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Genes as a factor in Drug Addiction

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ABSTRACT

With ever-increasing victims of drug abuse, research on the genetic factors fuelling a drug addiction can play a vital role. The involvement of certain neurotransmitters and hormones that stimulate the addiction can tell a lot about the addiction. This paper explores the possible genetic variations which make a difference in susceptibility to drug addiction along with factors such as the environment an individual thrives in.

INTRODUCTION

According to the United Nations Office on Drugs and Crime, around 275 million people had used drugs worldwide in 2021 and over 35 million had experienced Substance Use Disorders[1] (SUD). To alleviate the situation, it is necessary to identify the factors which promote drug addiction. There are many social, familial and individual factors which affect drug use- mainly: dual diagnoses, environment and childhood. [2] [3]Over the years, although genetics has been identified as accounting for 40-60% of a person's susceptibility to addiction[4], pinpointing the exact genes associated has not been completely achieved: accomplishing which could aid rehabilitation and prevention of substance abuse."Addiction can be defined as a diverse set of common, complex diseases that are to some extent tied together by shared genetic and environmental etiological factors. Its three, central characteristics are: craving, binge (intoxication) and withdrawal." (Bevilacqua, L., & Goldman, D., 2009).[5] Research into the field proves that natural variation on proteins can lead to different vulnerabilities to addiction.[6] Mutations, alterations caused in a person's DNA due to faulty DNA replication, can also cause a change. Enzymes metabolising drugs and catalysing every reaction in the body, are proteins. Proteins are coded by a person's genes: composed of DNA. Thus, a person's genes affect how a drug is metabolised. Enumerating the different neurotransmitters responsible for addiction, their genetic aspect and the alterations they can cause, this paper also explores the different factors that influence an individual's chances of developing an addiction. This paper aims to reinforce that although the environment plays an important role in a person's susceptibility to drug addiction, genetics is a more significant factor.

Neurons, Neurotransmitters and Drugs

While interfering with transmission of signals between neurons via neurotransmitters, drugs can also activate neurons by attaching to them. Having chemical structures similar to that of a natural neurotransmitter, they fit into the receptors. However, being unnatural, the stimulation differs, leading to erroneous message transmission. Releasing 'abnormally large amounts of natural neurotransmitters'[7] is possible, along with stopping the normal

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[1]United Nations (2021, June 24) *UNODC World Drug Report 2021: pandemic effects ramp up drug risks, as youth underestimate cannabis dangers.* Retrieved May 28, 2022, from https://www.unodc.org/unodc/press/releases/2021/June/unodc-world-drug-report-2021_-pandemic-effects-ramp-up-drug-risks--as-youth-underestimate-cannabis-dangers.html

[2] Whitesell, M., Bachand, A., Peel, J., & Brown, M. (2013). Familial, social, and individual factors contributing to risk for adolescent substance use. *Journal of addiction, 2013*, 579310. Retrieved May 28, 2022 from https://doi.org/10.1155/2013/579310

[3]Legg T.J., & Tyler M. (August 25, 2016). *Risk Factors for Addiction.* Retrieved May 28, 2022, from https://www.healthline.com/health/addiction/risk-factors

[4](2006) *The Role of Genes in Drug Addiction.* Retrieved May 28, 2022, from https://headsup.scholastic.com/students/the-role-of-genes-in-drug-addiction

[5] Bevilacqua, L., & Goldman, D. (2009). Genes and addictions. *Clinical pharmacology and therapeutics*, *85*(4), 359–361. Retrieved May 28, 2022, from https://doi.org/10.1038/clpt.2009.6

[6] (2006) *The Role of Genes in Drug Addiction.* Retrieved May 28, 2022, from https://headsup.scholastic.com/students/the-role-of-genes-in-drug-addiction

[7] (NIDA. 2022, March 22. *Drugs and the Brain*. Retrieved June 6, 2022 from

recycling of these neurotransmitters by damaging transportation: changing communications with the brain. The most common neurotransmitters involved in addiction are:

