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The Genetic Role of Alcoholism

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What is Alcoholism?

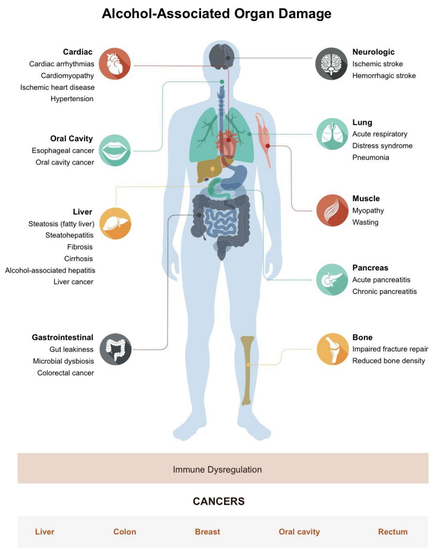
Alcohol use disorder, also known as alcoholism, is characterized by the continued and uncontrolled consumption of alcohol, despite it risking one's health and safety. Additionally, individuals with the disorder develop a tolerance to alcoholic beverages, requiring more alcohol to get the same effect. Alcoholics experience withdrawal symptoms when drinking is decreased or stopped completely, which typically occurs within several hours to days later [1].

Alcohol Intoxication
This occurs as there is an increased level of alcohol in the bloodstream, which increases the likelihood of experiencing negative effects. Alcohol intoxication can lead to behavioral problems and mental alterations, such as: inappropriate behavior, mood swings, lowered inhibitions, slurred speech, memory and attention impairment, and poor coordination and balance. Very high blood alcohol levels can lead to coma, brain damage, and ultimately death [1].

Alcohol Withdrawal
This occurs when alcohol use has been continuous and is then reduced or completely stopped. This occurs within several hours to days later. Symptoms of alcohol withdrawal include perspiration, tachycardia, tremors, insomnia, nausea and emesis, hallucinations, agitation, anxiety, and potentially seizures [1].

Risk Factors
Alcoholism occurs most frequently in adults in their 20s and 30s, but it can begin at any age. Besides the preexisting genetic mutations in individuals with a family history of alcoholism, there are several risk factors for alcoholism:
- Drinking too much on a regular basis
- Starting to drink at an early age
- Mental health issues, especially depression
- Bariatric surgery patients
- Social and cultural factors [1]

Impacts of Alcoholism
- Increased risk of dangerous behavior
- Relationship problems
- Poor performance at work or school
- Increased likelihood of committing a crime
- Risk of developing other addictions
- Increased risk of suicide
- Liver disease
- Gastrointestinal disease
- Heart disease
- Diabetes complications
- Impaired sexual function
- Neurological disease
- Eye disease
- Birth defects
- Bone disease
- Increased risk of cancer
- Compromisation of immune system [1]



Source: National Institute on Alcohol Abuse & Alcoholism

Genes & Proteins Involved in Alcoholism

OPRM1: This gene encodes the mu opioid receptor (MOR) in humans and has an important role in dependence to alcohol and other drugs of abuse such as nicotine and cocaine via its mutation of the dopamine system. Transcription of this protein occurs in abundance within the brain, adrenal glands, and testis. This mutation is located on the 118th loci of chromosome 6 and has been associated with opioid and alcohol addiction [2].

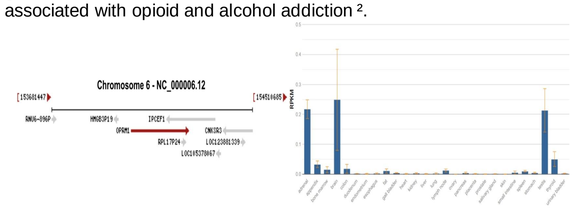


Figure 1. OPRM1 Loci on Chromosome 6 [2] Figure 2. OPRM1 transcription levels [2]

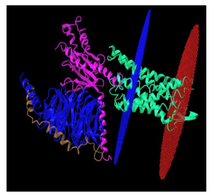


Figure 3. OPRM1Protein [3]

ALDH2: Aldehyde dehydrogenase 2 protein is the second enzyme of the major oxidative pathway of alcohol metabolism and is located on chromosome 12. There are two major liver isoforms of ALDH2, cytosolic and mitochondrial. Caucasians have both isoforms, while approximately 50% of East Asians lack the mitochondrial isoform, resulting in a higher frequency of acute alcohol intoxication among this group. Transcription of this protein occurs in abundance within the fat and liver [4].

