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Understanding genetics and genetic polymorphism in tobacco cessation: A public health perspective

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Abstract

Genetics has played a significant role in the interaction between the tobacco use and its environment which is evident through molecular epidemiological studies. This has come a long way in understanding the neurobiology of nicotine addiction, genetic polymorphism in demographic variables and treatment intervention. Molecular genetic studies in tobacco have further enhanced our understanding in modifying tobacco cessation therapy effectively in clinical setup. This has led to the concept of modifying the risk factors in public health. Understanding these interactions have led to the emphasis of tailor-made cessation therapy. Public health experts can overcome their weaknesses and threat in tobacco session through their strength and opportunities of scientific understanding of genetic and genetic polymorphism in tobacco cessation. It is important to understand that the given determinants just help in characterizing the risk and modifying risk factors still remains the best priorities in public health.

Keywords: Genetic Polymorphism, CYP2A6, Tobacco Cessation

Introduction

Genetics has played a significant role in the interaction between the tobacco use and its environment which is evident through molecular epidemiological studies. This has come a long way in understanding the neurobiology of nicotine addiction, genetic polymorphism in demographic variables and treatment intervention. Genetics research in tobacco use has been predominated with phenotypic and genotypic variability. Phenotypic variation as a function of demographic determinants and genotypic variability due to the distribution and expression of susceptible genes. Identifying susceptible genes and its interplay with environment is essential in understanding tobacco cessation.

Genome Wide Association Studies (GWAS) continue to provide information on common genetic variation based on p-value of 5×10^{-8} for statistical significance [1]. Genome and epigenome projects are step further in identifying the rare variants and altered gene expression due to the chronic addiction. Genetic study analysis is based on gene association (Association study), multiple gene variant study (Pathway study), prevalence of variant type of gene (Exploratory study). Genetic epidemiological studies report multiple genetic variability of moderate effect size. The homogeneity of effect size assumption in genetic studies is based on genetic and environment interplay. Further this is based on the genetic and environment correlation (GE) and genetic and environment interaction (G X E). GE correlation is related to genetic predisposition that influences the likelihood of exposure in the environment. GXE interaction seen as moderation of genetics by environment [2, 3].

Studies report the mean heritability of nicotine addiction was 0.59 in twins [4]. Further heritability is affected by age, gender, ethnicity, cultural background. Twin studies reported heredity of 33-70% in nicotine addiction [5]. There are three stages in addiction, initiation stage, chronic stage and final problematic/addiction stage and studies are suggestive of the later stage to be more heritable than the initiation stage which is more under the influence familial environment [1]. The overlap of nicotine addiction with other addiction shows only 37% heritability indicating the genetic specificity for nicotine addiction. This possible overlap is also due to the shared mechanism of action among these addiction types [1]. Many quantitative indices like Fagerstorm Test for Nicotine dependence (FTND) and Heaviness smoking index

have been used in epidemiological studies and in clinical practices these are done through Diagnostic and Statistical Manual of Mental Disorders (DSM). Lessov *et al.* [6] reported that FTND-Nicotine dependence is more heritable than DSM-Nicotine dependence and Moolchan *et al.* [7] reported small overlap.

So, understanding the role of genetics will help in the translation of tobacco cessation efforts into best practices in behavioral counseling and drug therapy. It is important for the public health dentist to understand molecular genetics that explains the various interactions at genetic and environmental level. This also provides an explanation to all possible interaction understood both at clinical and community level in tobacco cessation. Further genetic studies though robust, difficult to replicate and expensive, but do provide an effective solution to modify the treatment in tobacco cessation. With this back ground we aim in understanding the role of genetics and genetic polymorphism in understanding tobacco cessation in the purview of public health.

Neurobiology of nicotine addiction

Addiction can be conceptualized into three-stage, recurring cycle:

1. Binge/Intoxication mediated by Basal ganglia producing feeling of pleasure
2. Withdrawal/Negative effect mediated by Extended Amygdala producing Fight /Fight
3. Preoccupation/Anticipation mediated by Prefrontal Cortex concerned with executive function producing craving.

Nicotinic receptors are present on the cell bodies of dopaminergic neurons from the Ventral Tegmental Area, and on their endings in the Nucleus Accumbens. Nicotine has a role in modulating the release of many neurotransmitters through presynaptic nicotinic receptors [8].

