The promise of an evolutionary perspective of alcohol consumption

Benjamin L. Clites, Ph.D.[1], Hans A. Hofmann, Ph.D.[2] and Jonathan T. Pierce, Ph.D.[1,*]

1 Department of Neuroscience; Waggoner Center for Alcohol and Addiction Research; Institute for Cellular & Molecular Biology; Institute for Neuroscience; University of Texas at Austin, Austin, Texas, United States.

2 Department of Integrative Biology; Institute for Cellular & Molecular Biology; Institute for Neuroscience; University of Texas at Austin, Austin, Texas, United States.

* Corresponding author:

E-mail: jonps@utexas.edu

ORCID iD

Benjamin L. Clites https://orcid.org/0000-0002-5591-8412

Hans A. Hofmann https://orcid.org/0000-0002-3335-330X

Jonathan T. Pierce https://orcid.org/0000-0002-9619-4713

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ABSTRACT

The urgent need for medical treatments of alcohol use disorders has motivated the search for novel molecular targets of alcohol response. Most studies exploit the strengths of lab animals without considering how these and other species may have adapted to respond to alcohol in an ecological context. Here, we provide an evolutionary perspective on the molecular and genetic underpinnings of alcohol consumption by reviewing evidence that alcohol metabolic enzymes have undergone adaptive evolution at two evolutionary junctures: first, to enable alcohol consumption accompanying the advent of a frugivorous diet in a primate ancestor, and second, to decrease the likelihood of excessive alcohol consumption concurrent with the spread of agriculture and fermentation in East Asia. By similarly considering how diverse vertebrate and invertebrate species have undergone natural selection for alcohol responses, novel conserved molecular targets of alcohol are likely be discovered that may represent promising therapeutic targets.

Keywords

Ethanol, genetic variation, selection, comparative approach

Abbreviations

alcohol use disorder, AUD

genome-wide association, GWA

alcohol dehydrogenase, ADH

aldehyde dehydrogenase, ALDH

INTRODUCTION

Alcohol use disorder (AUD) is one of the most common psychiatric diseases in the US affecting more than 1 in 10 American adults[1]. Globally, the World Health Organization estimates nearly 6% percent of deaths and 5% of injury burden can be attributed to alcohol abuse[2]. Despite

the magnitude of the damage that alcohol abuse causes, there are relatively few treatment options available[3]. One approach to identify viable treatments has focused on studying molecular genetic contributions for AUD. A genetic approach is promising because twin and adoption studies estimate that about half of the risk for alcohol dependence is heritable[4]. Thus, identifying these genetic factors that underlie AUD may lead to sorely needed novel treatments, while also providing insights into the basic biology of AUD. Candidate targets for treatments may be identified by searching for specific genetic variants associated with molecules that contribute to population-wide differences in AUD risk[5]. Early genome-wide association (GWA) studies on individual variation in AUD risk identified only a few replicable associations in human populations, most notably genes involved in the metabolism of alcohol (for review see Tawa et al.[6]). However, recent GWA efforts have used expanded sample sizes and genomic resources that cross multiple populations to identify promising new candidate genes, as well as shedding light on the shared architecture of alcohol abuse and other psychiatric traits[7,8]. Even still, GWAS on human populations cannot be causally validated, and often end with correlations. Novel population genetic strategies are needed to identify additional genetic effectors of alcohol response.

An ethological perspective of alcohol use

Ethanol is an ecological challenge to a wide array of species across taxa and time. While ethanol is toxic when consumed to excess[9], it can also serve as both a signal of calorie rich food sources (e.g., fruit patches containing rotting fruit)[10,11], and as a source of calories in and of itself[12]. For those organisms that have adapted to exploit it, alcohol represents a longstanding dietary niche that poses common challenges across distant taxa. Understanding the evolutionary relationship between alcohol and the variety of species that have evolved to exploit it will expand our view of alcohol, its effects on humans today, and novel ways to identify conserved molecular targets of alcohol response.

