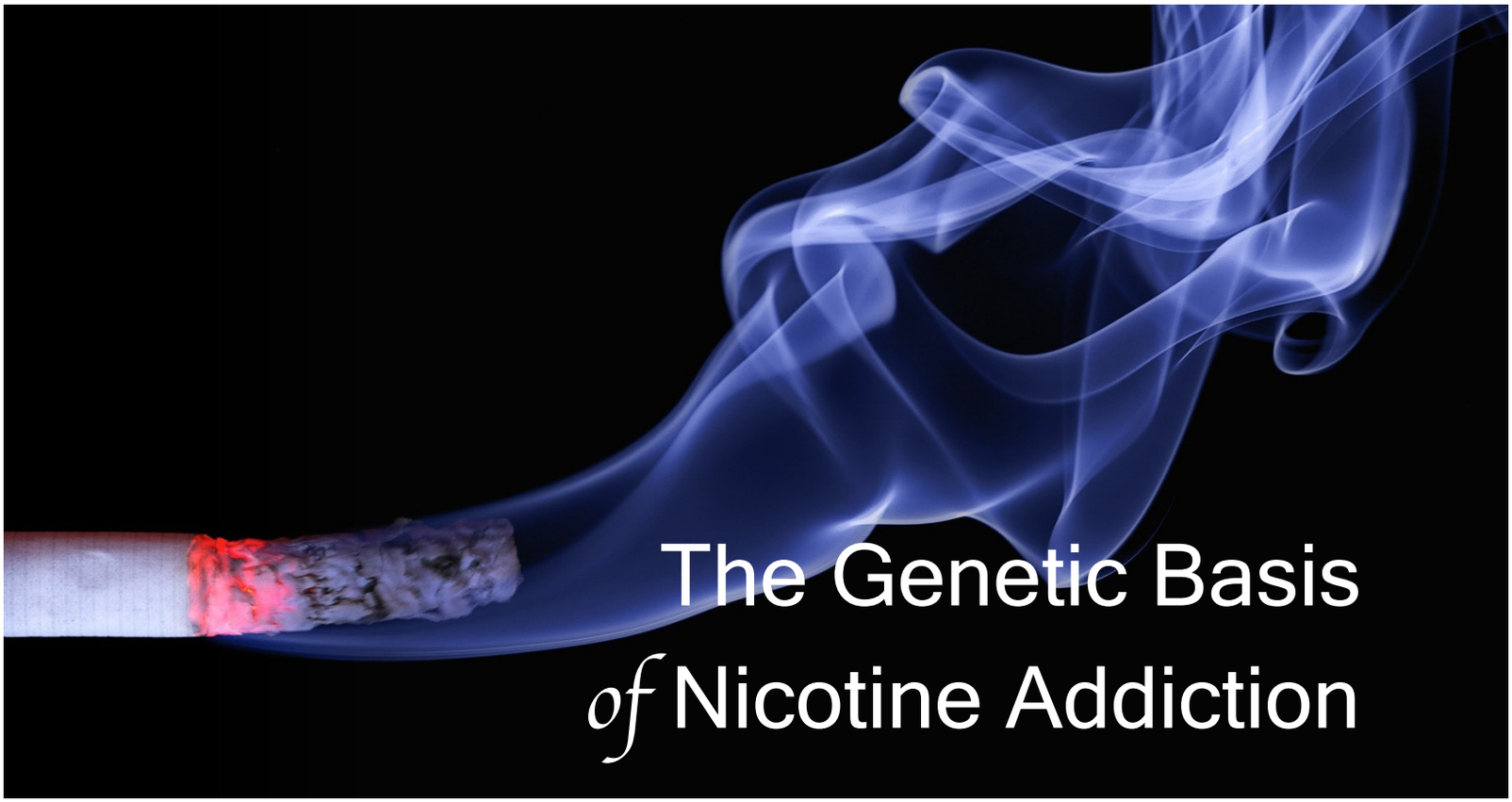


The Genetic Basis *of* Nicotine Addiction

By Anh Nguyen

Nicotine acts as an addictive neurotransmitter that plays a crucial role in the development of smoking and tobacco dependence. However, many individuals have different responses to smoking, and not all are susceptible to developing an addiction. Therefore, there must be other factors that influence the development of tobacco addiction.