A. Dopamine[8]:

Dopamine is at the centre of drug reward system. The reward cycle, a natural cycle which boosts dopamine production after essential biological actions (to help with survival), is also linked to addiction.[9]According to the reward prediction error hypothesis[10], in addiction the addict overestimates the pleasure derived from the drug: leading to increased uptake to experience the same 'high'. Common drugs such as cocaine, amphetamine, opiates, alcohol, nicotine, cannabis, barbiturates, and benzodiazepines activate the dopamine system but at different levels. Addicts mostly engage in delayed reward discounting[11]: making them aversive[12] and suppressing the dopamine system. Addicts work to avoid cues indicating these delays (and prevent the aversiveness) in cocaine and other drugs as well.[13]

Differing for each substance, dopamine can be:

a. Released from intracellular vesicles (amphetamines)[14]
b. Prevented from being up- taken by transporters (cocaine, benzos,flowering quince)[15]
c. Move by unblocking its receptors in the brain by the drug (opiates- synthetic and natural).
d. Fire up dopaminergic neurons, inhibit GABA neurotransmitter[16]— which inhibits dopamine (alcohol and cannabis).

Dopamine receptor genes largely shape up one's susceptibility to addiction. The genes, namely DRD1, DRD2, DRD3, DRD4 and DRD5 genes[17].

Impairment in the DRD1 gene could lead to neuropsychiatric disorders including addiction. This gene dictates the defects caused in the offspring through the use of substances such as ethanol, cannabis, heroin, cocaine and other drugs by the mother during the mother's pregnancy. [18]

The DRD2 gene and DA[19] might be parts of the reward cycle. The Taq1 A1 allele of the DRD2 gene ensures that the brain lacks enough dopamine receptor sites to achieve adequate DA sensitivity. This dopamine deficit in the reward site of the brain can results in unhealthy appetites and craving for addictive substances[20], resulting in addicts consuming higher quantities of drugs to get a satisfactory 'high'. Additionally, the DRD2 gene of addicts contains

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https://nida.nih.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain

8 Garza C. *Neurotransmitter chart.* Retrieved June 6, 2022 from https://studylib.net/doc/25359463/neurotransmitter-chart

9 Gardner E. L. (2011). Addiction and brain reward and antireward pathways. *Advances in psychosomatic medicine*, *30*, 22–60. Retrieved June 6, 2022
https://doi.org/10.1159/000324065

10 Retrieved June 6, 2022 from https://neuroscientificallychallenged.com/posts/sorting-out-dopamines-role-in-reward

11 Counting the reward as unworthy due to delay in its procurement.

12 Associating certain unpleasant symptoms with the drug (mostly used for rehab)

13 Wise R. A. &Robble M.A. (2020). Dopamine and Addiction. *Annual Review of Psychology*. Retrieved June 7, 2022 from https://www.annualreviews.org/doi/10.1146/annurev-psych-010418-103337?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed#_i16

14 Wise R. A. &Robble M.A. (2020). Dopamine and Addiction. *Annual Review of Psychology*. Retrieved June 7, 2022 from https://www.annualreviews.org/doi/10.1146/annurev-psych-010418-103337?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed#_i16

15 Wise R. A. &Robble M.A. (2020). Dopamine and Addiction. *Annual Review of Psychology*. Retrieved June 7, 2022 from https://www.annualreviews.org/doi/10.1146/annurev-psych-010418-103337?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed#_i16

16 Gamma-aminobutyric acid (GABA) is a neurotransmitter, a chemical messenger in the brain. It slows down your brain by blocking specific signals in your central nervous system.

17 Dopamine Receptor D1, D2, D3, D4 and D5 genes, coding for proteins.

18 Blum, K., Oscar-Berman, M., Barh, D., Giordano, J., & Gold, M. (2013). Dopamine Genetics and Function in Food and Substance Abuse. *Journal of genetic syndromes & gene therapy*, *4*(121), 1000121. Retrieved June 7, 2022 from https://doi.org/10.4172/2157-7412.1000124

19 Dopamine

20 Blum, K., Oscar-Berman, M., Barh, D., Giordano, J., & Gold, M. (2013). Dopamine Genetics and Function in Food and Substance Abuse. *Journal of genetic syndromes & gene therapy*, *4*(121), 1000121. Retrieved June 7, 2022 from https://doi.org/10.4172/2157-7412.1000124

the D2A1 allele which has been established as a factor for severe alcohol dependence only along with a higher-level consistency with other studies showing an association with the severity of alcoholism. In a study, out of 104 subjects with a discharge diagnosis of drug and alcohol abuse/dependence, 42.3% possessed the D2A1 allele. Similarly, people with D2A1 allele comprised 56.9% of the group which spent more than $25/week on two or more substances. Multiple studies exhibit a highly significant association between multiple substance abuse based on money spent and the presence of the D2A1 allele in the persons.[21]DRD3 gene has been detected to be playing an integral role in nicotine addiction. [22]

