The Genetics of Being a Lightweight: Tipsy Genes

By **Jessica Khrakovski**

It is a standing tradition that every annual Thanksgiving dinner commences with each legally aged member of my family giving a toast to something they are thankful for. Once this ceremony is finished, so is every glass of wine. It is also a standing tradition for my Aunt Rebecca to be visibly and positively tipsy after only two toasts.

Why is it that some people, like my Aunt Rebecca, are unable to hold their liquor and seem intoxicated after merely sniffing alcohol, while others seem to be unaffected by multiple servings? What is it that earns someone the label of a lightweight drinker?

The designation as a "lightweight" is typically earned by those who feel the psychological, physical, and emotional effects of low doses. The lightweight drinker likely gets intoxicated at a disproportionately rapid rate. The lightweight drinker is someone who is more likely to get sick from alcohol or someone who generally is incapable of holding their liquor. Needless to say—my Aunt Rebecca is a lightweight drinker. It is likely that you have encountered multiple lightweight drinkers, and perhaps you even are one!

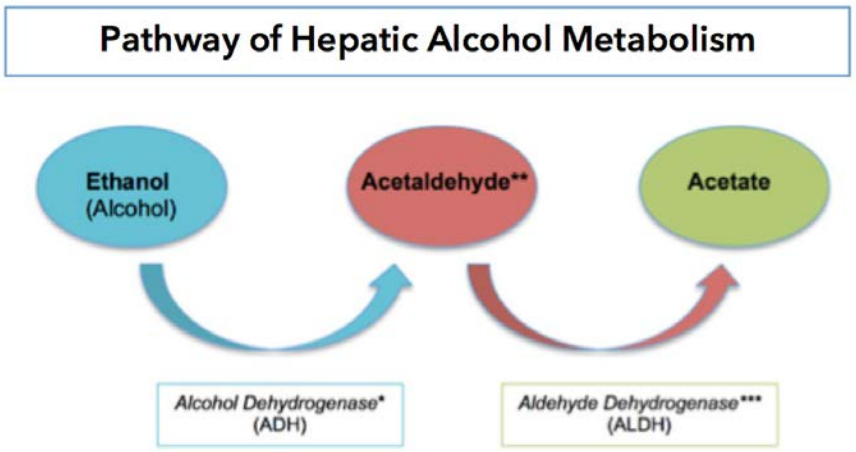
For convenience and ease, the behavioral response to alcohol use is generally discussed with respect to the blood alcohol content (BAC).[1,2] Though there is minimal consensus on standardization, it is a commonly used tool for estimating the concentration of alcohol in the blood and the expected behavioral effects resulting from a certain number of drinks.

Beyond purely the number of drinks consumed, there are numerous physiological and molecular factors that affect BAC, and consequently the level of response to alcohol. Thus, genetic factors are largely responsible for individual reactions to ethanol consumption and could dictate why someone is, or is not, a lightweight.

Why do females get drunker than males?

Sexual Dimorphism of Muscle and Blood Content It is well established that equal quantities of alcohol consumed in the same time frame will disproportionately affect females when compared to males.[1,2] This phenomenon is partially attributable to the fact that males, on average, are larger than fe-

Figure 1 "Pathway of Hepatic Alcohol Metabolism" was created by Jessica Khrakovski.



males. However, after accounting for differences in size, it is evident that differing alcohol distribution rates result from sexually dimorphic muscle mass and blood volume, both of which are disproportionately greater in males than in females.[3,4] Conversely, females have higher subcutaneous fat content and smaller liquid compartments for the dissolving and distribution of alcohol.[4,5]

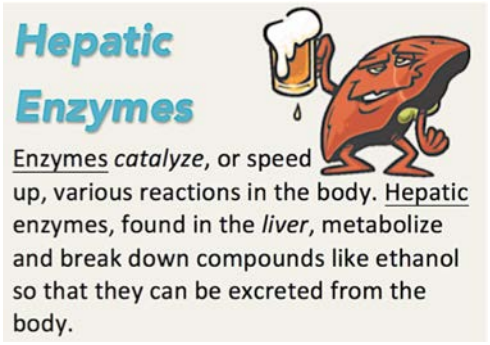
Ethanol, the active ingredient in drinking alcohol, is both water and lipid-soluble and travels though the blood to disperse into tissue for processing.[3,6] Because muscle tissue is highly vascularized, with more extensive blood vessel connectively than fat, alcohol is more rapidly distributed throughout the male body. In females, alcohol remains concentrated within fat because it is unable to disperse through the blood as rapidly.[7] The accumulation of alcohol within fatty tissue prolongs its duration in the body, leading females to maintain higher BACs for longer.[2]

