ALCOHOL AND HEALTH

# ALCOHOL AND GENETICS

Éduc'alcool

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Legal deposit
Bibliothèque et Archives nationales du Québec
Library and Archives Canada
ISBN 978-2-925145-13-4 (2022) (PDF)
ISBN 978-2-925145-12-7 (2022) (printed copy)

# FOREWORD

“My father was an alcoholic. Does that mean I’m at risk, too?”

“They all drink too much. It runs in the family.”

“In my family, we can all hold our liquor. It’s hereditary.”

How many times have we heard people say such things when discussing their own or other people’s drinking?

Are they looking for another way to justify excessive drinking? Are they questioning the root of their problems? Are they concerned—with or without reason—that they are heading down a path that scares them? People always seem to want to blame genetics for their drinking habits.

“Like father, like son. Like mother, like daughter.” That may be true in a very general way, and parents’ relationship with alcohol is definitely one of the key factors determining their children’s attitude toward drinking. But is drinking behaviour a matter of nature or nurture?

Many Quebecers are asking that very question.

In this publication on alcohol and genetics, Éduc’alcool provides some of the answers and shows that, whatever your genetic profile, moderation is always in good taste.

# INTRODUCTION

Alcohol does not affect everyone the same way. There can be huge differences from one person to the next, due to our individual genetic codes, which dictate how every organ in our bodies will function. So many parts of the body are exposed to the impact of alcohol: the blood absorbs it, the brain responds to it, the liver metabolizes it.

The specific way alcohol interacts with these different organs depends on a number of factors related to such things as enzymes, hormones and neurotransmitters, whose functions are determined by genetic code. As a result, the harms associated with drinking are not the same for everyone.

Aside from how much and how frequently a person drinks, individual genetics do play a role in how alcohol affects the human body. We know this now, thanks in part to technological advances that have allowed for huge studies on the relationship between genetic differences and various drinking-related behaviours and diseases.

When we understanding this genetic susceptibility more clearly, we can see which biological pathways are involved in drinking-related problems. And that better understanding, by both the individuals suffering from the problems and those who treat them, can help reduce stigmatization and lead us to develop more effective treatment programs.


# ALCOHOL USE DISORDER

Alcohol use disorder (AUD), formerly known as alcoholism, is a serious problem that causes harm to the health of the person suffering from it, to their loved ones, and to society as a whole. According to the latest data, genetics account for about 50% of the risk of developing AUD, while acquired behaviours, particularly related to a person's family and social environment, explain the other 50%.[1]

Because of their genetic makeup, some people are actually more likely than others to progress quickly from regular, non-problematic drinking to AUD[2] and to develop AUD at an earlier age.[3] This is true at least among people of European descent.

It is therefore important to be aware of the risk of developing AUD, particularly when there is a family history of it. Also, a number of genes may play a role in such heritability, even though they have not all been identified yet.[4]

As to whether AUD is a matter of nature or nurture, both seem to be involved equally. It's time to put to bed, once and for all, the fatalistic notion that AUD is 100% hereditary, and therefore beyond a person's control. Someone may well have a genetic predisposition to AUD, but that does not mean it's a guaranteed outcome.

## How the brain reacts to alcohol

### Dopamine

Dopamine is an essential neurotransmitter associated with rewards and pleasure in the brain's "reward system." When exposed to a rewarding stimulus, the brain responds by releasing dopamine. People seek pleasurable sensations by engaging in various activities, some of which are healthy, such as eating good food or doing exercise, and some of which are not, such as using potentially harmful psychoactive drugs.

Two genes that affect dopamine activity in the brain have been linked to the risk of AUD:

- the *SLC6A3* gene, which provides instructions for making a protein called the dopamine transporter, which transports dopamine molecules to nerve cells;
- the *DRD2* gene, which affects the sensitivity with which some D2 dopamine receptors react when dopamine is released in the brain.

The role that D2 receptors play in developing AUD is not clear, but the link could be explained by their influence on the emergence of mood disorders, such as depression and anxiety, which are risk factors for AUD.[5]

The same variations in the *DRD2* gene—which increase the risk of AUD—also increase the risk of developing an addiction to other substances,[6] suggesting that D2 receptors act on something common to all kinds of addictions.