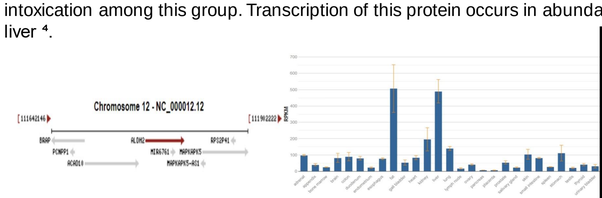


Figure 4. ALDH2 loci on chromosome 12 [4] Figure 5. ALDH2 transcription levels [4]

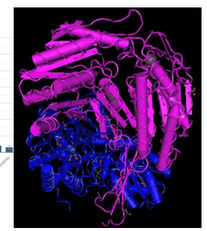


Figure 6. ALDH2 Protein [5]

DRD4: Dopamine receptor D4 encodes the D4 subtype of the dopamine receptor in humans. Mutations in this gene have been associated with autonomic nervous system dysfunction, attention deficit/hyperactivity disorder, and the personality trait of novelty seeking [6]. DRD4 polymorphism is associated with cravings for alcohol and binge drinking [7].

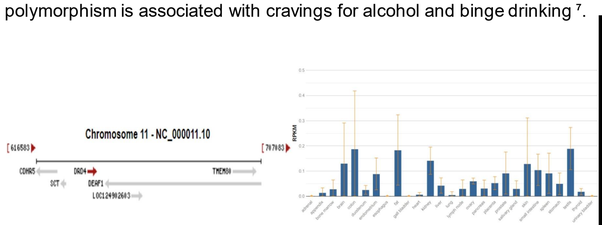


Figure 7. DRD4 loci on chromosome 11 [6] Figure 8. DRD4 transcription levels [6]

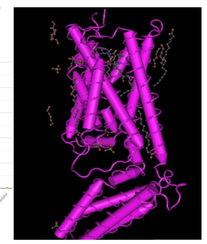


Figure 9. DRD4 Protein [8]

Gene Mutations Involved in Alcoholism

There are several polymorphisms in the OPRM1 gene that may be associated with alcohol use and dependence. The most common mutation is *A118G*. It is theorized that the lower expression of the receptor observed in G carriers leads to an increase in alcohol intake. Studies have found significant association between the 118G allele and alcohol dependence, alcohol craving, the presence of alcohol use disorder, and total alcohol intake, specifically in East-Asian populations [9].

Alcohol dehydrogenase enzymes play a large role in the metabolization of alcohol. Mutations of these enzymes can affect an individual's vulnerability for alcohol dependence. ALDH2(2) is a mutation in the ALDH2 allele in which amino acid is substituted from glutamic acid to lysine at the 504th position, resulting in an inability to eliminate acetaldehyde. This causes high blood alcohol concentrations after drinking and results in a painful effect called flushing. This polymorphism is found exclusively in East-Asian populations [7].

Genotype factors that may increase susceptibility showed a higher frequency of a five repeat allele of dopamine D4 receptor polymorphism in alcoholics with ALDH2(2). Alcoholics with the five repeat allele were also found to abuse other drugs more frequently [10].

Epigenetics is significantly associated with the genetics of alcoholism. The disease is largely associated with environmental factors. The epigenetic mechanisms that regulate changes in gene expression observed in addiction respond not only to alcohol exposure, but also to the presence of mental health disorders such as anxiety and stress. Both genetic and epigenetic factors have been shown to aid in the transition from use to abuse via neuroadaptations in the brain. Alcohol has been shown to affect epigenetic pathways in peripheral tissues, such as the gastrointestinal and biliary systems [11].

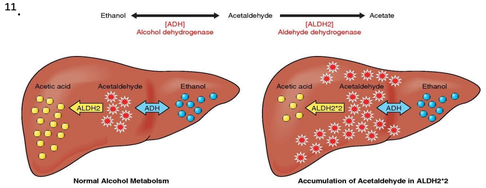


Figure 10. ALDH2(2) and the inability to metabolize acetaldehyde[12]

Future Outcomes

In recent years, doctors at the Medical University of South Carolina have experimented with memory alteration to treat addiction. Pharmaceuticals that interrupt the brain's ability to form memories, such as propranolol, have been used to treat addicts. Experiments performed on rats have proven that memory can be manipulated to lessen its influence on addictive behavior. Addicts respond to various cues, some subconsciously, before they indulge in the addictive behavior. The purpose of targeting memories is to expose the addict to said cues without allowing them to consume the drug. Overtime, the cues will lose their power and no longer induce cravings. Memory manipulation and behavioral therapy have proven to be the most effective methods thus far in treating addiction[13].

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