A Mechanism of Nicotine

Nicotine is a chemical that alters an individual's mood, behavior, cognition, and body functions. Nicotine binds to nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels found in neurons. When activated, the nAChRs undergo a conformational change that allows ions to pass through the channels and transmit an action potential throughout the neurons. Researchers found that nicotine causes increased levels of dopamine when the nAChRs are located on dopaminergic neurons [1]. Thus, the release of dopamine contributes to nicotine's addictiveness.

Variation in Nicotinic Receptor Subunits

An individual's physical response to nicotine depends on the types of subunits that make up the receptor. There are twelve genes that code for different subunits of nAChR, labeled α2–α10 and β2–β4. The nAChR is composed of five subunits arranged in a ring around a channel [1]. The most abundant high-affinity nAChRs in the human brain are composed of two α4, two β4, and a fifth subunit that is variable [2]. This suggests that addiction can have a genetic basis.

Dizziness Caused by the First Cigarette Predicts Genetic Predisposition To Nicotine Addiction

Every addiction begins with the first encounter with the drug, and nicotine addiction starting with smoking the first cigarette is no exception. Many first time tobacco smokers show a range of responses such as dizziness and nausea. Various phenotypic responses can be attributed to genetic variations in neuronal nicotinic receptor genes (CHRN). These genetic variations affect long term nicotine dependence. Genetic variation can influence an individual's initial response to a cigarette, which might affect their perception and dependence on nicotine in the long term. Ehringer and his colleagues discovered that the phenotypic response of dizziness was linked to single nucleotide polymorphisms (SNPs) in the promoter region of the CHRNB3 gene. Data from the experiments showed different levels of RNA expression resulting from SNPs in the CHRNB3 in smokers who reported dizziness after smoking their first cigarette. Notably, there was a strong correlation between dizziness and nicotine dependence. Individuals who had developed nicotine addiction reported a primarily negative physical response to the first cigarette [3]. Genetic varia-

tion is responsible for differences in physical responses to nicotine, which also affect the development of long term nicotine dependence.

The results of this study can be applied in clinical practice. Clinicians can use dizziness as an indication of an early smoking-related phenotype that is closely related to the underlying genetic mechanisms of tobacco addiction.

Youth and Nicotine Dependence

Nicotine dependence is also affected by the initial age of the smoker. Smokers who start at an earlier age are more likely to develop a lifelong nicotine addiction. Therefore, youths and adolescents have the greatest vulnerability for developing nicotine dependence. Specific genetic markers that are associated with a smoking phenotype, such as cigarettes smoked per day, can be a quantitative measure of nicotine dependence. In a longitudinal study led by Cannon, researchers identified the relationship between genetic variants and the smoking phenotype of cigarettes per day (CPD) in European smokers between ages 15 and 21. SNPs in several CHRN regions in young smokers (CHRNB3A6 SNP rs2304297, CHRNA5A3B4 haplotype C, CHRNA2 SNP rs2271920) were found [4]. Each SNP independently contributed to an increase in cigarettes per day. These genetic markers are associated with increased smoking behavior in youth, supporting the claim that genetic variants can influence nicotine dependence.

Risk-taking Genes Might Explain Risk Taking Behavior in Youth

Risky behavior varies among different populations due to genetic variation. Some individuals are more likely to start drinking or smoking because they have certain risk-taking alleles that contribute to their behavior. In a study of different ethnic populations, researchers found significant differences in the allele frequency of SNP markers between Caucasians, Hispanics, and African Americans. Researchers found three SNPs in the CHRNA5, A3, and B4 (A5A3B4) gene cluster that are associated with an earlier age of initiation of both alcohol and tobacco consumption. Researchers concluded that variation in these genes might influence behaviors that promote early age experimentation with drugs and other risks. Considering how the A5A3B4 gene cluster influences nicotine dependence and alcohol consumption, it is very likely that these genes are involved in the development of risk-taking behavior. Individuals with these alleles tend to experiment with harmful substances since they perceive nicotine and alcohol as a low risk [5]. Genetic variation contributes to both behavior and risk perceptions. Consequently, genetics has a strong influence on nicotine dependence.

"Some people will become addicted after smoking just one cigarette, while others will never become addicted."

Genetic Variation in Nicotine Dependence

Individuals have varied response to nicotine; some people become addicted after smoking just one cigarette, while others will never become addicted even after smoking one hundred cigarettes. To observe how genetic variation can affect smoking behavior, researchers must study a quantifiable phenotype that indicates nicotine dependence. Thus, in order to identify genes that influence nicotine dependencies, they must study a highly heritable and quantifiable phenotype such as the number of cigarettes per day (CPD). Individuals who have a higher CPD are at a greater risk of developing long term nicotine dependence. In a genome wide study of three European populations, Berrettini et al examined if there were certain SNPs associated with an increase in CPD. The results found certain SNPs in the CHRNA5 within individuals who smoke more cigarettes per day [6]. Thus these SNPs were linked to an increase smoking behavior and higher risk of developing an addiction to nicotine.