[1] Verhulst et al., 2015.
[2] Yeung et al., 2022.
[3] Nurnberger et al., 2021.
[4] Lopez-Leon et al., 2021.
[5] Zhang et al., 2014.
[6] Lopez-Leon et al., 2021.

## GABA

GABA (gamma-aminobutyric acid) is a neurotransmitter that inhibits activity in the areas of the brain it affects. When molecules of alcohol and its metabolites enter the brain, this stimulates GABA activity, thereby intensifying the inhibition effect in those regions controlled by GABA.

However, it has also been shown that some variations in the *GABRA2* gene (a GABA protein coding gene) may affect the sensitivity of certain areas of the brain, in particular those that regulate anxiety.

Some people may therefore have a genetic sensitivity to the relaxing and anxiolytic (anxiety-reducing) effects of alcohol. This particularly calming effect could lead at-risk individuals to abuse alcohol in an attempt to regulate feelings of anxiety.

# The role genes play: The metabolism of acetaldehyde

Some genes can protect against AUD. The most important ones are those linked to the production of alcohol dehydrogenase—the *ADH1B* and *ADH1C* genes—and aldehyde dehydrogenase 2—the *ALDH2* gene—both of which are critical enzymes in metabolizing alcohol.

Normally, alcohol is metabolized in the body as follows: the alcohol is transformed into acetaldehyde, which is then further metabolized into acetate. Some people who have certain variations in the genes that encode the enzymes involved in alcohol metabolism may end up with excessive amounts of acetaldehyde, either because alcohol is being metabolized too quickly, or because the acetaldehyde is turning into acetate too slowly.

A number of studies have shown that only 8% of people of European descent have mutations in the genes involved in metabolizing acetaldehyde. The percentage can vary, depending on an individual's heritage; for example, the same mutations are found in close to 50% of people who trace their origins to such regions of East Asia as Japan, China and Korea.[7]

Acetaldehyde is a toxic substance that causes relatively unpleasant physiological reactions, including nausea, headaches, accelerated heart rate and facial redness. Due to the discomfort caused by excess acetaldehyde, people with this particular genetic variation tend not to enjoy alcohol and therefore are likely to drink less, which reduces their risk of developing AUD.

[7] Guo & Ren, 2010.

# THE HARMFUL IMPACT OF ALCOHOL ON HEALTH

Excessive drinking can have serious medical consequences. Many people who suffer from AUD develop liver disease, various cancers, cardiovascular issues and other problems. A number of factors contribute to a person's sensitivity to the health impacts of alcohol. Studies show that genetics are responsible for about 30% of the risk and involve different genes than the ones linked to AUD.[8]

## Cancer

Drinking is a risk factor for various cancers, the most common ones being cancers of the upper aerodigestive tract, the liver and the stomach, as well as breast and colorectal cancers. The risk of developing cancer varies not only according to the amount of alcohol consumed, but also according to certain genetic predispositions the drinker may have.

For example, someone with a genetic predisposition for high acetaldehyde levels is more at risk for stomach cancer.[9] The harmful impact of that genetic predisposition is observed in people who drink moderately or excessively, although the risk is much more pronounced among excessive drinkers. This suggests that the risk of developing stomach cancer is directly linked to the degree of exposure to acetaldehyde.

A genetic predisposition to an accumulation of acetaldehyde caused by variations in the *ALDH2* gene is associated with an increased risk of breast cancer.[10] However, that increase seems not to be connected to drinking, i.e. the link between alcohol and breast cancer is probably caused by something other than increased acetaldehyde, such as increased hormones in the blood or alcohol-related changes in the metabolism of folic acid.[11]

*ALDH2* also works to eliminate other toxic molecules present in the body. So, for example, a genetic predisposition resulting in a deficiency in the enzyme coded by *ALDH2* could lead to an accumulation of other toxic substances that increase the risk of cancer.