Enzyme Concentrations Not only does the rate of alcohol distribution contribute to the maintenance of higher BACs in females, but also the rates of alcohol processing and metabolism. The majority of alcohol metabolism occurs through hepatic enzymes in the liver, where ethanol is converted into other molecules for excretion and clearance from the system.[2,8,9,10] The process begins with the breakdown of ethanol into a metabolite called acetaldehyde (Fig 1.). This conversion is catalyzed by alcohol dehydrogenase (ADH), the enzyme in metabolism that is directly responsible for decreasing BAC.[10,11,12] Acetaldehyde, a compound even more toxic than ethanol that can produce unpleasant and even detrimental effects, is then transformed into acetate by aldehyde dehydrogenase (ALDH).[13,14]

Though the primary metabolic pathway for alcohol is conserved in the livers of both males and females, the contribution of gastric first-pass metabolism is not.[2,13] Males contain ADH not only in their livers, but also in their stomachs, where alcohol can be broken down as soon as it enters the body. Thus, prior to hepatic ethanol metabolism, up to 30% of alcohol consumed by a male will be converted into acetaldehyde in the stomach, allowing for a substantially lower amount of ethanol to circulate through the bloodstream and absorb into tissue.[7,10,12,14] On the other hand, females have nearly negligible amounts of ADH in their stomachs, such that their BACs are virtually unaltered until alcohol reaches the liver for hepatic metabolism.[2,9]

By nature of design, females are less efficient than males at spreading alcohol throughout their systems, and consequently at metabolizing alcohol in preparation for excretion, resulting in higher BACs and more behavioral symptoms. Nonetheless, the sexual dimorphisms of alcohol processing are insufficient to explain what exactly it is that makes someone a lightweight. Although my Aunt Rebecca is female and all of these factors undoubtedly contribute to her inability to process alcohol well, sexual dimorphism fails to account for lightweight males. What else could account for the unleveled playing field regarding alcohol consumption?

The Lightweight Traits



Aldehyde Dehydrogenase (ALDH)

Within the pathway of hepatic ethanol metabolism, aldehyde dehydrogenase (ALDH) is the enzyme that catalyzes the conversion of acetaldehyde to acetate.[10] Though ALDH does little to reduce BAC, it is essential in clearing the body of acetaldehyde, a compound that is markedly more toxic than ethanol itself.[13, 14] The accumulation of acetaldehyde within the body during metabolism leads to perceived hangover effects such as headache, nausea, dizziness, and hypnotic sedation.[8,15]

Generally, ALDH is more efficient than enzymes that oxidize ethanol into acetaldehyde, such as ADH, and works concurrently to clear acetaldehyde faster than it is produced.[7] Thus, within most individuals, the toxic, hangover symptoms of residual acetaldehyde are apparent after a night of heavy drinking, during which the metabolism system is oversaturated and ALDH cannot outpace acetaldehyde production.[7,10,15]

In some instances, consuming even the smallest amount of alcohol has the same effect as flooding the entire system. Individuals in which this phenomenon occurs possess an allele, or a gene variant, called ALDH2*2, which encodes a dysfunctional version of the ALDH enzyme.[15,16] ALDH2*2 delays the clearance of acetaldehyde so drastically that the accumulation of acetaldehyde manifests as immediate sickness in response to alcohol.[16]

While it is estimated that nearly 50% of individuals of Eastern Asian descent possess the ALDH2*2 allele, the variant is almost nonexistent in those of African and European descent.[10,16] Thus, the alcohol flush reaction and reddening of the face that is common in ALDH2*2 individuals has been colloquially termed "Asian flush." Additionally, markedly lower rates of alcoholism in Asian populations are thought to be attributable to the high numbers of ALDH deficiency acting as a protective mechanism. The ALDH2*2 enzyme produces a similar response to ethanol as does Antabuse (Disulfiram), a drug used to treat alcoholism that interferes with functional ALDH. The inhibition of ALDH causes toxic acetaldehyde sickness that should prevent consumption in alcohol abusers.[15,16]

Since alcohol flush due to the ALDH2*2 allele induces sickness and toxic effects, there must be another tipsy gene that accounts for different sensitivity to alcohol.