The DRD4 gene VNTR has been presently confirmed to be involved in nicotine addiction. Its functional role involves signals for the craving of alcohol, tobacco, heroin and even binge eating. The gene increases the vulnerability to behavioural disorders along with nicotine, alcohol, cocaine and marijuana addictions.[23]Similarly, mutation in the COMT gene- which codes for the COMT enzyme, the enzyme that breaks down dopamine, can also lead to increased risk for addiction. Polymorphism in the DAT protein, an important protein that helps in transporting dopamine from the synaptic cleft into surrounding cells, is associated to dopamine disorders. This polymorphism is a result of mutation/ is inherited from ancestors. In essence, dopamine processing and reception is highly dependent on genes leading to the fact that addiction to dopaminergic drugs is highly genetic.

B. Serotonin

Serotonin is the hormone regulating mood. Also known as 5-hydroxytryptamine (5-HTP), it is made from tryptophan (an essential amino acid). Tryptophan is converted into 5-HTP, which is changed into serotonin.[24] The chief genetic variations in the 5-HT system, such as SLC6A4, HTR1B, HTR2A, HTR2C, HTR3 (HTR3A, HTR3B, HTR3C, HTR3D, and HTR3E), play a role in development of SUDs. [25]The most common drugs: cocaine, amphetamines, MDMA(ecstasy), ethanol and opioids work by inhibiting the neuronal activity of 5-HT via activating 5-HT_{1A} receptors and increasing extracellular levels of 5-HT receptors.[26] Consequently, the natural serotonin levels diminish, making depression a withdrawal symptom. The 5-HT transporter (5-HTT) protein regulates the reuptake of 5-HT following its synaptic release. The 5-HTT is encoded by a single gene (SLC6A4) on chromosome 17q11.1–17q12 has two well-studied polymorphisms associated with vulnerability to SUDs.[27]The 5-HTTLPR gene helps to regulate serotonin transporter expression, post-synaptic serotonin reuptake, and neuronal activity (Ho et al., 2012) in relation to mood disorders and susceptibility to addiction. A significant association between Alcohol Disorder (AD) diagnosis and the presence of at least one S allele was found. Stronger association was found for participants who had two copies of the S allele.[28]A 5-HT contribution to the establishment and maintenance of addiction-related behaviours and their neuronal mechanisms. The 5-HTTLPR S allele exhibits the

[21]Comings, D. E., Muhleman, D., Ahn, C., Gysin, R., & Flanagan, S. D. (1994). The dopamine D2 receptor gene: a genetic risk factor in substance abuse. *Drug and alcohol dependence*, *34*(3), 175–180. Retrieved June 7, 2022 https://doi.org/10.1016/0376-8716(94)90154-6

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[23]Gorwood P., Le Strat Y., Ramoz N., Dubertret C., Moalic J.M., &Simonneau M. (2012) Genetics of dopamine receptors and drug addiction. *Human genetics.* Retrieved June 7, 2022 from https://www.researchgate.net/profile/Philip-Gorwood/publication/221848071_Genetics_of_dopamine_receptors_and_drug_addiction/links/0912f507274c080f81000000/Genetics-of-dopamine-receptors-and-drug-addiction.pdf?origin=publication_detail

[24]*5-Hydroxytryptophan (5-HTP), Health Library.* Retrieved June 7, 2022 from https://www.mountsinai.org/health-library/supplement/5-hydroxytryptophan-5-htp

[25]Herman, A. I., & Balogh, K. N. (2012). Polymorphisms of the serotonin transporter and receptor genes: susceptibility to substance abuse. *Substance abuse and rehabilitation*, *3*(1), 49–57. Retrieved June 7, 2022 from https://doi.org/10.2147/SAR.S25864

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[27]Herman, A. I., & Balogh, K. N. (2012). Polymorphisms of the serotonin transporter and receptor genes: susceptibility to substance abuse. *Substance abuse and rehabilitation*, *3*(1), 49–57. Retrieved June 7, 2022 from https://doi.org/10.2147/SAR.S25865

