Genetics of addictive behavior: the example of nicotine dependence

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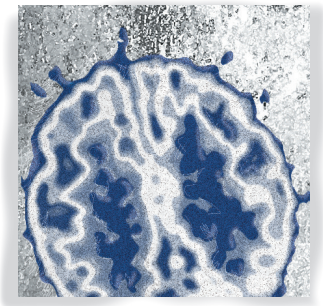

The majority of addictive disorders have a significant heritability—roughly around 50%. Surprisingly, the most convincing association (a nicotinic acetylcholine receptor CHRNA5-A3-B4 *gene cluster in nicotine dependence), with a unique attributable risk of 14%, was detected through a genome-wide association study (GWAS) on lung cancer, although lung cancer has a low heritability. We propose some explanations of this finding, potentially helping to understand how a GWAS strategy can be successful. Many endophenotypes were also assessed as potentially modulating the effect of nicotine, indirectly facilitating the development of nicotine dependence. Challenging the involved phenotype led to the demonstration that other potentially overlapping disorders, such as schizophrenia and Parkinson disease, could also be involved, and further modulated by parent monitoring or the existence of a smoking partner. Such a complex mechanism of action is compatible with a gene-environment interaction, most clearly explained by epigenetic factors, especially as such factors were shown to be, at least partly, genetically driven.*

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Introduction

Addictive disorders, as addressed in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*),[1] refer to behavioral or substance-use disorders for which a minimum of two symptomatic diagnostic criteria must be met. These are as follows: (i) the substance was taken in larger amounts and for longer than intended; (ii) there was a failure to cut down or quit use; (iii) much time is spent obtaining the substance; (iv) there is a craving or a strong desire to use the substance; (v) the patient is unable to carry out major obligations; (vi) there is continued use despite problems caused by the substance; (vii) there is a reduction in important activities because of the substance; (viii) the substance is used in physically hazardous situations; (ix) the patient uses the substance despite physical or psychological difficulties; and the presence of (x) tolerance or (xi) withdrawal symptoms. Addictive disorders are more frequently observed in relatives of addicted patients than in the relatives of healthy subjects, favoring the existence of familial aggregation. The analyses of adopted children and twins later led to the conclusion that such familial aggregation was at least in part due to genetic factors (instead of common familial en-

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vironmental risk factors only) as monozygotic twins appear more alike for addictive disorders than dizygotic twins, and as biological parents of an adopted child having an addictive disorder are more frequently affected than adoptive parents.[2]

Heritability and what we should learn from twin studies

As monozygotic twins (who share the same genome) are different from dizygotic twins (who share up to 50% of the same genome), twin studies allowed a relatively precise estimation of the proportion of the phenotypic variance attributed to addictive genetic factors in addictive disorders, ie, their heritability (*Figure 1*). There are many reviews covering the topic, but a simple figure can be proposed, gathering large twin cohorts and available meta-analyses (*Figure 1*). The most interesting conclusion is that the heritability more or less fluctuates around 50% for each (and all) addictive disorder(s).[3]

Such a high heritability may have important consequences. Clinicians' better understanding of the involved risk factors could be the first one, for example, implying that a systematic search for addictive disorders in relatives should be systematically performed.

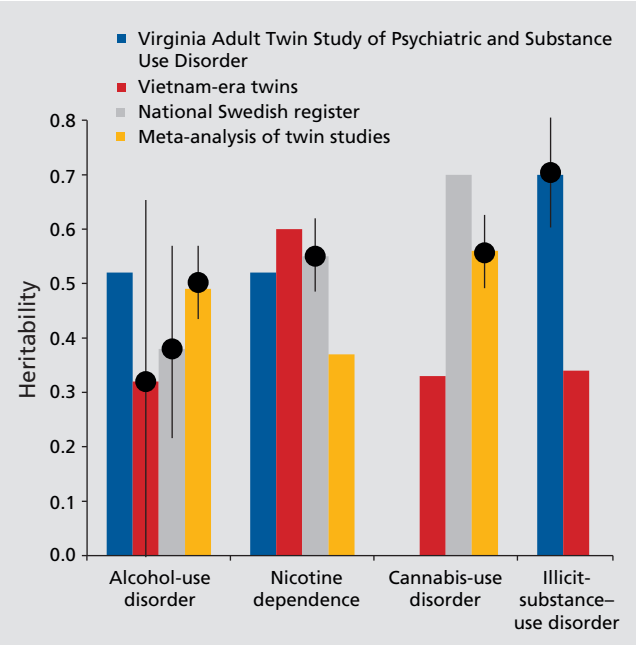

Figure 1. Heritability of substance-use disorders according to the substance and the type of sample.

