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Genetic and Environmental Influences in Nicotine Addiction: A Review.

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ABSTRACT

Tobacco is the most widely abused drug in the world. Nicotine, the deadly chemical in tobacco that causes addiction and is the central reason behind continuous use of tobacco products contributing to various illnesses. The pharmacologic and behavioral processes that regulate nicotine addiction are comparable to other abusive drugs such as heroin and cocaine that determine dependence. Tobacco dependence can be influenced by gene and environmental interactions and display features of a complex genetic trait. An integrative understanding of the gene and environmental interaction (e.g., additive, multiplicative, or synergistic), will explain the probable impact of susceptibility for tobacco initiation, tobacco addiction and tobacco cessation. This review focuses on physical & chemical properties of tobacco, reason for nicotine addiction and its effect on youth, various environmental and genetic factors responsible for addiction.

Keywords: Tobacco, nicotine addiction, environment, gene

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INTRODUCTION

Amongst the various drugs abused, the most widely distributed and commonly used drug in the world is 'Tobacco'. Despite public policies to discourage tobacco use the epidemic continues unabated and is even accelerating in many parts of the world. Nicotine, the deadly chemical in tobacco that causes addiction and is the central reason behind continuous use of tobacco products contributing to various illnesses. The pharmacologic and behavioral processes that regulate nicotine addiction are comparable to other abusive drugs such as heroin and cocaine that determine dependence [1]. WHO International Classification of Diseases (ICD-10) has classified tobacco use under the "Mental and behavioral disorders" [1].Of the individuals who have tried smoking, about one-third become regular smokers, of them many make quit attempts, which may last for extended periods and yet they still relapsed [2]. Even though not all tobacco users may get addicted to nicotine, the prevalence of nicotine addiction is greater than any other substance abuse disorder. Even a slight upsurge in the success rate of tobacco quitting would have significant effects on the prevalence. Any attempt to lessen tobacco-related disease burden must take into consideration the addiction potential of the tobacco product. Additional attention needs to be focused on deciphering quit-related activity into long-term abstinence.

Tobacco a plant product

Tobacco is obtained from an important member of Solanaceae family of the plant kingdom. After harvesting and curing, tobacco leaves are manufactured into consumable products, which are smokeless and for smoking.More than 70 species of tobacco are known, and the chief commercial crop is Nicotiana tobaccumand the more potent variant Nicotiana rustica. N rustica contains up to nine times more nicotine than common species of Nicotiana such as N tabaccum (common tobacco) [3]. In N tobaccum the nicotine content varies between 1 - 3% and is used for cigarette, bidi, cigar and cherrot purpose as compared to N rustica where nicotine content as high as 9% and is used for preparation of hookah, commercial smokeless tobacco products (SLT) such as gutka, pan parag and snuff4.Nicotine is dissolved in the moisture of tobacco leaf as a water soluble salt in smokeless tobacco whereas in smoking tobacco, nicotine volatilizes and is present in the smoke as free nicotine suspended on minute droplets of tar [4].

Tobacco use in India

India's tobacco problem is very complex with a large use of a variety of smoking forms and an array of SLTproducts.The estimated number of tobacco users in India is 274.9 million, with 163.7 million users of smokeless tobacco, 68.9 million are smokers, and 42.3 million use both smoking and smokeless tobacco [5, 6]. India has one of the highest rates of smokeless tobacco use in the world. The use of SLT is on the rise in India, especially among women, since it does not have the stigma of smoking attached to it. Tobacco is used in a number of smokeless forms in India, which include **betel quid** chewing, **mishri, khaini, gutka**, snuff, and as an ingredient of **pan masala**. SLT products range in complexity from tobacco-only, to products containing numerous chemical ingredients that are toxic, mutagenic or carcinogenic chemicals and additives with areca nut (Supari), been the major ingredient [7, 8]. The International Agency for Research in Cancer (IARC) has classified SLT as a Group 1 human carcinogen [9]. The chief constituents of areca nut are carbohydrates, fats, proteins, crude fiber, polyphenols, alkaloids such as arecoline, arecaidine, guvacine, guvacoline and minerals like sodium, magnesium, chlorine, calcium, vanadium, manganese, bromine, and copper [7].In India bidi smoking is also popular and inexpensive associated with a lower social standing and considered a poor man's cigarette. Bidis require deeper, more frequent inhalation 28 times as opposed to nine times in cigarettes as they extinguish easily. Besides this, bidi contains more particulate matter as they do not have filters, more nicotine content, higher amounts of chemicals such as phenol, hydrogen cyanide, benzopyrenes, carbon monoxide, and ammonia as compared to cigarettes [7].