[28]Herman, A. I., & Balogh, K. N. (2012). Polymorphisms of the serotonin transporter and receptor genes: susceptibility to substance abuse. *Substance abuse and rehabilitation*, *3*(1), 49–57. Retrieved June 7, 2022 from https://doi.org/10.2147/SAR.S25868

strongest association with SUD, the onset of drug abuse at a younger age[29] and with dual diagnoses (addiction in morbid individuals). The L allele shows relation with nicotine addiction. Although genes involved in the 5-HTT processes differ for ethnic groups[30], some relation has been established for the S allele. Thus, environmental factors and dual diagnoses play an essential role in serotonin processing.

C. Endorphins

Endorphins are natural painkiller hormones with inherent addictive properties. They are significant in reward mechanisms in the brain. They possibly facilitate physiological feelings of euphoria and lead to a state of ecstasy[31]: an important factor in addiction to various substances and habits as most people value the physiological effects of 'highs'. Beta endorphins are released to counter pain. Persons with naturally low- levels of beta endorphin production are more likely to procure endorphins exogenically, from sources such as alcohol.[32] Consequently, their natural endorphin production also dips. According to prior studies, low beta endorphin production is likely if one parent is alcoholic and is worse when both the parents are.[33]

The various endogenous peptides[34], including beta endorphin, fit into mu and kappa receptors. The mu-opioid receptor (MOR) is encoded by the OPRM1 gene. Rapid activation of the mu opioid receptor, such as that occurring during drug abuse, results in euphoria, linking endorphins to development of addiction. The rs2236861 allele of the OPRM1 gene and opioid dependence show positive relation.[35] Although this is promising, there is no strong suggestion of relation between variation in mu- receptor and opioid addiction. Only the C17T variant was present in addicts by a marginal difference in the study.[36] Additionally, "the A118G polymorphism may change the receptor with respect to the binding affinity of β-endorphin and the potency of its cellular activity." *(*Crist, R. C., Reiner, B. C., &Berrettini, W. H. (2019*)* The approximately 3-fold difference in binding affinity of β-endorphin indicates differences in activities controlled by beta endorphins which could confirm if this allele alters susceptibility to addiction.[37]

Other factors

A. Environment and age

Environment undoubtedly plays a vital role in addiction. Evidence suggests that racial and socioeconomic inequities in the environmental factors, differing all over the world, including access and exposure to substances of abuse, presence of neighbourhood disadvantage and disorder along with environmental barriers to treatment, lead to differing rates of substance abuse and its treatment.[38]

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[29]Thompson, M. D., & Kenna, G. A. (2016). Variation in the Serotonin Transporter Gene and Alcoholism: Risk and Response to Pharmacotherapy. *Alcohol and alcoholism (Oxford, Oxfordshire)*, *51*(2), 164–171. Retrieved June 7, 2022 fromhttps://doi.org/10.1093/alcalc/agv090

[30]An association of the S allele with AD in studies conducted with European, Asian and Mexican populations while the L allele was associated with AD in studies conducted with African populations. The A allele of an intronic HTR3B SNP rs3782025 was associated in individuals with both AD in a Finnish sample, but not in Bethesda and Plains Indian samples.82

[31]Van Ree, J.M. (1986). Endorphin systems, pain and addiction. In: Van Miert, A.S.J.P.A.M., Bogaert, M.G., Debackere, M. (eds) Comparative Veterinary Pharmacology, Toxicology and Theraphy. Springer, Dordrecht. Retrieved June 7, 2022 fromhttps://doi.org/10.1007/978-94-009-4153-3_43

[32]*Alcohol abuse is hereditary.* Retrieved June 7, 2022 from https://www.medicalnewstoday.com/releases/75738#1

[33]*Alcohol abuse is hereditary.* Retrieved June 7, 2022 from https://www.medicalnewstoday.com/releases/75738#1

[34]Including Met-enkephalin-Arg-Phe, and the recently identified endomorphins. Receptor is also the major target for clinically important opioid analgesic agents including morphine, methadone, fentanyl, and related drugs

[35]Crist, R. C., Reiner, B. C., &Berrettini, W. H. (2019). A review of opioid addiction genetics. *Current opinion in psychology*, *27*, 31–35. Retrieved June 7, 2022 fromhttps://doi.org/10.1016/j.copsyc.2018.07.014