Such high heritability might also reinforce the idea that genetic analyses of addictive disorders might be an efficient type of research in efforts to detect new treatments or allow for more personalized treatments. On the other hand, as heritability is not 100%, meaning that they are not mendelian disorders, these numbers also imply that a purely molecular genetic approach will not suffice.

It is intriguing that the twin studies used to assess heritability were performed one or two decades ago, with very few being recent, which should raise questions.

A critical view on heritability in addictive disorders

There is little doubt that twin studies were extremely helpful to disentangle the role of environmental and genetic risk factors in psychiatric disorders, but even more so for addictive disorders, which were frequently seen as a non–brain-based, nongenetic, and purely social and psychological problem.[4] On the other hand, it may be too simplistic to state that "50% of the phenotypic variance is explained by genetic factors," for a number of reasons.

First of all, there is no gene coding specifically for the pathophysiology of addiction. The survival and dominance of humankind is probably linked to our high adaptability in a life-threatening and changing world, with poor chances that addictive substances were part of the process.

The second limit is that nearly all twin studies relied on syndromic cases, usually having dependence criteria. But in order to demonstrate dependence, one has to: (i) be initially exposed (and this is not systematically the case, for example, because of religious or cultural reasons); then (ii) be able to tolerate the product; and have (iii) repeat experiences of consumptions, usually because the first experiences had reinforcing properties; and finally, (iv) repeat the exposures despite negative consequences (which represent the main criteria of "use disorders"). The involved genetic factors might therefore reflect one aspect only, and they might not be the same in different populations or patients, reducing the chances of detecting common genetic factors. For example, as many as 30% of Asian subjects may carry a genotype of the *ALDH* gene, which codes for acetaldehyde dehydrogenase, an isozyme with lower activity

for elimination of ethanol, provoking accumulation of acetaldehyde, which induces a stressful flush syndrome, significantly reducing the risk of alcohol-use disorder. This allele has a low frequency in white populations and thus has a modest impact on the risk of alcohol-use disorder in this ethnic group.[5]

A third limitation is the interplay between genetic and environmental factors. A heuristic study on the heritability of tobacco dependence according to generation shows the limits of this concept.[6] In this work, the heritability of nicotine dependence has apparently "increased" in women from 0% (in those born at the beginning of the 20th century) to 50% for those born after 1940, whereas it did not change significantly in men. This can probably be explained by a large access to tobacco use in women in the second part of the 20th century (mainly for social reasons, that is, nongenetic factors), allowing the expression of the involved susceptibility genes, an expression that could not be estimated when women had a very limited access to tobacco. This study was therefore able to demonstrate that when nongenetic factors vary (eg, access to tobacco in women), the estimation of heritability is modified. Observational twin studies do also have strong limitations to consider when investigating gene-environment interactions. A role for nongenetic factors might be easy to propose with regard to access to tobacco, but many unknown or latent nongenetic risk factors with significant impact on the estimation of heritability might also be involved, and beyond our ability to detect. This means that the concept of heritability is valid within a certain period of time and with a specific set of other risk factors and might not be reproducible in a different population or in another time period.