In the early 2000s, alongside the emerging field of evolutionary medicine[13], some asked whether the cross-cultural phenomenon of alcoholism could be attributed to an "evolutionary mismatch"[14]. This idea posited that some traits, which were adaptive in the ancestral environment,

become deleterious when "mismatched" to the modern environment[15]. Lieberman, for example, speculated that in our supposedly resource-scarce ancestral environment it was beneficial to crave and consume high-sugar foods, as they were rare and high in calories[16]. Others hazarded that human contact with alcohol began with the advent of agriculture and fermentation some 9,000 years ago[17]. In modern industrialized society, where sugary foods are ubiquitous and cheap, those same traits may then lead some individuals to consume sugars to the point of chronic illness (e.g., diabetes and obesity)[18,19]. In this view, when these behavioral adaptations met a society where highly concentrated alcohol became easily accessible, a mismatch occurred, and the "evolutionary hangover" began[20-23]. The lack of evidence did not deter researchers from making such claims, as appears to be common in human evolutionary biology. Be it as it may, given new evidence accumulated over the last two decades, we need to reevaluate the behavioral ecology of alcohol consumption and its potentially long history with the human lineage.

Frugivores and alcohol consumption

An evolutionary perspective of alcohol abuse based on evidence must first acknowledge that our hominoid ancestors, who consumed ripe fruits, ingested alcohol at low levels already ~24 million years ago (m.y.a.)[21], a time frame that provided ample opportunity for adaptation to occur (Figure 1). The hominid transition to terrestrial foraging some 10-20 m.y.a.[23] may have accelerated this process due to the consumption of low-levels of alcohol via overripe and rotting fruits on the savannah floor. Independent of the ultimate cause, several mechanisms for realizing a fitness benefit have been proposed. One hypothesis posits that natural selection favored primates attracted to alcohol, even if the benefits of this attraction were indirect. For example, volatile ethanol molecules emanating from a piece of fermenting fruit might act as a sensory cue used to locate a food patch[10,11,24], or as an appetite stimulant, an effect demonstrated in a number of species including modern humans[25,26]. Others contend that the direct caloric content of alcohol provides a fitness benefit to those that can exploit those calories whilst avoiding the toxic effects of alcohol consumption[9,12]. Still, there remains a dearth of data on the alcohol content of wild fruits at

different stages of ripeness or rot. Dudley[22] assayed wild Panamanian Palm fruits and found them to contain average levels of about 0.56 ± 1.04% v/v alcohol, with some overripe fruit samples containing up to 5% alcohol (about the content of typical beers).

Despite earlier claims to the contrary, many recent studies find that frugivores *do* prefer overripe and rotting fruits, whilst others have observed the direct consumption of alcoholic solutions. For example, Peris et al.[24] looked at the dietary habits of wild seed disperser and pulp feeding species across two biomes and found that rotting fruits inoculated with *Penicillium digitatum* fungus were overwhelmingly preferred by local frugivores. Others found that African elephants (*Loxodonta africana*) could identify fruit sugar content based on scent alone, with volatile ethanol in the scent plume accounting for nearly 50% of the variance in which fruits were preferred[27]. Similarly, two nectar-feeding primates, the slow loris (*Nycticebus coucang*) and aye-aye (*Daubentoniab madagascariensis*), were found to prefer 1%-5% v/v ethanol solutions over sucrose-sweetened control solutions in a two-choice test[28]. Strikingly, Hockings et al.[29] reported that wild West African chimpanzees consume alcoholic palm nectar (3.1% – 6.7%) repeatedly over a period 17 years. These observations suggest that incidental or voluntary alcohol consumption in our frugivorous ancestors is more plausible than was previously thought[30-32].

Evidence of molecular adaptations to alcohol metabolism amongst frugivores

Frugivory is common across animals, so we might ask whether diverse fruit-eating species share molecular adaptations to alcohol metabolism. Across species, alcohol is first metabolized by alcohol dehydrogenase (ADH), producing a toxic intermediate, acetaldehyde, which is in turn converted to harmless acetate by the enzyme aldehyde dehydrogenase (ALDH) (for a more complete review of alcohol metabolic genes, see Oota et al.[33]). Interestingly, in the fruit fly (*Drosophila melanogaster*), increased alcohol metabolism correlates with ethanol content of species-specific food niches[34], and intra-specific variation in alcohol sensitivity correlates with ADH activity towards alcohol in *D. melanogaster*[35]. A similar pattern has been found in birds: ADH enzymes of passerines with higher proportions of fruit in their diets show increased capacity

to metabolize alcohol 36. A recent study by Janiak et al.[37] used comparative genomics to analyze the relationship between dietary niche and alcohol metabolism. They found that the fraction of the diet that is plant-based significantly correlated with *ADH7* pseudogenization across 79 mammal species. Thus, some adaptations towards alcohol appear to either be conserved across a wide range of tropical frugivorous species or have evolved convergently.