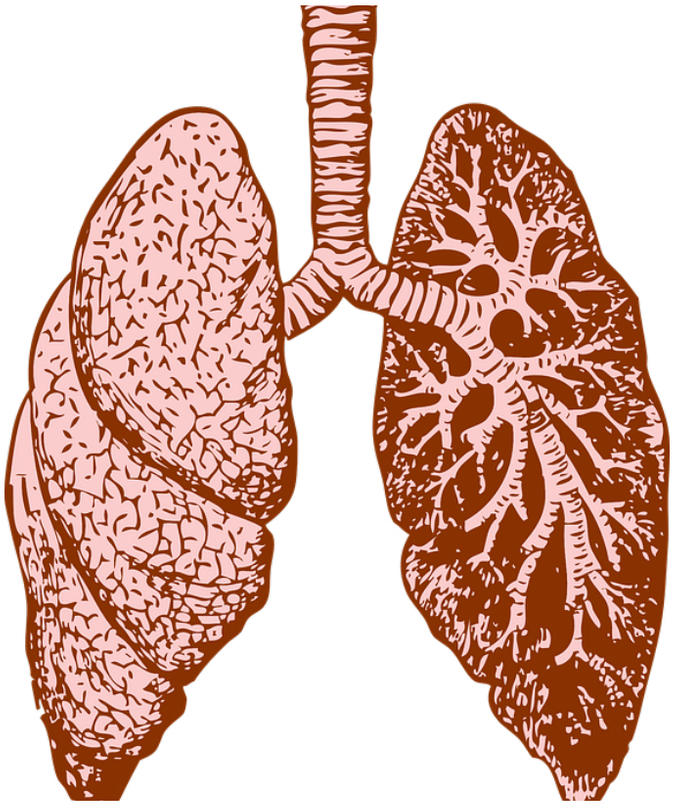
Additional evidence suggests a strong genetic association with nicotine dependence. A recent study by Saccone found that a non-synonymous SNP in CHRNA5, in the genes of nicotine dependent individuals, increased the risk of nicotine dependence [7]. A non-synonymous SNP is an SNP in a protein-coding region that results in a change in an amino acid, thus changing the overall protein structure. Researchers found the SNP caused an amino acid located at 398 to change from the normal allele containing asparagine to the risk allele with aspartic acid. This SNP had an autosomal recessive

mode of inheritance, meaning that individuals would have to inherit two mutated risk alleles in order to be nicotine dependent. Individuals who were homozygous for the risk allele experienced a two-fold increase in the risk of developing nicotine dependence [7]. This supports the hypothesis that nicotine dependence has a genetic basis. Uncovering genetic factors that affect nicotine dependence will provide doctors with more knowledge to prevent, diagnose, and treat nicotine addiction.

Genetic variation contributes to both increases and decreases in nicotine dependence. In a study by Feng, researchers found an association between the CHRNA4 rs1044396 SNP and an increased nicotine dependence in Chinese males. A genetic variant of CHRNA4 causes the C nucleotide to become a T nucleotide. The C allele increases the risk of nicotine addiction while the T protects against nicotine addiction. The researchers found that individuals with the C allele smoked more cigarettes and also had a greater dependence on nicotine. Interestingly, the CHRNA4 rs1044396 polymorphism is a synonymous polymorphism, insofar as there is no change to the protein sequence [8]. This polymorphism must be further studied in order to understand its mechanisms with other CHRN genes.

Smoking Related Diseases

In addition to nicotine dependence, genetic variation can influence the likelihood of contracting other nicotine-related diseases. Thorgeirsson et al discovered a genetic association between an SNP in the CHRNA3 gene and an increase in smoking quantity, nicotine dependence, and the risk of smoking related diseases, such as lung cancer and peripheral arterial disease in patients of European descent. They also found this genetic variant in 18% of lung cancer samples and 10% of peripheral arterial disease samples, which supports the conclusion that the SNP increased the chances of contracting both nicotine-related diseases [9].