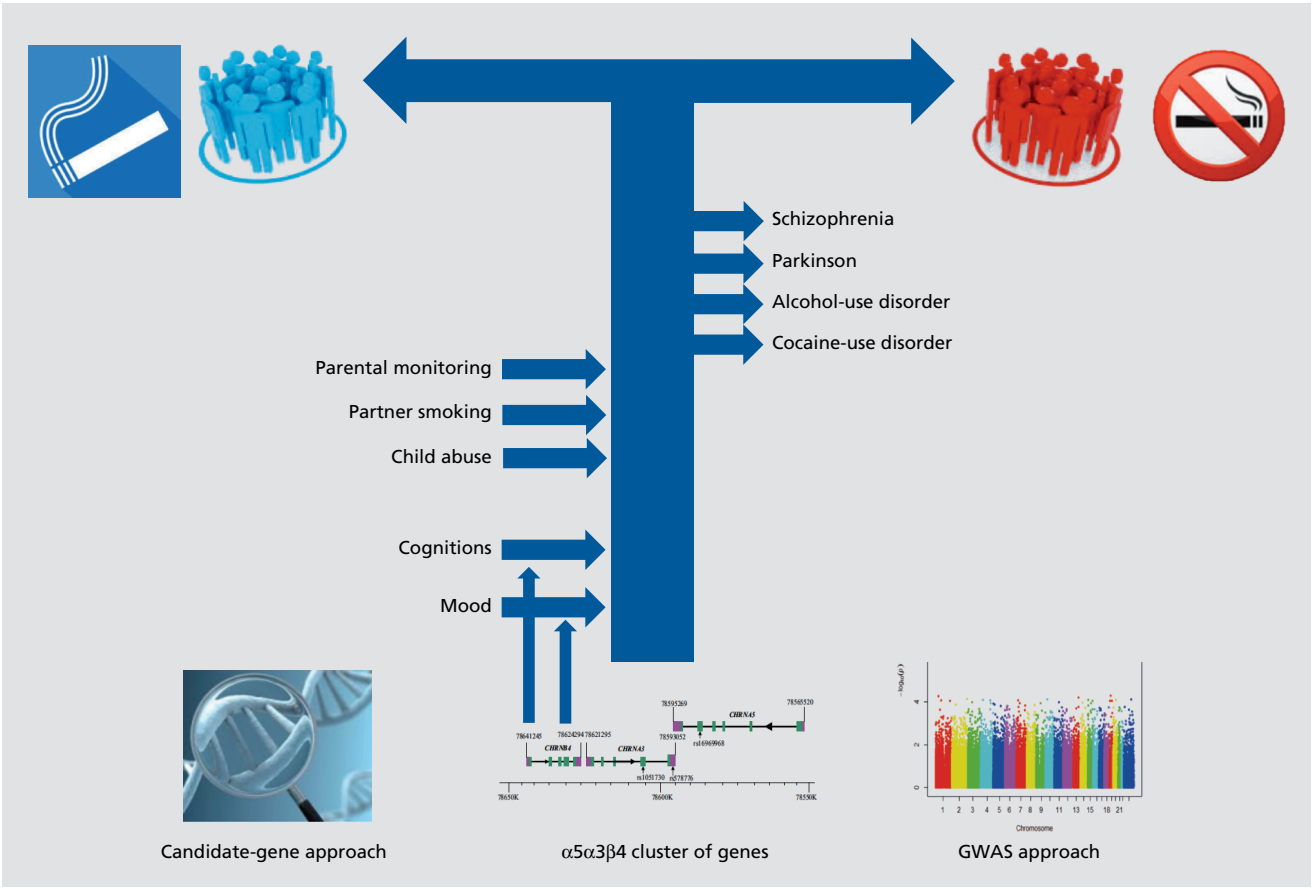

Figure 2. The association between the *α5α3β4* cluster of genes and nicotine dependence, the techniques used (candidate-gene approach and GWAS approach [bottom]), intermediate factors (left), and potential overlapping disorders (right).

The fourth limit is that genes do not act completely independently of each other. The genetics of addictive disorders could indeed be oligogenic (with few genes involved) or more likely polygenic (with many genes involved), an interaction between these different genes (ie, epistatic interactions) being highly likely. Statistical models are designed to detect significant single signals but have important limitations in detecting the role of combinations—the reason involving the number of tests—and therefore have the risk of false-positive results.