Evidence of adaptation to alcohol metabolism in great apes

Recent research has also provided evidence that the consumption of fermented fruit was accompanied by adaptive evolution of genes involved in alcohol metabolism in great apes. For example, Carrigan et al.[38] assayed enzyme activity of *ADH4* genes from across the primate clade and found a single amino acid variant that arose in the last common ancestor of chimps, gorillas, and humans (Figure 2). This variant causes high activity towards ethanol, in contrast to the other primate ADH4 proteins, which show low activity towards ethanol, but high activity toward anti-feedant terpenoids commonly found in leafy plants such as geraniol. This variant appears to have arisen ~10 m.y.a, around the time that our ancestors moved from the trees to the forest floor, where overripe and rotting fruits would be more common. Interestingly, the only other primate species that harbored this variant was the aye-aye, which prefers the higher concentration of alcohol offered in a two-choice test[28].

Evidence of adaptation to alcohol metabolism in modern humans

The alcohol metabolic pathway presents also the best evidence of recent human adaptations toward alcohol consumption. Studies on the numerous *ADH* and *ALDH* genes provide perhaps the most compelling evidence that humans have undergone recent evolution with respect to alcohol consumption. These genes vary within and between populations, and allelic variation correlates strongly with AUD risk. Variants that either increase ADH activity or decrease ALDH activity cause build-up of toxic acetaldehyde which quickly causes facial flushing, tachycardia, nausea, that together serve as a deterrent to drinking[39]. These variants are more common in East Asian

populations than they are in European, African or North American populations, and these differences correlate with markedly lower rates of alcoholism (for review see Edenberg[40]). These loci also show signs of recent selection in East Asia[41-44], suggesting that these patterns are not merely consequences of genetic drift.

A closer look at the variation within Asian populations provides even more evidence for recent adaptation in alcohol metabolism after the advent of fermentation after the introduction of agriculture. Peng et al.[41] found that the *ADH1B*2* allele (rs1229984), which results in a ADH1BArg47His polymorphism and is protective against alcoholism, becomes less frequent in an east to west gradient, with contemporary populations ranging from 98.5% allele frequency in south-east China to only 2% in south-west China (Figure 3). The *ADH1B*2* allele gain-of-function allele increases production of acetaldehyde. Intriguingly, this pattern mirrors the pattern of early agriculture and fermentation, which first appeared in the southeast (8,000-12,000 y.a.) before spreading west (3,000-6,000 y.a.). A separate study directly tracked the allelic expansion of *ADH1B*2* in northern China across time by genotyping ancient remains dated from between 2,500 BC - 220AD. They found that a marker of *ADH1B*2* allele increased rapidly over the last 4,000 years, suggesting temporal and geographical bounds on a putative selective mechanism[45]. These data provide persuasive evidence that *Homo sapiens* underwent recent selection with respect to alcohol consumption, at least in Southeast Asia. Similar large studies on potential selective variation in alcohol metabolic enzymes remain to be conducted on populations from other global origins of agriculture and fermentation. If patterns of selection are found, they may be distinct from those in East Asia. For instance, the protective effect of *ADH1B*2* variant against AUD was found to be weaker in a modern population of Europeans than in Asians[46].

Interestingly, the adaptive genetic variation in alcohol metabolism found in humans is already the target of one of three currently approved pharmaceutical interventions to treat AUD[47]. Specifically, the drug Disulfiram acts by interfering with ALDH activity. When administration is supervised, Disulfiram pharmacologically confers protection against AUD to a degree that resembles that of

Japanese individuals who are homozygous for the hypomorphic variant in ALDH[48]. Left unsupervised, however, patients often fail to adhere to Disulfiram treatment and risk relapse of alcohol consumption[47]. Modern AUD treatments therefore aim to target candidate physiological and brain mechanisms that are thought to underlie maladaptive patterns of alcohol consumption[49].

