

# Alcohol: Myth, Magic and Migraine (part 2)



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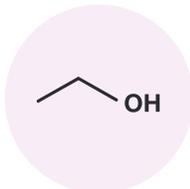
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## The evolution of humans' response to alcohol and why that affects migraines

Genetics may explain why alcohol appears to be a migraine trigger in some individuals and a protector in others. Even though humans can now metabolize alcohol, the trait is certainly not universal in the animal kingdom, even small amounts are toxic to man's best friends, cats and dogs. When and how did humans acquire the ability to metabolize alcohol?

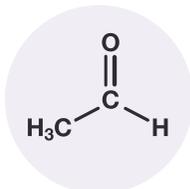


Around 10 million years ago two amazing things happened in our evolution. The first was that our primate ancestral species moved from being primarily arboreal (tree-dwelling) to terrestrial.



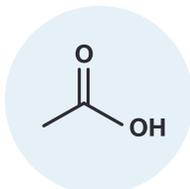
Ethanol

ADH ↓



Acetaldehyde

ALDH2 ↓



Acetate (acetic acid)

The probable motive for moving to the ground and risking ground-based predators was the availability of new food sources such as fallen fruit. Fallen fruit has an interesting feature – it undergoes decay which, among other things is mediated by bacteria and yeast that use the sucrose and fructose contained in fruit to produce vinegar and alcohol (with ethanol levels that can exceed 4%). At first this sounds like the basis for a rollicking primate party, but if fallen fruit is part of the diet – not being able to metabolize alcohol poses a serious problem. Lying around inebriated on the forest floor for extended periods of time is not beneficial for any animal (except perhaps large predatory cats).

The second thing that happened in our evolution was revealed last year when Matthew Carrigan of Sante Fe College in Florida, USA published a study that found that our ability to efficiently metabolize alcohol – acquired about 10 million years ago – is due to a single DNA mutation in a gene now called the alcohol dehydrogenase (ADH) gene.<sup>(1)</sup>

Although ADH's main role in nature is not to metabolize ethanol, but rather a series of other non-ethanol molecules, this new mutation allowed a 40-fold increase in the ability to metabolize ethanol.

The discovery that the genetic ability to metabolize ethanol occurred around the same time that our

ancestors moved to the forest floor says that we evolved the genes to metabolize ethanol a very, very long time ago. Not surprisingly, over the last 10 million years a number of other mutations appeared in the ADH genes of our ancestors and were subsequently inherited by certain populations of people. These mutations can further increase or decrease ADH's ability to metabolize and remove alcohol from the body and they are known to have significant health consequences for that individual. For example, **the greater an individual's ability to remove alcohol from their body the lower their risk of becoming alcoholic<sup>(2)</sup>.**

The job of the ADH gene in humans is to turn ethanol into acetaldehyde, a highly reactive and toxic intermediate that is then metabolized (thanks to another gene) into acetic acid (diluted this is also known as vinegar). The metabolization of acetaldehyde into vinegar is governed by the gene ALDH2 (aldehyde dehydrogenase 2).

**It is of no surprise that alcohol, acetaldehyde and vinegar have profound health effects in humans and thus the genes that govern their levels in our bodies are of great interest to us, especially considering that any of these compounds could potentially act as a migraine trigger. Therefore, is there also genetic variation in the genes responsible for converting acetaldehyde into acetate and do the resulting differences in acetaldehyde levels in the body have effects on our health?**



Yes. Here's one interesting example: A few thousand years ago a mutation in the ALDH2 gene spread throughout East Asia by migration of the Han Chinese<sup>(3)</sup> who originally came from the Yellow River. Today about 50% of East Asians possess the ALDH2 mutant gene. This variant gene means individuals who possess it show severely reduced ALDH2 activity resulting in accumulation of acetaldehyde which increases alcohol toxicity and produces a skin flushing reaction ("Asian flush"), headaches and nausea. Ironically, individuals who have



ADH mutation allowed us to drink



ALDH2 mutation makes it difficult to drink

### The genetics of alcohol metabolism: giveth and taketh?

Why did evolution generate a mutation 10 million years ago that allowed us to metabolize alcohol and presumably increase our ancestors chances of survival, only to have it "taken away" a few thousand years ago by the appearance of the ALDH2 mutation? Around 10,000 years ago humans acquired the ability to ferment foods to produce alcohol and for the first time allow for widespread drinking. This was probably a mixed blessing with respect to human reproduction and survival and under these circumstances, the ALDH2 mutation essentially revoked the ability to metabolize alcohol and presumably restored the survival fitness of those individuals.



this mutation tend to avoid drinking and thus have a lower risk of alcoholism – and this probably accounts for how this mutation spread beneficially to a wide population. In fact pharmaceutical companies in the 1920's developed a fairly effective drug (Antabuse) against alcoholism that essentially mimics the effects of the naturally occurring ALDH2 mutation by inhibiting its activity in the body and producing discomfort during drinking.



**But what about vinegar? Here we finally hit gold, metabolically speaking. Vinegar turns out to be a beneficial regulator of insulin. A recent study<sup>(4)</sup> showed that vinegar lowers glycemic index of carbohydrate based meals and this would in fact be expected to have long term cardiovascular benefits. So it is possible that at least some, if not all of the cardiovascular benefits classically**



**attributed to alcohol are actually mediated through alcohol's metabolization into vinegar<sup>(5)</sup>. By the way, this would mean that you are metabolically correct in beginning meals with salad (and lots of vinegar) and that eating pickled foods is good for you.**

**We'll explain some of the puzzling observations of effects of alcohol on migraine in part 3 of this article.**

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**References:**

- <sup>1</sup>Carrigan *et al.* Hominids adapted to metabolize ethanol long before human-directed fermentation (2015) *Proc. Natl. Acad. Sci USA*, **112**: 458
- <sup>2</sup>Edenberg, H. The genetics of alcohol metabolism. *Alcohol Res Health.* (2007) **30**:5-13t
- <sup>3</sup>Li *et al.* Refined Geographic Distribution of the Oriental ALDH2\*504Lys (nee 487Lys) Variant. *Ann Hum Genet.* (2009) **73**: 335
- <sup>4</sup>Ostman *et al.* (2005) *Eur J Clin Nutr.* **59**:983
- <sup>5</sup>Pownall *et al.* (2015) *Nutrients.* **7**:1992