[36]Bond, C., LaForge, K. S., Tian, M., Melia, D., Zhang, S., Borg, L., Gong, J., Schluger, J., Strong, J. A., Leal, S. M., Tischfield, J. A., Kreek, M. J., & Yu, L. (1998). Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(16), 9608–9613. Retrieved June 7, 2022 from https://doi.org/10.1073/pnas.95.16.9610

[37]Crist, R. C., Reiner, B. C., &Berrettini, W. H. (2019). A review of opioid addiction genetics. *Current opinion in psychology*, *27*, 31–35. Retrieved June 8, 2022 from https://doi.org/10.1016/j.copsyc.2018.07.015

[38]Mennis, J., Stahler, G. J., & Mason, M. J. (2016). Risky Substance Use Environments and Addiction: A New Frontier for Environmental Justice Research. *International journal of environmental research and public health*, *13*(6), 607. Retrieved June 9, 2022 from https://doi.org/10.3390/ijerph13060613

An important factor being, ready access to substances: acquiring, using, and abusing substances becoming easier with presence of, proximity to, and density of alcohol as well as tobacco outlets, which may be the case for other more illicit drugs. Escalating violence at home and in the community along with adolescent addiction is higher.[39]

Neighbourhood disorders are common in areas with lower socio- economic status. To deal with chronic stress, people, particularly adolescents may use drugs. Contrarily, if social bonds in neighbourhoods are strong, the possibility of falling prey to addiction decreases, given that the community doesn't embrace substance use. Similarly, witnessing drug abuse in family and peers significantly triggers one's urges to become an addict. Another integral factor is social media, its interactions and the unrealistic portrayal of life on it. Some persons may label drug abuse as acceptable and representative of higher status, promoting other people to use it too.[40] Additionally, addictive products may be advertised as glorious and quite a remedy to various ailments: attracting more people. An important study in drug addiction- The Virginia Twin Study revealed that in early adolescence drug abuse is more strongly determined by familial and social factors which gradually decline in importance during the progression to young and middle adulthood. Here, the effects of genetic factors become maximal, declining somewhat with ageing.[41]Furthermore, "Family, adoption, and twin studies prove that an individual's risk tends to be proportional to the degree of genetic relationship to an addicted relative. Inheritance of addictive disorders range from 0.39 for hallucinogens to 0.72 for cocaine" (Bevilacqua, L., & Goldman, D., 2009), differing for each drug. A study found that genetic factors have minimal influence on the degree of cigarette use at age 13 years. At ages 15 to 19 years, importance of genetic influences rises fast and is followed by a slower and somewhat irregular pattern, stabilising at nearly 60% heritability by the early 30s.[42]

Hence, environment and age play an extremely essential role in addiction.
GABA - an example of a neurotransmitter with polymorphisms not affecting addiction. GABA stands for Gamma-aminobutyric acid. It is an amino acid and is the primary inhibitory neurotransmitter for the central nervous system (CNS). It reduces neuronal excitability by inhibiting nerve transmission. Low levels of GABA can cause anxiety. Some GABA has addiction potential. Depressants, such as alcohol, barbiturates, and benzodiazepine trigger reception in GABA receptors - producing a calming effect.[43]Though GABA plays an essential role in addiction with respect to mu and kappa- opioid receptors, its polymorphisms, in a study lack of significant differences between the two groups did not provide evidence that GABRA 1 and GABBR1 and 2 genes are candidates for alcoholism in a population.[44] This provides evidence that though genetic polymorphisms in pathways of other neurotransmitters may change vulnerability to addiction, all involved neurotransmitters do not.

CONCLUSION

As hypothesised, genetics does play a significant role in susceptibility to addiction, especially for dopamine- the central neurotransmitter involved in drug addiction. Yet, environment is an integral part in developing addiction. In conclusion, an individual's genes may greatly affect how they respond to different factors promoting or demoting drug abuse and its addiction. Moreover, responses to different substances can differ for different genes and for people with different ages. Conclusively, genes play an important role in one's susceptibility to drug addiction. While helping to find treatments and prevention of drug addiction via genetic treatment and other substances this can also make persons aware of their natural vulnerability to drug addiction- helping them lead a healthy life. With

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further research, links between different polymorphisms of genes regulating addiction and responses to drugs, treatment of drug abuse victims will be possible.

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