The last limitation we raise is the cost-efficiency of twin studies. Face-to-face studies are now the gold standard, especially when performed in the general population, and these studies are extremely costly. Simultaneously, the molecular genetic approach has increasing capacity, in one sense, with a quickly decreasing price (respecting Moore's law)—for example, human genome sequencing cost[7] millions of dollars 10 years ago, 50K$ 5 years ago, 10K$ 3 years ago, and now can be done for 1K$. However, with this decrease in price, a shift was observed in that now preference is given to a direct assessment of the genome rather than trying to check the relevancy of this approach through twin studies. Are we moving too fast? Is it reasonable to look for the genes involved when we are not sure that the studied phenotype has a strong heritability? There is one example that clearly pleads in favor of moving from twin studies to molecular genetic studies—the detection of the *CHRNA5-CHRNA3-CHRNB4* gene cluster (cholinergic receptor, nicotinic α5, α3, β5 subunits), the first with a strong attributable risk in an addictive disorder (ie, nicotine dependence) and explained in more detail later in this article. Indeed, its role has been very convincingly demonstrated in a large population of patients with lung cancer,[8] although the heritability of lung cancer[9] is usually considered modest. A possible explanation is that heritability is not an indicator of the number of involved genes. A limited set of genes could indeed have a relatively large role in diagnoses with limited heritability; whereas a large number of genes, and even more of their combinations, could be involved in a disorder with high heritability. The trend to scrutinize the genome directly, without previously requiring twin studies, is therefore expected to become the rule. The technique with the lowest cost would be one that assesses only those genes that are potential candidates because of their function or location.

Possible genetic techniques to find involved genes: the candidate-gene approach

A "candidate-gene" approach means searching for mutations, or screening for polymorphic markers, in one or more genes chosen according to our knowledge of the role of some enzymes or proteins potentially involved in substance-use disorders. Different strategies can be chosen; for example, a "case-control" study (addressing the question "is the studied allele more frequent in patients than healthy controls?"), a family "trio" approach (addressing the question "are vulnerability alleles more frequently transmitted from a heterogeneous parent(s) to the affected proband"), a "siblings" approach ("do affected siblings have the vulnerability allele in common more frequently than expected by chance only?"), or even a "multiplex families" approach ("is the vulnerability allele more frequently transmitted to affected cases than to healthy relatives?").

Dopamine is involved in many neurobiological processes, but is also considered as the major neuromodulator for the balance between reward and aversion and therefore plays a key role in different components of drug addiction, eg, the reinforcing effects of addictive drugs and their aversive effects. The candidate gene most largely studied is the *DRD2* gene, which encodes the dopamine D_2 receptor.[8] With regard to the *DRD2* gene, one variant named TaqIA (SNP rs1800497), was screened for in 80 case-control studies, involving about 20 000 participants, with conflicting results. On the basis of different meta-analyses, the A1 allele of the *DRD2* gene polymorphism TaqIA may increase the risk of addictive disorders,[10,11] especially alcohol-use disorder (31% increase, $P=4.5\times10^{-8}$). The TaqIA polymorphism was later found to be located at the 3' region of the *DRD2* gene, in a new gene for which the symbol is *ANKK1* (Ankyrin repeat and kinase domain containing 1); this gene encodes a protein that interacts with the D_2 receptor, partly controlling its expression.[12] Other candidate genes related to the reward process have been analyzed in substance-use disorders, such as the *DRD1* and *DRD3* genes, but most of them had negative results. *DRD4*, *DRD5*, *SLC6A3* (solute carrier family 6 member 3; also known as *DAT1*), *DBH* (dopamine β-hydroxylase), and *COMT* (catechol-*O*-methyltransferase) genes had some positive results in specific addictive disorders, but because

of small sample size or absence of replication none of them have been proven to be involved in the risk of addictive disorders.[9] Furthermore, some genetic variants of the enzymes involved in the metabolism of ethanol—namely, alcohol dehydrogenase and acetaldehyde dehydrogenase—have also been associated with lower risk of developing alcohol-use disorder, mainly in the Southeast Asian population (for review see ref 13).