Biological basis of tobacco addiction

Tobacco addiction involves the interplay of pharmacology, learned or conditioned factors, genetics, and social and environmental factors including tobacco product design and marketing. The pharmacologic reasons for nicotine use are enhancement of mood, either directly or through relief of withdrawal symptoms, and intensification of mental or physical functions. Though nicotine is a highly toxic and potentially lethal chemical it plays an inconsequential role in causing tobacco -induced diseases, addiction to nicotine is the

proximate cause of these diseases [10]. It is also a gateway drug to other abusive abuse drugs such as marijuana, alcohol etc. Studies suggest that alpha-4 beta-2 nicotine acetylcholine receptor subtype is the main receptor that mediates nicotine dependence11. Nicotine acts on these receptors to enable neurotransmitter release i.e. dopamine and others, producing pleasure and mood modulation. Repeated exposure to nicotine develops neuroadaptation of the receptors, resulting in tolerance to many of the nicotine [11]. On tobacco cessation, withdrawal symptoms irritability, anxiety, increased eating, dysphoria, and hedonic dysregulation occur. Hence, the purpose of giving nicotine replacement therapy (NRT) to individuals quitting tobacco is to replace nicotine from cigarettes\SLT products which lessens the withdrawal symptoms associated with cessation thus helping resist the urge to smoke or chew tobacco.

Physiological effects of nicotine and the basis for addiction:

Among smokers the nicotine enters the blood stream through the lungs and pulmonary absorption while nicotine in smokeless tobacco enters through the oral mucosal membrane and GIT. After absorption, nicotine travels rapidly and readily crosses the blood–brain barrier and reaches brain within few seconds among smokers, whereas among smokeless tobacco users absorption is gradual [12]. This rapid surge of nicotine in the brain acts on both the peripheral and central nervous system and is distributed throughout the body, mostly to skeletal muscles and brain and activates specific receptors recognized as cholinergic receptors. This leads toraise in blood pressure owing to stimulation of adrenal glands with subsequent discharge of epinephrine, which causes rapid release of glucose and escalation in respiration rate, heart rate, constriction of arteries and increased alertness [13]. Following dopamine release by nicotine, the psycho-active rewards occur quickly and these rewards are extremely reinforced [13]. If nicotine were not absorbed rapidly from the lungs, people would not take it in the form of smoke; if it were not taken up into the brain, it would not exert its psycho-pharmacological effects; if it were not rapidly metabolized and excreted, it would perhaps not be used habitually in repeated doses(craving) [14].

Nicotine absorption rate among smokers varies owing to individual differences in how cigarettes are smoked like number of puffs, intensive puffing, occlusion of ventilation holes in the filter, length of breath holding, unsmoked butt length etc and among chewers it is primarily determined by the product itself, the pH of the product, size of tobacco cuttings and not the experience or actions of the user [15]. Nicotine intake ranges from 10 mg/day to 80 mg/day, or 0.4 mg to 1.6 mg/cigarette. Average serum nicotine concentration among cigarette smokers at the end of 30 minutes following intake ranged between 180(110-320)ngs\ml, at 60 minutes 40(30-50)ngs\ml and at 90 minutes 10(0-20)ngs\ml , among bidi smokers at the end of 30 minutes, it was 260(240-450) ngs\ml, at 60 minutes 70(50-90)ngs\ml and at 90 minutes 10(10-30)ngs\ml; among tobacco chewers at the end of 30 minutes it was 140(90-200)ngs\ml, at 60 minutes 50(40-60)ngs\ml and at 90 minutes 30(10-40)ngs\ml [15].

