°N	22.8	1613-1917 C.E
Qing	43.88°N	14.7	1644-1911 C.E

The Mongol, Russian and Qing empires were considered outliers and neglected from the correlation in Figure 1 because all of them originated in the greater Eurasian land mass that did not provide as many geographic barriers for latitudinal expansion as did the landmass around the Mediterranean, Black and Caspian seas and the empires that originated in their proximity (the regression coefficient would have a value of 0.32 if these empires were included).

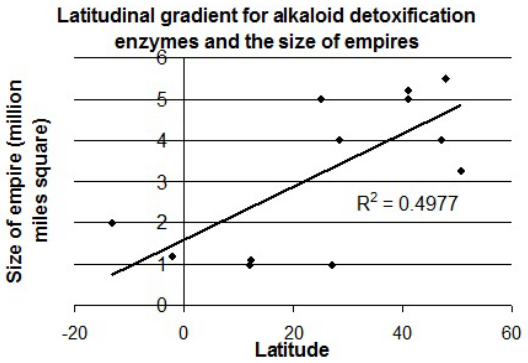

Figure 1 The variation of the size of empire with latitude

Paradoxically, the data in Table 1 was presented to illustrate the "east-west" orientation of historical empires based on Diamond's (20) argument that food production spreads more easily latitudinally (in the East-West direction) rather than longitudinally because similar climates and soil types tend to be arranged in east-west oriented bands. The fact that this data can be fit to another variable (latitude), albeit with a lesser correlation, implies that while food distribution may be a factor that determines the size of empires, the contribution of the variation of XME levels with latitude cannot be entirely discounted. This is especially so because biochemical evidence exists (albeit with confounding factors) for the latter.

CONCLUSION

Various explanations have been proposed to assign cause(s) to historical events. For example, Pomeranz's economic explanation (17), Weber's doctrine of the Protestant work ethic (18), Landes's hypothesis of superior European cultural mores (19), Diamond's geographical determinism (20) and Apte's biochemical 'genius germs' hypothesis (21) all seek to provide causation to European domination of world history.

In this paper, we have presented evidence that correlates the latitudinal gradient in xenobiotic metabolizing enzymes to the (latitudinal) propensity for aggression and predatory acquisition of property and goods. A quantitative surrogate (Figure 1) that confirms to this hypothesis is the pre-common-era direct correlation of the size of empire with latitude. The paper demonstrates a non-discountable influence of the selective pressure of (alkaloidal) food ingredients on geo-political and anthropological trajectories.

It would be hubris to assume that historical events can be influenced by a single variable, or indeed, even by a combination of variables, because no analytical methods exist to either prove or disprove such hypotheses. Having said that, it cannot be discounted that a combination of all the factors outlined above (as well as the one proposed in this manuscript) may be responsible, in part, for the manner in which history has unfolded. The 'evolutionary determinism' aspect outlined in this manuscript is expected to assume lesser significance with greater globalization, mobility and contact between peoples of different latitudinal clines.

REFERENCES

1 Levin DA, Alkaloid – Bearing Plants: An ecogeographic Perspective, 1976, The University of Chicago Press.

2 Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Feyereisen R, Waxman DJ, Waterman MR *et. al.* Cytochrome P450 superfamily; update on new sequences, gene mapping, accession numbers, and nomenclature. Pharmacogenetics, 1996, 6: 1-42.

3 Gonzales FJ, Nebert DW. Evolution of the P450 gene superfamily: animal-plant "warfare", molecular drive, and human genetic differences in drug oxidation. Trends Genet, 1990, 6: 182-186.

4 Jablonski D, Roy K, Valentine JW. Out of the tropics: Evolutionary dynamics of the latitudinal diversity gradient. Science, 2006, 314: 102-106.

5 Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P4502D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J. 2005, 5: 6-13.

6 AynaciogluAS, Sachse C, Bozkurt A, Kortunay S, Nacak M, Schroder T, Kayaalp SO, Roots I, Brockmoller J. Low frequency of defective alleles of cytochrome P450 enzymes 2C19 and 2D6 in the Turkish population. Clin Pharmacol. Ther. 1999, 66(2): 185-192.

7 Thompson EE, Kuttab-Boulos H, Witonsky D, Yang L, Roe BA, Di Rienzo A. CYP3A variation and the evolution of salt-sensitivity variants. Am.J. Hum.Genet. 2004, 75: 1059-1069.

8 Funae Y, Kishimoto W, Cho T, Niwa T, Hiroi T. CYP2D in the Brain. Drug Metab. Pharmacokin. 2003, 18(6): 337-349.

9 Dorado P, Penas-Lledo EM, Llerena A. CYP2D6 polymorphism: implication for antipsychotic drug response, schizophrenia and personality traits. Pharmacogenomics. 2007, 8(11): 1597-608.

10 Gonzalez I, Penas-Lledo EM, Perez B, Dorado P, Alvarez M, Llerena A. Relation between CYP2D6 phenotype and genotype and personality in healthy volunteers. Pharmacogenomics. 2008, 9(7): 833-840.

11 Llerena A, Edman G, Cobaleda J, Benitez J, Schalling D, Bertilsson L. Relationship between personality and debrisoquine hydroxylation capacity. Suggestion of an endogenous neuroactive substrate or product of the cytochrome P4502D6. Acta Psychiatr Scand. 1993, 87(1): 23-28.

12 Bertilsson L, Alm C, De Las Carreras C, Widen J, Edman G, Schalling D. Debrisoquine hydroxylation polymorphism and personality. Lancet, 1989: 555.

13 Sindrup SH, Poulsen L, Brosen K, Arendt-Nielsen L, Gram LF. Are poor metabolizers of sparteine/debrisoquine less pain tolerant than extensive metabolizers? Pain. 1993, 53: 335-349.

14 Kinney DK, Teixeira P, Hsu D, Napoleon SC, Crowley DJ, Miller A, Hyman W, Huang E. Relation of schizophrenia prevalence to latitude, climate, fish consumption, infant mortality and skin color: A role for prenatal vitamin D deficiency and infections? Schizophrenia Bull. 2009, 35(3): 582-595.

15 Crockett MJ, Clark L, Tabibnia G, Lieberman MD, Robbins TW. Serotonin modulates behavioral reactions to unfairness. Science, 2008, 320(5884): 1739.

16 Turchin P, Adams JM, Hall TD. East-West orientation of historical empires and modern states. J. World-Systems Research. 2006, XII(II): 219-229.

17 Pomeranz, K. (2000) The great divergence. China, Europe, and the making of the modern world economy. Princeton University Press, Princeton, NJ.

18 Webber, M. (eds) (2002) The Protestant ethic and the spirit of capitalism. Penguin Classics.

19 Landes, D.S. (1999) The Wealth and Poverty of Nations: Why some are so Rich and some so Poor. W.W.Norton.

20 Diamond, J. (1997) Guns, Germs, and Steel: The fates of Human Societies. W.W.Norton

21 Apte S. The "genius germs" hypothesis: Were epidemics of leprosy and tuberculosis responsible in part for the great diver-gence? *Hypothesis* 2009, **7**(1):e3