Possible genetic techniques to find involved genes: genome-wide association study (GWAS)

The genome-wide association study (GWAS) uses millions of single-nucleotide polymorphisms (SNPs) as markers of genomic regions, with the majority of them having minimal or no impact on biological systems. Contrasting with the candidate-gene approach, this genome-wide technique does not require any assumptions about the role of potentially involved genes or specific regions to be tested. The first GWAS of alcohol-use disorder compared 1024 cases with 996 controls, using more than 500 000 SNPs,[14] with no SNP reaching the required *P*-value for statistical significance. The largest independent GWAS published to date involved more than 16 000 participants.[15] This study added to the evidence for an association of variants of the *ADH* gene (coding for an alcohol dehydrogenase, an alcohol-metabolizing enzyme) in alcohol-use disorder, an association that has been described since the early 1980s.

Other addictive disorders were also studied through the GWAS technique, including opioid, cannabis, cocaine, and nicotine dependence. *KCNG2*, which encodes a potassium voltage-gated ion channel,[14] and *CNIH3* (cornichon family AMPA receptor auxiliary protein 3), encoding a glutamate receptor–associated regulatory protein, were detected in the three GWAS on opioid-use disorder. A novel antisense transcript RP11-206M11.7, the *SLC35G1* gene (solute carrier family 35 member G1), and the *CSMD1* gene (CUB and Sushi multiple domains) were also discovered in cannabis-use disorder,[16] and the *FAM53B* gene (family with sequence similarity 53 member B), whose product is involved in the regulation of cell proliferation, was associated with cocaine dependence.[16]

Successful genome-wide association study (GWAS) in addictive disorders: lessons to learn?

The most compelling evidence from GWAS pertains to nicotine dependence, as explained above, showing an association of the nicotinic acetylcholine receptor CHRNα5-α3-β4 subunits, encoded by the cluster of *CHRNA5*, *CHRNA3*, and *CHRNB4* genes on chromosome 15 (15q25) with nicotine dependence.[8] An interesting result is not only the level of significance of the association (P=5x10^{-20}) but also its attributable risk, which was computed as being 14%. Another article, this time directly assessing nicotine dependence instead of lung cancer, found exactly the same association (P=6x10^{-20}); the main associated phenotype was therefore considered to be nicotine dependence. More precisely, one human *CHRNA5* rs16969968 polymorphism was specifically involved, with numerous replications[17]; it caused the replacement of the aspartic acid residue (Asp) at position 398 with an asparagine (Asn), and there was evidence of a loss of function caused by this α*5* subunit in native neurons.[18] In fact, the rs16969968 polymorphism (α5 Asn 398) lowered Ca^{2+} permeability and increased short-term desensitization in $(\alpha4\beta2)_2\alpha5$ acetylcholine receptors in one study,[19] and a functional study demonstrated that the risk allele decreased response to a nicotine agonist.[20]

To our knowledge, there is no other example of a cluster of genes that can explain one-seventh (14% in one study and 18% in another) of the total variance of any psychiatric or addictive disorder, as was the case for the cluster of *CHRNA5*, *CHRNA3*, and *CHRNB4* genes and lung cancer.[8,21] So, how was it possible to detect such an impressive genetic risk when the heritability of lung cancer[7] is relatively low, ranging between 8% and 26%? This result could be informative of how to organize GWAS to increase the chances of successfully detecting involved genes. Some specificities of this finding could be particularly relevant for genetic research on psychiatric and addictive disorders.

Severity of the selected phenotype

As previously explained, the fact that the first strong evidence on the role of the α5α3β4 cluster of genes is derived from a study that was not based on nicotine dependence, but instead on lung cancer, is astonishing. An