Cytochrome p450 2e1 (CYP2E1)

Though the majority of alcohol within the body is metabolized by ADH in the liver, a small but significant portion is metabolized in the brain within the microsomal ethanol oxidizing system (MEOS). The MEOS normally accounts for up to 10% of ethanol oxidation to acetaldehyde in the body, but it increases activity to ameliorate oversaturation of the hepatic pathway when BAC is elevated.[14,17,18] Cytochrome p450 2e1 (CPY2E1) is the brain enzyme that helps breakdown ethanol into acetaldehyde through an unstable intermediate called a gem-diol.[17,19]

In a similar vein to ALDH, there are multiple genetic variants of the CYP2E1 enzyme, some of which are linked to behavior. Alleles that increase CYP2E1 The Microsomal Ethanol Oxidizing System (MEOS) (MEOS) expression, such as the CYP2E1*5B allele that specifically increases gene transcription, are associated with a heightened level of response to alcohol.[20] Elevated levels of CYP2E1 not only produce greater concentrations of toxic acetaldehyde, but also generate high amounts of unpaired electrons as a result of oxidation. These free radicals form reactive oxidative species (ROS) that cause oxidative stress, inflammation, and cellular damage in the brain and interfere with cell pro-

Did you know?

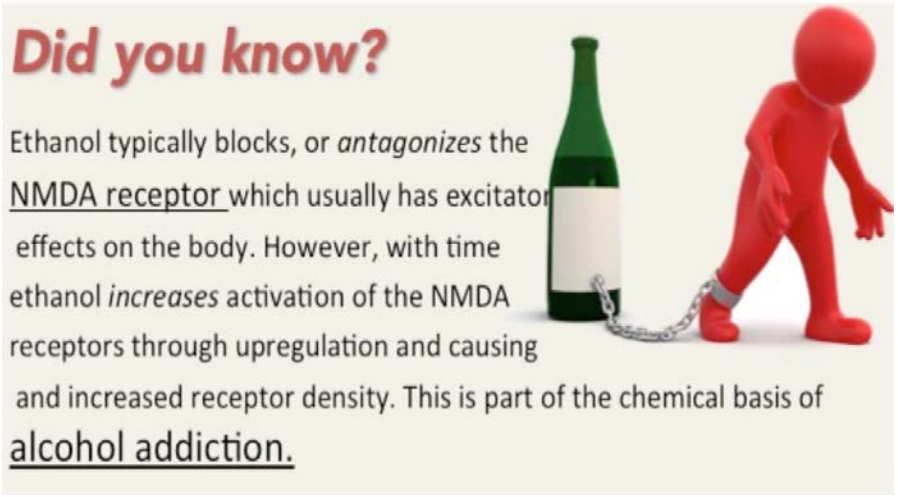
Recent studies have shown that extract from the Oriental Raisin Tree (HDE), *Hovenia dulcis*, is a promising treatment for alleviating symptoms of increased acetaldehyde in ALDH2 individuals such as nausea, dizziness, headaches, and weakness.

cesses.[19,20] The oxidative stress that results from high levels of CYP2E1 increases ethanol sensitivity and the prevalence of sedative/hypnotic effects of alcohol.[20,21] Counterintuitively, high levels of the CYP2E1 enzyme marginally lower BAC, but result in unprecedented alcohol sensitivity due to oxidative stress. It is estimated that 10-20% of the population is affected by this tipsy gene![20]

The tipsy genes work to increase behavioral sensitivity to alcohol, but there are also factors that shift the response to alcohol in the opposite direction.

Does drinking more eventually turn you into a "heavyweight?"

The human body, in particular the brain, is an ever-adapting, plastic organism that adjusts its connectivity and functions to accommodate for changes in alcohol intake. In other words—it learns.[12] Theoretically, a female who heavily uses alcohol might process and metabolize alcohol faster than an equally sized male who rarely imbibes. It is essential to note that chronic use of alcohol will eventually have detrimental consequences on one's health, not the least of which include addiction, liver disease and cirrhosis, and heart disease, [22,23] and that the body cannot be trained to combat these effects. However, the body of a cautious, occasional, social drinker will develop ways in which to more efficiently respond to alcohol and build tolerance.



Tolerance A brain can undergo pharmacodynamic changes in response to alcohol, in which the receptors that ethanol binds to, such as the GABA A receptor, are affected.

The GABA A receptor is responsible for the anxiolytic and sedative-hypnotic effects of alcohol.[23] With time, the receptors could either become desensitized to alcohol or decrease in density of these receptors to become downregulated.[24] Thus, ethanol levels that were once sufficient to activate the receptors would no longer produce effects of the same magnitude, leading the drinker to consume more.

Alternatively, concentrations of metabolizing enzymes that breakdown alcohol, particularly ADH, could elevate with time to account for increased alcohol in the system.[24,25] This pharmacokinetic tolerance results in increased metabolic activity that allows for faster alcohol processing, lowers BAC at an elevated rate, and produces a sort of behavioral tolerance to higher doses of alcohol.