Sex differences in alcohol metabolism are widespread

It is unlikely, however, that shared natural genetic adaptations towards alcohol consumption amongst frugivores are limited to its metabolism. Conserved sex differences provide another example. In *H. sapiens*, males are less sensitive to alcohol consumption and have higher rates of alcoholism than females[50]. In the crab-eating macaque (*Macaca fascicularis*), a primate model that shares a frugivory with humans, males are also more likely than females to voluntarily consume alcohol and to maintain high consumption, at least in a lab setting[51]. Similarly, *D. melanogaster* males show higher ethanol hyperactivity and resistance to sedation than do females[52]. By contrast, studies in Long-Evans rats find the opposite effect[53]. While these sex differences have some basis in differential metabolism, there are likely other shared mechanisms that explain this pattern as well. Thus, frugivorous species may be better suited as model systems for elucidating the antecedent causes of individual differences in alcohol consumption (e.g., genetic bases of attraction to alcohol, sex differences in alcohol phenotypes, etc.) than their non-frugivorous counterparts, such as rodents.

Beyond metabolism: Conserved molecular pathways regulate alcohol sensitivity across diverse species

Although rodents are widely used in alcohol research, the ethological relevance of alcohol consumption for several invertebrate model systems has provided excellent opportunities to discover evolutionarily conserved genetic effectors of alcohol response. For example, in the wild, the nematode *Caenorhabditis elegans* reproduces on rotting fruits which may contain low levels of alcohol[54]. *C. elegans* has been used for decades to study alcohol response in the lab. However,

almost all research uses a single strain (N2) isolated nearly 50 years ago[55]. Early studies using a more recently isolated wild Hawaiian strain of *C. elegans* (CB4856) discovered that natural variation in the neuropeptide Y receptor affects *C. elegans* alcohol response[56]. Sequence variation in the neuropeptide Y receptor has also been implicated in variation in alcohol sensitivity in the fruit fly *D. melanogaster*[57], as well as AUD risk in human populations[58,59]. Efforts to study natural variation in *D. melanogaster* have also identified genes with effects later demonstrated to be conserved in humans. Examples include DOPA decarboxylase, which is essential for the synthesis of catecholamine neurotransmitters such as dopamine and serotonin[60,61], and the KCNQ family of potassium channels[60,62]. These convergent lines of evidence suggest that humans have adapted to alcohol consumption, both in recorded history and in our more distant hominid past, and even in deep evolutionary time. In fact, comparative studies have convincingly demonstrated that similar molecular mechanisms underlying convergently evolved traits are more common than was previously believed[63], even across vast evolutionary distances and involving complex behavior (e.g., aggression[64]; monogamy[65]). This evolutionary framework suggests that, rather than standard isogenic lab strains, wild populations with alcohol consumption in their natural history, and in conjunction with GWA, comparative transcriptomics, and other emerging –omics technologies, will uncover important new insights across diverse specie [66-68].

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DECLARATION OF CONFLICTING INTERESTS

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Author Contributions

BLC, HAH, and JTP collaborated to write and edit the manuscript. BLC conceived this project.

Significance Statement

In this mini-review, we highlight the usefulness of an evolutionary perspective across species to identify molecular genetic underpinnings of behavioral responses to alcohol.

REFERENCES

1. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders 5th ed. APA, Arlington, VA.

2. World Health Organization (2018). Global Status Report on Alcohol and Health 2018. WHO, Geneva 2018.

3. Franck J, Jayaram-Lindström N. Pharmacotherapy for alcohol dependence: status of current treatments. Curr Opin Neurobiol. 2013;23(4):692-699.

4. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med. 2015;45(5):1061-1072.

5. Schuckit MA. A critical review of methods and results in the search for genetic contributors to alcohol sensitivity. Alcohol Clin Exp Res. 2018;45(5):822-835

6. Tawa EA, Hall SD, Lohoff FW. Overview of the genetics of alcohol use disorder. Alcohol Alcohol. 2016;51(5):507-514.

7. Walters RK, Polimanti R, Johnson EC, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. Nat Neurosci. 2018;21(12):1656-1669.

8. Linner KR, Biroli P, Kong E, et al. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet. 2019;51(2):245-257.

9. Brooks PJ. DNA damage, DNA repair, and alcohol toxicity – a review. Alcohol. Clin Exp Res. 2006;21(6):1073-1082.

10. Dominy NJ. Fruits, fingers, and fermentation: the sensory cues available to foraging primates. Integr. Comp Biol. 2004;44(4)295-303.

11. Sanchez F, Korine C, Pinshow B, Dudley R. The possible role of ethanol in the relationship between plants and frugivores: first experiments with Egyptian Fruit Bats. Integr Comp Biol. 2004;44(4):290-294.

12. Sonko BJ, Prentice AM, Murgatroyd PA, Goldberg GR, van der Ven MLHM, Coward WA. Effects of alcohol on postmeal fat storage. Am J Clin Nutr. 1994;59(3):619-625.