interesting hypothesis could be related to the pleiotropic effect of this set of genes. Indeed, neuronal nicotinic acetylcholine receptors are widely distributed in both the central and the peripheral nervous systems.[17] More precisely, variation in this cluster is also associated with vulnerability to many smoking-associated diseases, such as chronic obstructive pulmonary disease (COPD),[22] airflow obstruction,[23] and lung cancer.[8,19,21,24,25] Interestingly, in one of the studies, an association between rs16969968 and lung cancer was detected, adjusting for cigarettes smoked per day ($P<10^{-20}$).[25] Such a result suggests that in this cluster of genes, some SNPs are associated with the disorder per se (increased tobacco exposure). This also suggests that other SNPs, related or not with the previous ones (eg, potentially in linkage disequilibrium) increase the risk of medical consequences of smoking (such as COPD). The consequence of such an observation is that focusing on more severe phenotypes, usually consisting of patients with complicated forms of the phenotype of interest, will increase the chances of detecting the vulnerability alleles if the gene is also involved in the associated consequences, as markers of severity of the disorder. These effects may impact not only neurons (α5α3β4 is associated with modification of the reward process) but also peripheral tissues (α5α3β4 affects the risk of lung cancer in tobacco users). We do not know if other genes might have a pleiotropic effect in other substance-use disorders, but this is at least plausible, for example, for liver and alcohol-use disorder.

G-E correlation and/or G-E interaction

Many association studies assessing the role of the α5α3β4 cluster of genes demonstrated that the associated phenotype could more precisely involve an earlier age for onset of tobacco dependence,[26] a higher exhaled carbon monoxide (CO) level in smokers,[27] or lower likelihood of or delayed smoking cessation.[28] We could therefore propose that lung cancer can be completely explained by an environmental factor (tobacco) and that the genes involved only modify the exposure to this environmental factor by increasing it. This is exactly the definition of a gene by environment correlation (G-E correlation). The alternative explanation is a gene by environment interaction (G-E interaction), where the independent risk of tobacco consumption is increased in subjects genetically at risk. In the specific case of the α5α3β4 cluster of genes in nicotine dependence, both G-E correlation and G-E interaction seem to be present, potentially explaining how such an important attributable risk was detected.

Room for other genes, even if one is already largely involved

As the genes coding for cholinergic receptors are strong candidates in tobacco dependence, it is interesting to look back at the first candidate-gene studies performed to assess their role.

Initial enthusiasm centered around, as it is the most widely and concurrently expressed high-affinity nicotinic acetylcholine receptor subunit in the brain[29] and upregulated under chronic nicotine exposure.[29] The analyses of 621 men from 206 families with a family-based association demonstrated that two SNPs, in the *CHRNA4* gene were significantly involved in the risk of nicotine addiction as either a dichotomized trait or a quantitative phenotype.[30] Even though many negative association studies were published afterwards, and this gene was not associated with lung cancer initially, it is interesting that much new evidence shows that the *CHRNA4* gene might play a significant role, beyond that of the α5α3β4 cluster of genes.[31,32]

Possibility to refine or broaden the concerned phenotype

Taking into account the blurred concept of addiction, and the numerous potential risk factors explaining nicotine dependence, defining the level at which this vulnerability gene exerts its role might be interesting and probably easier to detect regarding its high attributable risk.

Nicotine has broad psychological effects on humans,[33] explaining why, for example, smoking increases the risk of later developing major depressive disorder.[34] Variation in the observed mood and affect states after exposure to nicotine were predicted by genetic markers of the α5α3β4 cluster of genes, suggesting that the effects of nicotine on mood were linked to genetic risks of nicotine dependence.[35]

Another interesting intermediate factor is cognitions, as nicotine-deprivation–induced reductions in cognitive control may negatively reinforce smoking.[36] Two (rs588765 and rs17408276) out of 10 tested vari-

ants of the *CHRNA5* gene predicted nicotine-deprivation–induced reduction in P300 amplitude in 72 white subjects.[36]

Childhood adversity also significantly increases nicotine-dependence risk in both sexes, and significant interactive effects of childhood adversity and rs16969968 genotype were observed in men, increasing the risk of nicotine dependence[37] by 80%. Interestingly, when such interaction with child abuse is included in the model, there is no remaining effect of the rs16969968 SNP, providing strong evidence of a G-E effect of *CHRNA5* and childhood adversity on the risk for nicotine dependence.[37]

Parental monitoring and the presence of a smoking partner might also be involved, as the increased risk due to this set of genes may be mitigated by environmental factors, such as how parents interact with their children[38] or the presence of a smoking partner.[39]