Risk of Addiction Although tolerance might seem like a positive thing for those are not genetically endowed with the means to process or metabolize alcohol efficiently, the development of tolerance is a risk factor for addiction. As tolerance increases and the body becomes more efficient at processing higher concentrations of alcohol, previously effective doses become

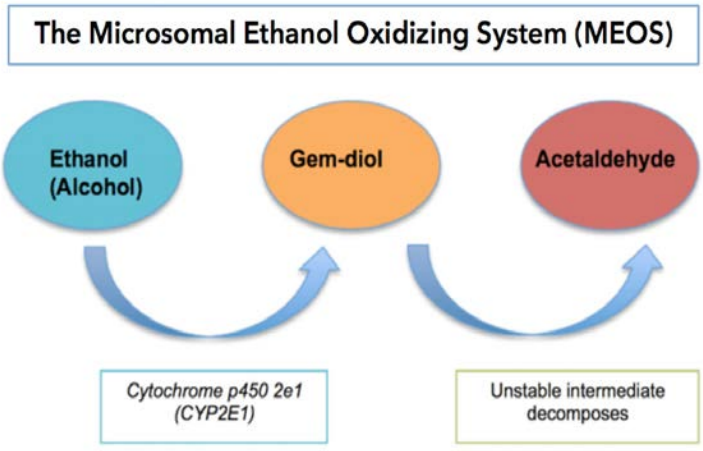


Figure 2 Created by Jessica Khrakovski.

insufficient to provide the desired sensations. Consequently, increasingly higher doses of alcohol are required to achieve effects.

Overview and Recap

While BAC charts may be useful in estimating one's blood-alcohol concentration, there are underlying genetic mechanisms that might explain why my Aunt Rebecca cannot be classified with such a table. Beyond the amount consumed, sexual dimorphism and differing enzyme concentrations result in gendered differences in alcohol processing that affect BAC and behavioral and physiological sensitivity to alcohol.

Further, tipsy genes result in deviation from behavior predicted at certain BACs. Though it is unknown exactly how prevalent the ALDH2*2 and CYP2E1*5B alleles are within the population, further research is critical in understanding the vast effects than alcohol can have on an individual. The creation of BAC tables that link expected behavioral effects to the amount of alcohol consumed is not a trivial task. It is still unknown what percentage of the population is affected by tipsy genes and shows disproportionate behavioral effects to seemingly small amounts of alcohol. This could have implications for reform regarding the legal driving BAC of 0.08 in the United States,[26] at which Aunt Rebecca surely would be incapable of safely driving.

While the development of tolerance through increased consumption trains the body to process more alcohol, it is also linked with a higher risk for alcohol dependence and addiction. Perhaps the lightweight trait is not the most desirable, but it does provide inherent protection against alcoholism. I do not know for sure if Aunt Rebecca has the tipsy gene,

NUMBER OF DRINKS	BLOOD ALCOHOL CONCENTRATION (BAC)	TYPICAL EFFECTS	ANTICIPATED EFFECTS ON DRIVING
1-2	0.02%	❖ Some loss of judgment ❖ Relaxation ❖ Slight body warmth ❖ Altered mood	❖ Decline in visual functions (rapid tracking of a moving target) ❖ Decline in multitasking ability-divided attention
2-3	0.05%	❖ Exaggerated behavior ❖ Loss of small muscles control (i.e. focusing eyes) ❖ Impaired judgment ❖ Usually good feeling ❖ Lowered alertness ❖ Release of inhibition	❖ Reduced coordination ❖ Reduced ability to track moving objects ❖ Difficulty steering ❖ Reduced response to emergency driving situations
3-4	0.08% *	❖ Poor muscle coordination (i.e. balance, speech, vision, reaction time, hearing) ❖ Harder to detect danger ❖ Impaired judgment, self-control, reasoning, memory	❖ Concentration ❖ Short-term memory loss ❖ Speed control ❖ Reduced information processing capability (i.e. signal detection) ❖ Impaired perception
4-5	0.10%	❖ Clear deterioration of reaction time and control ❖ Slurred speech, poor coordination, and slowed thinking	❖ Reduced ability to maintain lane position and brake appropriately
5-7	0.15%	❖ Impaired muscle control ❖ Vomiting or blackouts may occur ❖ Major loss of balance	❖ Substantial impairment in vehicle control, attention to driving task, and in visual/ auditory processing

but I definitely do not anticipate her ever developing a tolerance!

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