13. Williams GC, Nesse RM. The dawn of Darwinian Medicine. Q Rev Biol. 199;66(1):1-22.

14. Anderson P. Global use of alcohol, drugs and tobacco. Drug Alcohol Rev. 2009;25(6)489-502.

15. Li NP, van Vugt M, Colarelli SM. The evolutionary mismatch hypothesis: implications for psychological science. Curr Direct Psych Sci. 2018;27(1)38-44.

16. Lieberman LS. Dietary, evolutionary, and modernizing influences on the prevalence of type 2 diabetes. Annu Rev Nutr. 2003;23:345-377.

17. McGovern PE, Zhang J, Tang J, et al. Fermented beverages of pre- and proto-historic China. PNAS 2004;101(51):17593-17598.

18. Eaton SB, Eaton SB. Physical inactivity, obesity, and type 2 diabetes: an evolutionary perspective. Res Q Exerc Sport. 2017;88(1):1-8.

19. Sjöblad S. Could the high consumption of high glycaemic index carbohydrates and sugars, associated with the nutritional transition to the Western type of diet, be the common cause of the obesity epidemic and the worldwide increasing incidences of Type 1 and Type 2 diabetes? Med Hypotheses. 2019:125:41-50.

20. Dudley R. Evolutionary origins of human alcoholism in primate frugivory. Q Rev Biol. 2000;75(1):3-15.

21. Dudley R. Fermenting fruit and the historical ecology of ethanol ingestion: is alcoholism in modern humans an evolutionary hangover? Addict. 2002;97:381-388.

22. Dudley R. Ethanol, fruit ripening, and the historical origins of human alcoholism in primate frugivory. Integr Comp Biol. 2004;44(4):315-323

23. Carbone L, Harris RA, Gnerre S, et al. Gibbon genome and the fast karyotype evolution of small apes. Nature. 2014;513(7517):195-201.

24. Peris JE, Rodriguez A, Pena L, Fedriani JM. Fungal infestation boosts fruit aroma and fruit removal by mammals and birds. Sci Reports. 2017:7:5646.

25. Nunez KM, Azanchi R, Kaun KR. Cue-induced ethanol seeking in Drosophila melanogaster is dose-dependent. Front Physiol. 2018;9:438.

26. Hetherington MM, Cameron F, Wallis DJ, Pirie LM. Stimulation of appetite by alcohol. Physiol Behav. 2001;74(3):283-289.

27. Nevo O, Schmitt MH, Ayasse M, Valenta K. Sweet tooth: elephants detect fruit sugar levels based on scent alone. Ecol Evol. 2020:10(20):11399-11407.

28. Gochman SR, Brown MB, Dominy NJ. (2016) Alcohol discrimination and preferences in two species of nectar-feeding primate. R Soc Open Sci. 2016;3:160217.

29. Hockings KJ, Bryson-Morrison N, Carvalho S, et al. Tools to tipple: ethanol ingestion by wild chimpanzees using leaf-sponges. R Soc Open Sci. 2015;2(6)2150150.

30. Borowicz VA. Do vertebrates reject decaying fruit? An experimental test with Cornus amomum fruits. Oikos. 1998;53:74–78.

31. Buchholz R, Levey DJ. The evolutionary triad of microbes, fruits, and seed dispersers: an experiment in fruit choice by cedar waxwings. *Bombycilla cedrorum*. Oikos. 1990;59:200-204.

32. Ruxton GD, Wilkinson DM, Schaefer HM, Sherratt TN. Why fruit rots: theoretical support for Janzen's theory of microbe –macrobe competition. Proc Biol Sci. 2014;281(1782):20133320.

33. Oota H, Oota H, Kidd KK. Duplicated gene evolution of the primate alcohol dehydrogenase family. Post-Genome Biol Primates. 2011;(1020):149-161.

34. McKenzie JA, McKechnie SW. A comparative study of resource utilization in natural populations of *Drosophila melanogaster* and *D. simulans*. Oecologia. 1979;40:299-309.

35. Van Delden W. The alcohol dehydrogenase polymorphism in *Drosophila melanogaster*: Selection at an enzyme locus. Evol Biol. 1982;15:187-222.

36. Eriksson K, Nummi H. Alcohol accumulation from ingested berries and alcohol metabolism in passerine birds. Ornis Fennica. 1982;60:2-9.