These studies also assessed the role of other addictive disorders, such as cannabis use, where the authors demonstrated a modest association between cannabis and these SNPs, but that was not independent of the comorbidity between tobacco and cannabis.[40] Comorbidity might indeed be interesting if assessing what type of phenotype (or endophenotype) is more directly associated with the studied gene. Addictive disorders in particular tend to be highly comorbid.[41] Assessing the role of this candidate cluster of genes in other addictive disorders is therefore interesting. Two samples of 2000 and 3000 patients and controls were tested for alcohol, cocaine, and opioid dependence with regard to 21 SNPs across the *CHRNA5*, *CHRNA3*, and *CHRNB4* locus,[42] demonstrating that at least one SNP was associated with either cocaine dependence (rs684513) or alcohol dependence (rs615470 and rs578776), leading the authors to conclude the importance of the nicotinic receptor subunit gene cluster for risk of dependence on multiple substances. One of the SNPs (rs588765) in the *CHRNA5-CHRNA3-CHRNB4* gene cluster was furthermore associated with alcohol use, defined as abstainers and low-frequency drinkers versus drinkers (odds ratio [OR]=1.15, *P*=0.00007); the effect of rs588765 was seen in never-smokers as well, showing that this genetic marker could have pleiotropic effects.[43]

The majority of severe psychiatric disorders also carry a higher risk for nicotine dependence, and this is particularly true for schizophrenia.[41] It is therefore interesting that two variants, rs8040868 and rs17487223, were significantly associated with the risk for schizophrenia and even more so in the presence of negative symptoms.[44] As three markers, including rs16969968, were associated with lower brain *CHRNA5* expression in publically available postmortem brain expression data, this SNP has proven functional consequences.[44] In contrast, smoking is considered to reduce the risk of Parkinson disease.[45] It is therefore interesting to note that the nicotine-dependence risk variant rs588765 had a protective effect in Parkinson disease and was associated with later age of onset, but only when individuals were previously exposed to nicotine.[46]

Genetic-epigenetic interaction

Epigenetics has emerged in recent years as one of the most important biological mechanisms linking exposures across the life course (such as nicotine exposure or child abuse) to long-term health. For example, lung cancer susceptibility genes might be regulated by methylation changes in response to smoking.[47]

Interestingly, a significant heritability of epigenetic status has been demonstrated in human twin studies.[48] Similarity of methylation status in genetically related individuals can result from heritable variation in the DNA sequence at the epigenetic target or in the genes that regulate epigenetic processes.[49] An alternative explanation is that epigenetic variabilities have behaviorally mediated transmission, as adversity in early life affects mothering behavior in later life, and these effects may be perpetuated intergenerationally.[50]

Lung cancer tissue offers an interesting opportunity to further analyze the connection between the associated SNPs of the α5α3β4 cluster of genes and the level of methylation within CpG units.[51] Hypomethylation was observed in the promoter region of *CHRNB4,* and hypermethylation was observed in *CHRNA3*, which resulted in overexpression of the transcript in the analyzed lung cancer tissue. Five SNPs were associated with tumor DNA methylation levels in the promoters of *CHRNB4*, testifying to the strong interaction between genetic vulnerability and methylation level, helping explain the previously mentioned gene-environment interaction.

Epigenetics might help to disentangle the role of intermediate factors. Accordingly, in a sample of male European-Americans, childhood adversity was associated with greater methylation of one CpG site at the *CHRNA5* promoter region of peripheral blood DNA.[52]