Genetic variation influences nicotine dependence and can increase one's susceptibility to developing smoking related diseases. Thus, smoking can have a variable impact on health. The variable phenotypes of nicotine dependence can be attributed to genetic variation. In addition, general precaution against nicotine use and abuse is necessary because individuals are usually unaware of their genetic susceptibilities.

The Genetic Risks of Lung Cancer

Longer term nicotine abuse generally leads to fatal diseases such as lung cancer, the most common cause of cancer death worldwide. Therefore, it is imperative to determine genetic factors that contribute to disease risk in order to understand the mechanism of the disease. In a genome-wide association study by Hung and others, researchers identified the genetic factors that increase the risk of lung cancer. In the study, they focused on the A5A3B4 gene cluster region since it is known for its role in nicotine dependence. Researchers determined a locus in the chromosome region 15q25 that is strongly associated with lung cancer [10]. This genetic marker contains six genes that encode the nAChR subunits, an iron sense response element, a gene used in DNA repair, and a gene that has a currently unknown function. The names of these genes are CHRNA5, CHRNA3, CHRNB4, IREB2, PSMA4, and LOC123688 [10]. The strongest evidence also indicated that the SNP in the CHRNA5 gene developed a non-synonymous variant that increased the risk of lung cancer.

Researchers concluded that these genetic variants influ-

ence an individual's risk and predisposition to lung cancer. Long term nicotine abuse, in the form of smoking, might increase one's chances of developing lung cancer in individuals who are genetically predisposed.

Neuropsychiatric Disorders Related to CHRNA SNPs

In addition to lung cancer risk, genetic variation in acetylcholine receptor genes also affects cognition. These effects increase the risk of developing other neuropsychiatric disorders, such as schizophrenia, Alzheimer's disease, and addiction. Researchers in a study led by Mobascher analyzed the genotypes of German individuals and compared the results to a cognitive processing test. As a part of the cognitive test, researchers used an electroencephalogram to record the individual's response to an auditory stimulus. The study in order to identify genes that influence nicotine dependencies, they must study a highly heritable and quantifiable phenotype such as the number of cigarettes per day (CPD). Individuals who have a higher CPD are at a greater risk of developing long term nicotine dependence. In a genome wide study of three European populations, Berrettini et al examined if there were certain SNPs associated with an increase in CPD. The results found certain SNPs in the CHRNA5 within individuals who smoke more cigarettes per day [6]. Thus these SNPs were linked to an increase smoking behavior and higher risk of developing an addiction to nicotine.

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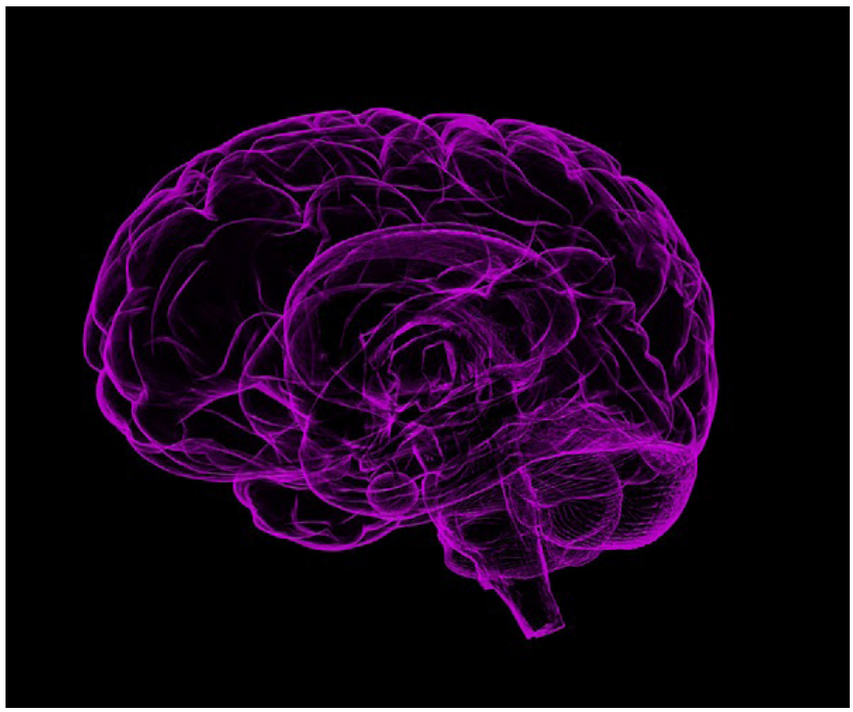

Researchers then examined the mean reaction time for three rs1044396 genotype groups (TT, CT, and CC). Although there was no statistical pattern in reaction time, there was a genotype sex interaction effect on reaction time. In females, the TT genotype was associated with a slower reaction time, while in males with TT had a faster reaction time. The results of this study found an SNP, specifically the CHRNA4 rs1044396 T-allele, that is associated with a decrease in attentiveness [11]. In future studies, this allele can be used as a marker for risk of neurodevelopmental disorders, such as schizophrenia and attention deficit disorders.