37. Janiak MC, Pinto SL, Duytschaever G, Carrigan MA, Melin AD. Genetic evidence of widespread variation in ethanol metabolism among mammals: revisiting the 'myth' of natural intoxication. Biol. Lett. 2020;16(4):20200070.

38. Carrigan MA, Uryasev O, Frye CB,et al. Hominids adapted to metabolize ethanol long before human-directed fermentation. PNAS, 2015;112(2):458-463.

39. Goedde HW, Agarwal DP. Polymorphism of aldehyde dehydrogenase and alcohol sensitivity. Enzyme. 1987;37(1-2):29-44.

40. Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health. 2007;30(1):5-13.

41. Peng Y, Shi H, Qi X, et al. The ADH1B Arg47His polymorphism in East Asian populations and expansion of rice domestication in history. BMC Evol Biol. 2010;10:15. doi: 10.1186/1471-2148-10-15.

42. Galinsky KJ, Bhatia G, Loh P-R, et al. Fast principal-component analysis reveals convergent evolution of ADH1B in Europe and East Asia. AJHG. 2016;98(3):456-472.

43. Gu S, Li H, Pakstis AJ, et al. Recent selection on a Class I ADH locus distinguishes Southwest Asian populations including Ashkenazi Jews. Genes. 2018;9(9):9090452.

44. Yasumizu Y, Sakaue S, Konuma T, et al. Genome-Wide natural selection signatures are linked to genetic risk of modern phenotypes in the Japanese population. Mol Biol Evol. 2020;37(5):1306-1316.

45. Li H, Gu S, Han Y, et al. Diversification of the ADH1B gene during expansion of modern humans. Ann Hum Genet. 2011;75(4):497-507.

46. Whitfield JB. Alcohol dehydrogenase and alcohol dependence: variation in genotype-associated risk between populations. Am J Hum Genet. 2002;71(5):1247-50

47. Worley J. Review of Evidence-Based Strategies to Treat Alcohol Use Disorder. J Psychosoc Nurs Ment Health Serv. 2021;59(12):7-11.

48. Brewer C, Streel E, Skinner M. Supervised disulfiram's superior effectiveness in alcoholism treatment: Ethical, methodological, and psychological aspects. Alcohol Alcohol. 2017;52(2):213-219.

49. Ray LA, Grodin EN, Leggio L, et al. The future of translational research on alcohol use disorder. Addict Biol. 2021;26(2):e12903.

50. Schuckit MA, Smith TL, Trim RS, et al. Sex differences in how a low sensitivity to alcohol relates to later heavy drinking. Drug Alcohol Rev. 2012;31(7):871-880.

51. Vivian JA, Green HL, Young JE, et al. Induction and maintenance of ethanol self-administration in cynomolgus monkeys (*Macaca fasicularis*): Long term characterization of sex and individual differences. Alcohol Clin. Exp Res. 2001;25:1087-1097.

52. Devineni AV, Heberlein U. Acute ethanol responses in *Drosophila* are sexually dimorphic. PNAS. 2012;109(51):21087-21092.

53. Lancaster FE, Spiegel KS. Sex differences in pattern of drinking. Alcohol. 1992;9:415-420.

54. Felix M-A, Braendle C. The natural history of *Caenorhabditis elegans*. Curr Biol. 2010;20(22):R965-R969.

55. Riddle DL, Blumenthal T, Meyer BJ, et al. editors. (1997) C. elegans II. 2nd edition. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; Section II, Origins of the Model.

56. Davies AG, Bettinger JC, Thiele TR, Judy ME, McIntire SL. Natural variation in the *npr-1* gene modifies ethanol responses of wild strains of *C. elegans*. Neuron. 2004;42:731–743.

57. Wen T, Parrish CA, Xu D, Wu Q, Shen P. *Drosophila* neuropeptide F and its receptor, NPFR1, define a signaling pathway that acutely modulates alcohol sensitivity. PNAS. 2005;102(6):2141–2146.

58. Mottagui-Tabar S, Prince JA, Wahlestedt C, Zhu G, Goldman D, Heilig M. A novel single nucleotide polymorphism of the neuropeptide Y (NPY) gene associated with alcohol dependence. Alcohol Clin Exp Res. 2005;29(5):702–707

59. Bhaskar LV, Thangaraj K, Kumar KP, Pardhasaradhi G, Singh L, Rao VR. Association between neuropeptide Y gene polymorphisms and alcohol dependence: a case-control study in two independent populations. Eur Addict Res. 2013;19(6):307-13.