Mendelian randomization

How can the genetics of nicotine dependence help determine the impact of tobacco use? Determining the relationships between tobacco and comorbidities—for example, depression—has been the focus of numerous controversies, given well-known problems of confounding and reverse causality.[17] Using mendelian randomization based on the known literature on the well-proven link between the *CHRNA5-CHRNA3-CHRNB4* cluster of genes and smoking, researchers have investigated the causal relationship between smoking and one phenotype of interest, using genetic factors as a proxy measure for smoking. For obvious ethical reasons—exposure to tobacco, because of its deleterious effect, cannot be imposed—Mendelian randomization is an interesting alternative to "gold standard" randomized, controlled trials. This approach has already been successful in confirming that smoking during pregnancy is causally associated with lower birth weight[53] and that smoking has a causal impact on body mass index[54]; however, it has also shown that the association of smoking with the development of depression or anxiety is not causal[55] and suggests, on the contrary, that depression and anxiety increase susceptibility to smoking (reverse causality). Mendelian randomization does have some limitations; it requires that the genetic variant: (i) is strongly associated with the exposure of interest; (ii) must not be associated with factors known to confound exposure-outcome; and (iii) must not affect outcome other than through the exposure.[56] Indeed, many genes are potentially involved, gene-environment interactions are likely and many confounding factors have already been raised.

Conclusion

For the last 10 years, our understanding of the genetics of addiction has undergone major refinements on the basis of what has been learned from a number of approaches, from hypothetical association studies to the determination of precise genes involved in risk of substance-use disorder, particularly in nicotine dependence as mentioned above. This discovery has led to new approaches in investigating the genetics of addiction, from studying of gene-environment correlations and gene-environment interactions to the consideration of new phenotypes or epigenetic interactions. Further studies will show how the determination of a strong relationship between a cluster of genes and a phenotype (eg, *CHRNA5-CHRNA3-CHRNB4* and nicotine dependence) can help in the elucidation of other genes or phenotypes involved in the pathophysiology of nicotine dependence and related complications. ❑

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La genética de la conducta adictiva: el ejemplo de la dependencia a la nicotina

La mayoría de los trastornos adictivos tienen una herencia importante, de aproximadamente el 50%. Sorprendentemente, mediante el estudio de asociación del genoma completo (GWAS) en el cáncer pulmonar, aunque es una patología con una baja heredabilidad, se detectó la asociación más convincente, con un riesgo único atribuible al 14% (genes CHRNA5-A3-B4 del receptor nicotínico de acetilcolina para la dependencia a nicotina). Se proponen algunas explicaciones para este hallazgo, las cuales ayudan potencialmente a comprender cómo una estrategia con el GWAS puede resultar exitosa. También se evaluaron muchos endofenotipos como potenciales moduladores del efecto de la nicotina, los cuales pueden facilitar indirectamente el desarrollo de la dependencia de nicotina. El análisis del supuesto fenotipo demostró que otros trastornos potencialmente sobrepuestos, como la esquizofrenia y la Enfermedad de Parkinson, también podrían estar involucrados, y modulados posteriormente por la supervisión de los padres o la existencia de una pareja fumadora. Dicho complejo mecanismo de acción es compatible con una interacción genes-ambiente, la que se ha explicado más claramente por factores epigenéticos, especialmente porque se demostró que tales factores son, al menos parcialmente, determinados genéticamente.

L'exemple de la dépendance à la nicotine dans la génétique des comportements addictifs

L'héritabilité de la majorité des troubles addictifs est significative, environ 50 %. Étonnamment, l'association la plus convaincante (gènes CHRNA5-A3-B4 du récepteur nicotinique à l'acétylcholine dans la dépendance à la nicotine), avec un risque unique attribuable de 14 %, a été détectée grâce à une étude d'association pangénomique (GWAS) sur le cancer du poumon alors que son héritabilité est faible. Nos propositions d'explication de ce résultat peuvent aider à comprendre comment la stratégie GWAS peut réussir. De nombreux endophénotypes ont également été évalués en tant que modulateurs éventuels de l'effet de la nicotine, facilitant indirectement le développement de la dépendance à la nicotine. Cette remise en question du phénotype concerné a permis de montrer que d'autres maladies qui peuvent être concomitantes, comme la schizophrénie et la maladie de Parkinson, pourraient aussi être impliquées et modulées ultérieurement par la surveillance d'un parent ou l'existence d'un partenaire fumeur. Un mécanisme d'action aussi complexe est compatible avec une interaction gène-environnement, qui s'explique par des facteurs épigénétiques, d'autant que ces facteurs sont, au moins partiellement, génétiques.