As regards genetics and the risk of colorectal cancer, there is still no consensus on the matter.[12]

## The liver

The liver is the main organ responsible for metabolizing alcohol. And yet, not all excessive drinkers have the same risk of developing a serious illness, such as cirrhosis of the liver. Unlike the cancer risks presented by variations in the *ALDH2* gene—which are responsible for excess acetaldehyde—it seems that, when it comes to liver diseases like cirrhosis, the same variations actually play a protective role.[13]

On the other hand, an analysis of several genome-wide association studies[14] shows that other genes may play a role in aggravating the risk of cirrhosis of the liver. While the exact mechanism is not yet clearly understood, we do know that these genes act on things other than acetaldehyde.

Such genes include *FAF2*, which acts on the metabolism of saturated fats, and *PNPLA3*, which can cause elevated triglyceride levels in the body.

Looking at all genetic variations combined, researchers find that, among people who drink excessively to the same degree, those who have a high number of such genetic variations are three to six times more at risk for developing cirrhosis of the liver than those who have few of them.[15]

Variations in the *ALDH2* gene are found more commonly among certain populations of East Asia. Similarly, it seems that certain variations in the *PNPLA3* gene, which cause higher triglyceride levels, are more common among the indigenous peoples of Mexico and South America than among those of European descent.[16] This discovery reveals the differences between populations regarding the risk of developing liver diseases caused by drinking alcohol.

[8] Edwards et al., 2021.
[9] Joo Kang et al., 2021.
[10] Ugai et al., 2019; Zografos et al., 2019.
[11] Ugai et al., 2019.
[12] Bhaskar et al., 2020; Chen et al., 2014; Zhao et al., 2014; Zuo et al., 2019.
[13] He et al., 2016.
[14] Schwantes-An et al., 2021.
[15] Whitfield et al., 2021
[16] Larrieta-Carrasco et al., 2014; Pontoriero et al., 2015.

# The cardiovascular system

The impact of drinking on cardiovascular health also depends on a person's genetic predisposition. Once again, acetaldehyde is the culprit, because of its toxic effects on the heart.

One meta-analysis[17] of nine studies involving Asian populations showed that people with variations in the *ALDH2* gene—which interferes with the elimination of acetaldehyde—are 36% more at risk of developing heart disease than people without variations, and 64% more at risk for myocardial infarction, commonly known as a heart attack.

At the same time, a Japanese study[18] has shown that people with a strong capacity for eliminating acetaldehyde are more at risk for multiple lacunar infarcts—small strokes caused by the interruption of blood flood in the small deep arteries of the brain—which are generally associated with hypertension (high blood pressure). This could be explained by the greater amounts of alcohol they consume, since they are not held back by the unpleasant effects of acetaldehyde.

All this data indicates that a genetic predisposition leading to an accumulation of acetaldehyde is particularly damaging to the heart, but it tends to protect against the excessive drinking that harms the blood vessels that feed the brain.

[17] Wang et al., 2013.
[18] Nagasawa et al., 2007.
[19] Van de Luitgaarden et al., 2021.

## Mendelian randomization studies

Genetics can be an analytic means to evaluate the causal relationship between a risk factor and a disease. Given that, at the moment of conception, hereditary genetic variations are considered to be random, and also that they cannot be modified by acquired behaviours or correlated to lifestyle, it is therefore possible to use genetics to assess whether higher or lower exposure to a risk factor leads to higher or lower risk of disease.

Mendelian randomization studies have been able to evaluate the health impact of reduced alcohol consumption, attributable to variations in the *ALDH2*, *ADH1B* and *ADH1C* genes, which make drinking less pleasant and cause people to drink less frequently.

These studies have confirmed that excessive drinking increases the risk of cardiovascular disease and diabetes.

However, because of the limits of the Mendelian randomization approach, these studies have not allowed for a definitive position on the potential benefits or harms of occasional or moderate drinking.[19]

# CONCLUSION

Alcohol is a substance that interacts in a complex way with various parts of the human body. Genetics explains about half of the risk of developing AUD, with acquired behaviours explaining the other half. The role of certain genes involved in the metabolism of acetaldehyde is well known, making drinking less pleasant for those who carry certain genetic variations. The genes associated with metabolizing acetaldehyde may protect against AUD, but the same genes can also present a risk for certain cancers and heart disease.