60. Morozova TV, Huang W, Pray VA, Whitham T, Anholt RR, Mackay TF. Polymorphisms in early neurodevelopmental genes affect natural variation in alcohol sensitivity in adult drosophila. BMC Genomics. 2015;16:865. doi: 10.1186/s12864-015-2064-5.

61. Hack LM, Kalsi G, Aliev F, et al. Limited associations of dopamine system genes with alcohol dependence and related traits in the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD). Alcohol Clin Exp Res. 2011;35(2):376-85.

62. Kendler KS, Kalsi G, Holmans PA, et al. Genome-wide association analysis of symptoms of alcohol dependence in the molecular genetics of schizophrenia (MGS2) control sample. Alcohol. Clin. Exp. Res. 2011;35(5):963–975.

63. Dunn CW, Giribet G, Edgecombe GD, Hejnol A. Animal phylogeny and its evolutionary implications. Ann Rev Ecol Evol Syst. 2014;45:371-195.

64. Thomas AL, Davis SM, Diereck HA. Of fighting flies, mice, and men: are some of the molecular and neuronal mechanisms of aggression universal in the animal kingdom? PLoS Genet. 2015;11(8):e1005416. doi: 10.1371/journal.pgen.1005416.

65. Young RL, Ferkin MH, Ockendon-Powell NF, et al. Conserved transcriptomic profiles underpin monogamy across vertebrates. PNAS, 2019;116(4)1331-1336.

66. Mackay TF, Richards S, Stone EA, et al. The *Drosophila melanogaster* Genetic Reference Panel. Nature. 2012;482(7384):173-8.

67. Huang W, Massouras A, Inoue Y, et al. Natural variadrosption in genome architecture among 205 *Drosophila melanogaster* genetic reference panel lines. Genome Research. 2014;24(7):1193-1208.

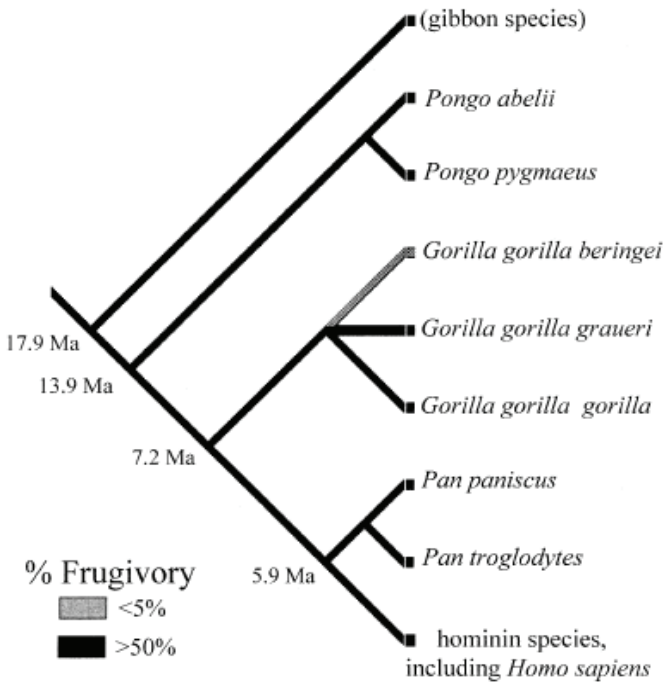
68. Cook DE, Zdraljevic S, Roberts JP, Andersen EC. CeNDR, the *Caenorhabditis elegans* natural diversity resource. Nucleic Acids Research, 2017;45(D1)D650-D657.

LEGENDS

Figure 1. Phylogeny of extant hominoid species. Branches are gray-scale coded by % fruit in average diet for each species. Ticked fills represent uncertainty with respect to dietary fruit contribution to the diet of ancestral hominine species. From Dudley.[21]

Figure 2. Neofunctionalization of hominid Alcohol Dehydrogenase 4 (*ADH4*) towards alcohol. *ADH4* genes of extant and ancestral primates were synthesized and assayed for activity against a variety of substrates. A variant in ADH4 (A294V) that arose in the last common ancestor of the great apes shifted activity of the enzyme away from common plant terpenoids towards ethanol. From Carrigan et al.[38]