Role of genetic and environmental factors in the onset and maintenance of tobacco use

The term “genetics” refers to a person’s biological coding scheme, which may become a phenotype (expression) that at times be determined by context and previous experience and exposures. The term “neurodevelopmental processes” refers to the impact of environmental experiences and maturation processes on cognitive function and, the probability that an individual may succumb to apparent social influences or curiosity and use tobacco products. Neurobiological processes are neurologic transmissions across brain structures that may predispose a person to seek out the use of tobacco or other drugs or that may be affected by tobacco or other drug use. Tobacco dependence is a consequence of environmental factors and pharmacological effects of nicotine, a psychoactive alkaloid found in tobacco products which is highly addictive [16]. Tobacco initiation among teenagers and young adults is a multidetermined behavior, influenced by distinctive and overlapping combinations of biological, psychosocial, and environmental factors. The environmental influences include availability and accessibility of tobacco products, illegal sales of tobacco to minors, advertising and promotion of tobacco products and peer and familial influences emerge as powerful motivators of behavior change [17]. Adolescence represent the social transition to adulthood, with associated risk-taking behaviors related to trying and acquiring adult behaviors in life when tobacco use might be appealing and even perceived as functional to individuals. It is found that smokeless tobacco is more strongly linked with playing sports, such as baseball, than is cigarette smoking though risk taking behavior is associated with use of both cigarettes and smokeless tobacco [18].

Tobacco dependence can be influenced by gene and environmental interactions and display features of a complex genetic trait. An integrative understanding of the gene and environmental interaction (e.g., additive, multiplicative, or synergistic), will explain the probable impact of susceptibility for tobacco initiation, tobacco addiction and tobacco cessation. The progress of youth tobacco use is a dynamic process in which they progress from experimentation, to intermittent use, to regular use and dependence. So identifying the factors that either deter the progression or potentiate continued use leading to addiction is critical to intervening with tobacco use behavior.

Influence of genetics has been recognized at each stage in the continuum of tobacco use, from initiation to dependence, in twin and family studies. Various large family-based genetic linkage analyses associated with different smoking outcomes have been rather inconsistent, directing to different regions on a number of chromosomes [19]. Even the implicated regions possibly comprise susceptibility loci and numerous candidate genes whose genetic variation may define differences in phenotypes. For example, a region on chromosome 9q22 has been strongly linked to tobacco dependence [21] and furthermore a location on chromosome 5q (D5S1354) has also been linked to smoking behavior [22]. Various studies has likewise found links between the gamma amino butyric acid receptor subunit B2 (GABA-B2) and neurotrophic tyrosine kinase receptor type 2 (NTRK2) genes and tobacco dependence [23, 24]. Candidate gene studies on tobacco use in neurotransmitter pathways (e.g., the dopamine and serotonin pathways), nicotine metabolism, and nicotinic receptors are conducted [22]. Various genes in the dopaminergic reward system like DRD2, DRD1, DRD4, DRD5, dopamine transporter (DAT), catechol-O-methyltransferase (COMT), monoamine oxidases A and B, and tyrosine hydroxylase (TH) though none of these variants has shown a strong relationship with smoking behaviors [22]. In the serotonin pathway, most studies investigating the 5-HTTLPR5 polymorphism within the SLC6A4 gene, including one meta-analysis, found a relationship with smoking behavior [25]. The most commonly studied gene in nicotine metabolism pathway is CYP2A6 gene; which suggest that CYP2A6 variants reduce nicotine metabolism and are associated with reduced smoking quantity and increased likelihood of cessation [26]. A large case-control study found nicotinic receptor genes including CHRNA5 and CHRNB3 to be associated with tobacco dependence27. Replication of these findings is a necessary step toward validating the roles of these genetic variants. Results in both genetic linkage analyses and candidate gene studies exhibit great heterogeneity, signifying that genetic influence on tobacco use and nicotine dependence is multifaceted and likely involves multiple genes.

Genome-wide association study (GWAS) is an examination of a genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait and typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major human diseases, but can equally be applied to any other organism. GWAS are useful for identifying genes influencing tobacco initiation, smoking behavior and dependence which could be useful for other phenotypes, as well.

Interaction effects between Genetic and Environmental Factors

Although genetic risk for cigarette smoking may be a vulnerability with which persons are born, it is not a static and obligatory influence on smoking behavior. In fact, the expression of genetic risk depends on certain environmental circumstances. Thus, smoking by peers may inhibit the expression of genetic influences on smoking behavior. In a study by White and colleagues, a heritability estimate of 15% for regular smoking by 13- to 18-year-olds was reduced to 0% after accounting for peer smoking [28]. In another study, Harden and colleagues (2008) found that genetic risk for tobacco and alcohol use in adolescents correlated with best-friend's substance use, a case of gene-environment correlation, and that adolescents at high genetic risk for tobacco and alcohol use also appeared to be more sensitive to adverse peer influences, a case of gene-environment interaction [28].