While it is the most obvious culprit, an accumulation of acetaldehyde in the body is not the only way in which drinking increases cancer risk. It is important to keep in mind that almost all the studies exploring the effects of the *ALDH2* gene have been done on Asian populations, given their greater likelihood of having the higher-risk alleles of the gene.

Furthermore, we cannot exclude the possibility that these population groups have other characteristics that distinguish them from groups in other regions of the world, which implies that the study results cannot be generalized with any certainty to the global population as a whole.

With the exception of breast cancer, which is more common among women than among men, there does not appear to be any difference between the sexes when it comes to the impact of the various genetic predispositions on the harmful effects associated with drinking.

Aside from the genetic variations in the metabolism of acetaldehyde, it is still too early to predict with any certainty who is at greater or lesser risk of developing AUD, or even of suffering alcohol-related damage to their health, due to their personal genetic profile.

Nonetheless, scientists agree that a number of genes are involved, and studies under way will shed some light on how these genes behave, to help guide the use and development of new treatment approaches.

**Recommendations: vigilance and moderation**

While family history is not deterministic, it can reveal a genetic predisposition to AUD or alcohol-related disease. That's why it could be a good idea to ask yourself about your family's drinking habits and behaviours, while also considering the health of each family member. If any close relatives who tend to drink excessively have already been diagnosed with AUD, or have health issues related to their drinking, it could be important to monitor your own drinking habits to avoid harmful consequences.

Also, anyone who has unpleasant reactions—such as nausea, headache, accelerated heart rate or skin redness—immediately after drinking alcohol may have a genetic predisposition to excess acetaldehyde in the body.

Such people should be extra careful, for even low levels of alcohol consumption could lead to a greater tendency to develop alcohol-related cancers and other diseases.

Whatever your luck in the genetic lottery, it's a good idea to put the odds on your side and remember that moderation is always in good taste.

**Acknowledgements**

Éduc'alcool would like to thank Dr. Marie-Pierre Dubé for her valuable contribution in reviewing this publication. Dr. Dubé is professor at Université de Montréal and Director of the Beaulieu-Saucier Pharmacogenomics Centre, as well as researcher, at the Montreal Heart Institute. She holds the Canada Research Chair in Precision Medicine Data Analysis and teaches genetic epidemiology at the School of Public Health at Université de Montréal.

# IN THE SAME COLLECTION

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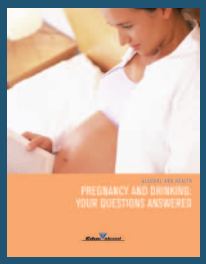


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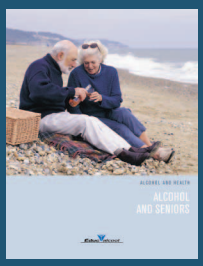


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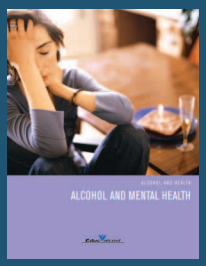


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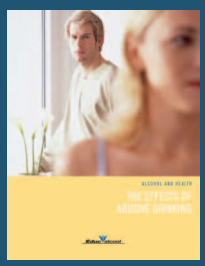

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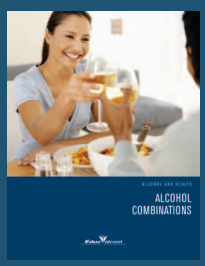


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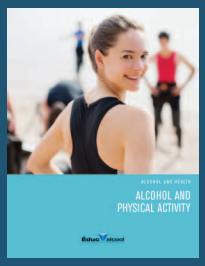


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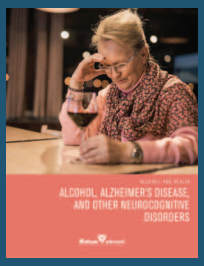


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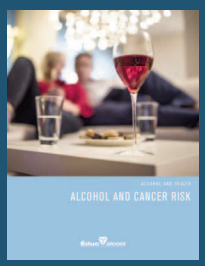


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Moderation is always in good taste.

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