Visuospatial Attention

A cognitive phenotype is defined as a distinct behavioral or cognitive characteristic that can be quantitatively measured. Cognitive phenotypes are used in neurobiology to diagnose and classify neuropsychiatric illness [12].

In a study by Greenwood and co-authors, researchers examined the cognitive phenotype of visuospatial attention produced by a SNP in the CHRNA4 gene. Components of the visuospatial attention depend on large scale neurocognitive networks that are moderated by the nAChRs [13]. Visuospatial attention strongly influences how quickly and accurately the brain evaluates and processes events.

Researchers also studied how nicotinic stimulation affects the brain's networking. A genetic variant of CHRNA4 causes the C nucleotide to become a T nucleotide. Researchers found that the C allele is associated with an increased risk of nicotine addiction, while the T allele is protective against developing a nicotine addiction[8]. Supposedly, an individual with two TT alleles for the CHRNA4 gene will have an increased number of low affinity nicotine receptors which is less likely to activate a response in the neuron.

By administering nicotine to non-smokers and measuring behavioral and brain activities via imaging, they found that nicotine causes a narrow focus of attention by binding to the intraparietal sulcus (IPS) and temporoparietal junction (TPJ). Researchers found an association between attention and the nicotinic cholinergic system. They hypothesized that the T allele of CHRNA4 rs1044396 SNP is associated with the ability of focusing attention on a target inside a region at the expense of events outside the region. Individuals who are CHRNA T/T homozygous may take longer both to redirect their attention and to change their perspective of an event based on new information [13].

"Genetic variation heavily contributes to an individual's development of nicotine addiction."

Depression and Loneliness in Elderly Males

Genetic variants in acetylcholine receptors play a role in smoking behavior, cognitive function, and negative emotion. Since nAChRs are a type of receptors located in the brain and play a role in dopamine regulation, they can also play a role in the development of depression. A recent study found that a genetic variation in CHRNA4 (rs1044396) had an effect on attention and negative emotion in normal adults [14]. In this study, led by Tsai, researchers established a genotype-phenotype correlation between genetic variation in CHRNA4 (rs1044396) and cognitive function/depressed moods [14]. Researchers evaluated the level of loneliness, diagnosed potential depression, and assessed cognitive functions in elderly (63-98 years old) male smokers living in Veteran's Home in northern Taiwan in comparison to their genotype [14]. In the study, the sample of elderly Chinese males with the CHRNA4 rs1044396 SNP and a C/C genotype had higher levels of depression and loneliness than the T allele carriers [14]. A possible explanation for the correlation between depression and nicotine dependence is that increased feelings of depression or loneliness in C/C homozygotes can lead to an increase in use of nicotine as a self-medicating substance to relieve negative emotions. These results indicate that nAChR genetic variants have an effect on the mechanism of depression.

Conclusion

The results of these experiments support the idea that genetic variation heavily contributes to an individual's development of nicotine addiction. Minute molecular changes such as SNPs can have significant impacts on one's health. An individual's physical response to nicotine can vary depending on genetic variation in nicotine receptors. Surprisingly, Ehringer et al found that individuals who had developed nicotine addiction later in life reported an initial negative response of dizziness after smoking the first cigarette [3]. Genetic variation can play a role in initiating risky behaviors such as alcohol and tobacco consumption in youths. A study found that individuals with certain SNPs in the CHRNA5, A3, and B4 gene-cluster perceived nicotine and alcohol substances as low risks and therefore were more likely to participate in risky behavior [5]. Additionally, researchers identified that a single SNP in a protein-coding region of the CHRNA5 gene can result in a two-fold increase in the risk of developing nicotine dependence [7]. Nicotine addiction can lead to other smoking-related diseases such as lung cancer and peripheral arterial diseases. Therefore, genetic variation can also contribute to an individual's risk of contracting such diseases. General precaution against nicotine use and abuse is necessary since individuals are usually unaware of their genetic susceptibilities.

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