Aside from peer influences, parental behavior may affect the expression of genetic risks for smoking. In a sample of 14-year-olds (with 67% shared environmental factors), estimated a 21% heritability for lifetime quantity smoked, but this estimate decreased to 15% under conditions of high levels of perceived parental monitoring and increased to 60% with perceptions that parental monitoring was low [28]. These results suggest that less perceived parental monitoring may provide conditions that are conducive for the expression of genetic risk for the smoking phenotype. In the study of 14-year-olds, the moderating effect of parental monitoring was not influenced by whether the parents were smokers [28].

Shared time with parents, another parental variable, may affect the expression of genetic risk on lifetime quantity smoked but in an unexpected direction. Among 14-year-olds, spending more time with parents was associated with 50% heritability for lifetime quantity smoked, but spending less time with parents was associated with almost no heritable effects.

The school environment may also moderate genetic risk for smoking behavior in adolescents. Boardman and colleagues (2008) examined the effects of the social and demographic composition of 7th- to 12th-grade students (mother's education, student's race/ethnicity), school smoking norms (smoking status of popular students), institutional control of smoking (teachers not allowed to smoke on campus, penalties for smoking infractions), and the prevalence of student smoking, on the heritability of ever smoking (heritability estimate, 51%) and daily smoking (58%) [28].

Peer influences, parental behaviors, school characteristics, and school-related activities, such as participation in team sports, are likely to be shared between twins and siblings and are, therefore, likely to be included in the overall estimate of shared environmental variance for smoking behavior unless their effects on genetic risk are explicitly tested. Considering the larger importance of shared environmental factors in the early stages of smoking behavior, it is important to understand the dynamics of measured and latent genetic risk and measured shared environmental factors on smoking behavior. Overall, the interactions of genetic and shared environmental factors are quite complex and call for continued research and careful analyses. More specifically, understanding how genes affect smoking behavior will necessitate identifying key specific factors or sets of factors in the adolescent environment that dynamically interact with genetic vulnerability to affect smoking or nonsmoking.

Genetic determinants of oral cancer risk associated with smokeless tobacco use

Susceptibility to malignancies produced by tobacco carcinogens is determined by genes associated with metabolism of carcinogens and repair of damaged DNA. GST M1 null genotype was reported to be the chief risk factor for development of oral cancer among tobacco users. An association was detected between GSTM1 null, GSTT1 null, polymorphic CYP2E1 alleles, and increased risk for oral cancer among SLT users. In a pooled analysis of data, an association between head and neck cancer risk and variations in MGMT and XRCC1 genes involved in DNA repair, alcohol dehydrogenase gene variants, and GSTM1 null genotype was found among tobacco users. A meta and pooled analysis evaluated interactive effect of two genotypes on cancer risk, GSTM1 null genotype and the CYP1A1 m1m2 variant allele which defined a greater risk for oral and pharyngeal cancer [28].

REFERENCES

[1] ICD-10 Chapter V: Mental and behavioural disorders.
[2] Borland et al. How much unsuccessful quitting activity is going on among adult smokers? Data from the International Tobacco Control 4- Country cohort survey. Addiction. 2012; 107(3): 673–682.
[3] E.Taioli. Gene–environment interaction in tobacco-related cancers. Carcinogenesis. 2008; 29 (8):1467–1474.
[4] Benowitz NL. Neurobiology of nicotine addiction: Implications for smoking cessation. Am J Med.2008; 121:S3–10
[5] Hukkanen, J., P. Jacob, 3rd, et al."Metabolism and disposition kinetics of nicotine." Pharmacol Rev. 2005; 57(1): 79-115.
[6] Kreek MJ, Nielsen DA, Butelman ER, LaForge KS. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat Neurosci 2005; 8:1450–1457.
[7] Bhisey R A. Chemistry and toxicology of smokeless tobacco. Indian J Cancer 2012; 49:364-72
[8] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 85. Betel-quid and Areca-nut Chewing and Some Tobacco specific N-Nitrosamines. Lyon, France: IARC; 2004.
[9] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.Vol. 89. Smokeless tobacco and some tobacco-specific N-nitrosamines. Lyon, France: IARC; 2007.
[10] Andrew Hyland, Joaquin Barnoya, Juan E Corral. Smoke-free air policies: past, present and future. Tobacco Control 2012; 21:154-161.
[11] Maskos U, Molles BE, Pons S, et al. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. Nature 2005; 436:103–7.