Figure 3. Distribution of *ADH1B*2* allele frequency in East Asia. Darker shades indicate higher allele frequency of *ADH1B*2*, a single nucleotide polymorphism associated with lowered risk of alcoholism. Archaeological sites of Neolithic rice cultivation are marked by squares, triangles, and stars, where each shape represents age of site from oldest to youngest respectively. From Peng et al. [41]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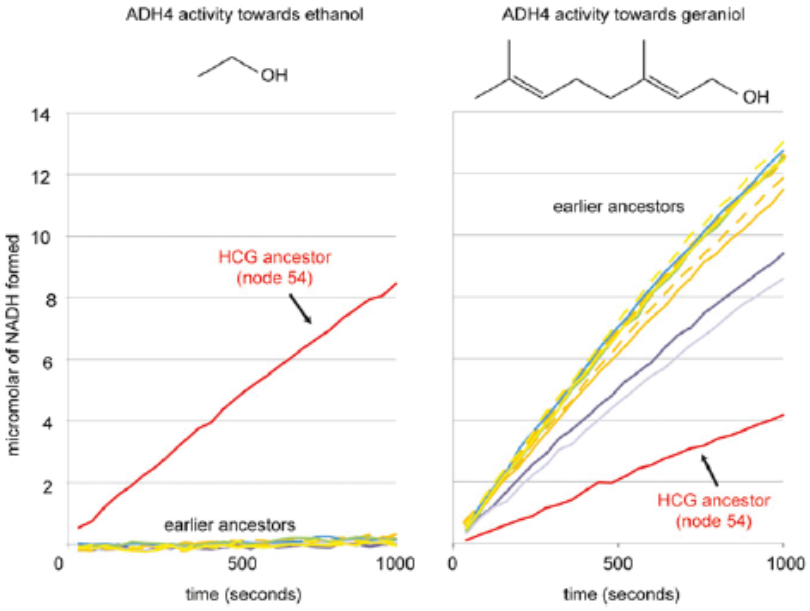
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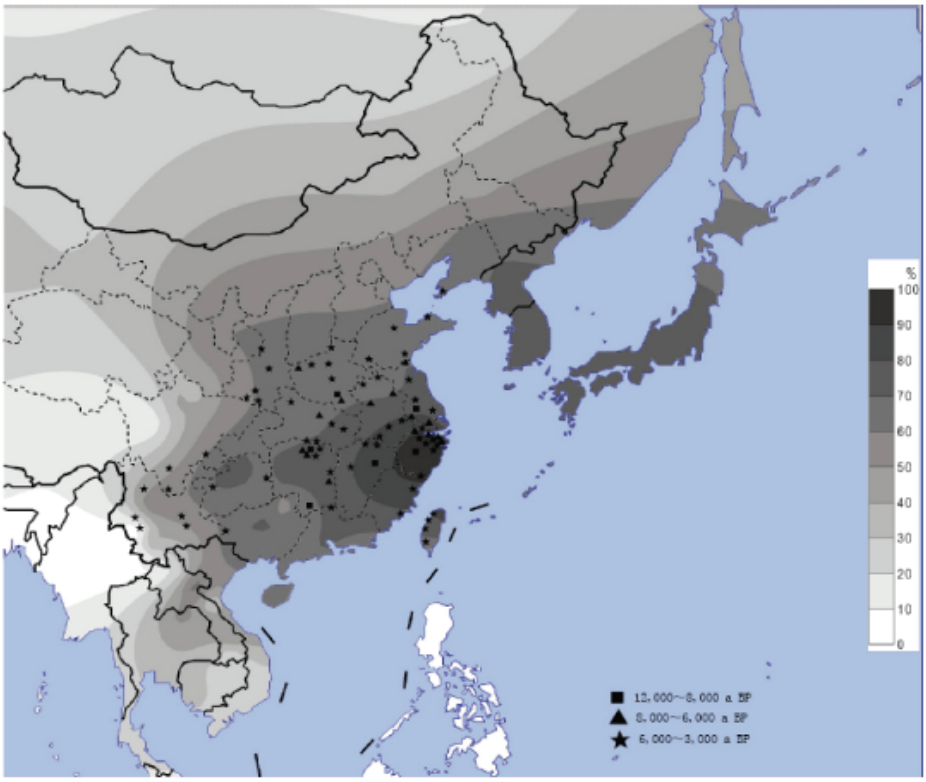
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40
30
20
10
0
12,000~8,000 a BP
8,000~6,000 a BP
6,000~3,000 a BP