[12] Benowitz NL, Porchet H, Sheiner L. Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarette and nicotine gum. Clin Pharmacol Ther. 1988; 44:23–8.
[13] Jain R, Mukherjee K. Biological basis of nicotine addiction. Indian J Pharmacol.2003;35:281-9.
[14] Jiloha RC. Biological basis of tobacco addiction: Implications for smoking-cessation treatment. Indian Journal of Psychiatry. 2010; 52(4):301-307.
[15] Sujatha S Reddy, Radha Prashanth. Estimation of Serum Nicotine Levels among Tobacco Users. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2013; 4(4): 1239-1246.
[16] Ashton H, Stepney R. Smoking: Psychology and Pharmacology. London: Travistock Publications; 1982.
[17] Soni Preeti and Raut D.K. Prevalence and Pattern of Tobacco Consumption in India. Int. Res. J. Social Sci. 2012; 1(4): 36-43.
[18] Melnick, Merrill J etal. Tobacco Use among High School Athletes and Nonathletes: Results of the 1997
[19] Youth Risk Behavior Survey. Adolescence. 2001; 36(44).
[20] Munafò MR, Johnstone EC. Genes and cigarette smoking. Addiction. 2008 Jun; 103(6):893-904.
[21] Bierut, l.j.; Rice, J.P.; Goate, a.; et al.a genomic scan for habitual smoking in families of alcoholics: common and specific genetic factors in substance dependence. American journal of medical genetics part. 2004; 124:19–27.
[22] Duggirala R, Almasy L, Blangero J. Smoking behavior is under the influence of a major quantitative trait locus on human chromosome 5q. Genetic Epidemiology. 1999;17(Suppl 1):S139–S144.
[23] Beuten J, Ma JZ, Payne TJ, Dupont RT, Cres KM, Somes G, Williams NU, Elston RC, Li MD. Single- and multilocus allelic variants within the GABAB receptor subunit 2 (*GABAB2*) gene are significantly associated with nicotine dependence. American Journal of Human Genetics. 2005; 76(5):859–64
[24] Beuten J, Ma JZ, Payne TJ, Dupont RT, Lou XY, Crews KM, Elston RC, Li MD. Association of specific haplo-types of Neurotrophic Tyrosine Kinase Receptor 2 gene (NTKR2) with vulnerability to nicotine dependence in African-Americans and European-Americans. Biological Psychiatry. 2007;61(1):48–55.
[25] Munafò MR, Clark TG, Johnstone EC, Murphy MFG, Walton RT. The genetic basis for smoking behavior: a systematic review and meta-analysis. Nicotine & Tobacco Research. 2004;6(4):583–97.
[26] Malaiyandi V, Goodz SD, Sellers EM, Tyndale RF. CYP2A6 genotype, phenotype, and the use of nicotine metabolites as biomarkers during ad libitum smoking. Cancer Epidemiology, Biomarkers & Prevention. 2006;15(10):1812–9.
[27] Saccone NL, Wang JC, Breslau N, Johnson EO, Hatsukami D, Saccone SF, Grucza RA, Sun L, Duan W, Budde J, et al. The *CHRNA5-CHRNA3-CHRNB4* nicotinic receptor subunit gene cluster affects risk for nicotine dependence in African-American and European-Americans. Cancer Research. 2009; 69(17):6848–56.
[28] Lynskey MT, Agrawal A, Heath AC. Genetically informative research on adolescent substance use: methods, findings, and challenges. Journal of the American Academy of Child & Adolescent Psychiatry. 2010;49(12):1202–14.
[29] White VM, Hopper JL, Wearing AJ, Hill DJ. The role of genes in tobacco smoking during adolescence and young adulthood: a multivariate behaviour genetic investigation. Addiction. 2003; 98(8):1087–100.
[30] Boardman JD, Saint Onge JM, Haberstick BC, Timber-lake DS, Hewitt JK. Do schools moderate the genetic determinants of smoking? Behavior Genetics. 2008; 38(3):234–46.
[31] Tanwar R, Iyengar AR, Nagesh KS, Patil S, Subhash BV. Prevalence of glutathione S-transferase M1 null polymorphism in tobacco users, oral leukoplakia and oral squamous cell carcinoma patients in South Indian population: A polymerase chain reaction study. *Contemporary Clinical Dentistry*. 2015;6(Suppl 1):S59-S64.