The changes in dopamine release induced by nicotine in the nucleus Accumbens may serve to maintain drug-taking behavior by contributing both to the positive reinforcing properties of nicotine inhaled in tobacco smoke and to the avoidance of the negative reinforcing properties like anhedonia or Dysphoria, induced by withdrawal during smoking cessation [9]. Nicotine acts on nicotinic acetylcholine receptors, which are ligand-gated ion channels composed of five subunits. Neuronal nicotinic receptors are distributed widely in the brain and ganglia, and are made up of α and β subunits. Eight neuronal genes for the α - subunit (α 2– α 9) and three neuronal genes for the β - subunit (β 2– β 4) have been identified. Two main nicotine binding sites have been described in the brain: one high-affinity site composed of a α 4 β 2 combination (hetero-oligomer: 2 α 4 and 3 β 2) and one low affinity site composed of α 7 subunits (homo-oligomer: 5 α 7) only [8, 9]. Nicotine has been shown to play a role in modulating the release of many neurotransmitters such as acetylcholine, nor epinephrine, dopamine, serotonin, γ -amino butyric acid (GABA) and glutamate through presynaptic nicotinic receptors. It is likely that neuro-adaptations of these neurotransmitter systems contribute to the development of tolerance to nicotine and the maintenance of addiction.

Role of Genetics in nicotine addiction

The susceptible gene identified for nicotine addiction is nAChR α 4 subunit gene associated with CHRNA4 [4]. CHRNB2 is associated with nAChR β 2 subunit and shows interaction with CHRNA4. Varenicline drug used in the

tobacco cessation is a selective partial agonist of α 4 β 2 nAChR [10]. CHRNA5/A3/B4 cluster encodes for subunits α 5, α 3, and β 4 at 15q24 chromosome predominantly seen in the European population and its susceptibility with nicotine addiction, lung cancer, nicotine dependence in early onset [4, 11]. These linkage and association is based on genome-wide association study (GWAS). ABCB1 (ATP-binding cassette transporter protein) is an efflux P-glycoprotein expressed in many tissues including the blood-brain barrier. Genetic polymorphisms reported in ABCB1 affect clinical responses to drugs [12, 13]. Muderrisoglu *et al.* [14] reported the genetic variant of ABCB1 were significantly associated with nonsmoking status in their Turkish population. This could serve as biomarker for protection against nicotine addiction though needs further studies on other population.

Pharmacokinetics of nicotine

Nicotine is the major addictive substance in the tobacco. It is metabolized by the liver microsomal cytochrome P450 enzyme into nicotine minimum intermediate compound which is metabolized to cotinine (70-80%) by aldehyde oxidase. This cotinine is further metabolized to trans-3'-hydroxycotinine (20-30%) by main CYP450 enzyme [15-17]. Nicotine N-oxide (4%) is formed by flavin-containing monooxygenase 3 (FMO3) and the rest is metabolized by glucuronide conjugation mainly by UGT2B10 [18]. Among 14 forms of CYP P450, CYP2A6 (90%) is the most commonly involved in the metabolism of nicotine at lower substrate concentration. The other forms are active at higher concentration like CYP2B6 that contribute 10% in cotinine formation [19]. CYP2A6 and 2B6 are expressed in respiratory organs as well as in liver.

Genetic Polymorphism

The enzyme CYP2A6 (Cytochrome P450 Family 2 Subfamily A Polypeptide 6) located in 19q13.2 shows genetic polymorphism contributing to individual variability in the rate of metabolism of nicotine. These are predictor for the given sociodemographic determinants. This variability is represented in the form of slow metabolizer and fast metabolizer. This affects the activity of the enzyme and is related to tobacco behavior, tobacco cessation and tobacco related harm [20, 21]. The genetic susceptibility is enhanced due to genetic polymorphism of enzyme associated with metabolism of the carcinogens. The genetic polymorphism causes increase catalytic activity and transcriptional activity. The procarcinogens is activated to carcinogen by group Phase I cytochrome enzymes like CYP1A1 (located on 15q22-q24) and CYP2E1 (located on 10q24.3), CYP2A6 (located on 19q13.2) and CYP2D6 (located on chromosome 22). CYP2A6 is most active among all even at low concentration [19]. These carcinogens are detoxified by Phase II like glutathione S-transferase (GST). Tobacco-related nitrosamines, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and N'-nitrosonornicotine (NNN), have been reported to be the constituents in tobacco smoke causing human cancers [22, 23]. NNN, NNK, NNAL are specific marker in saliva, NNN, NNK in human hairs, NNAL in urine. These carcinogens forms DNA adduct and increase the production of reactive oxygen species that may cause DNA damage. These DNA adduct are formed by the combination intermediate product formed during phase I with electron deficient DNA base like guanine [24]. CYP1A1 (located on 15q22-q24) and CYP2E1 gene (located on 10q24.3) is

associated with metabolic activation of PAH and nitrosamine [25, 26]. Genetic polymorphism in these metabolic enzymes influences the susceptibility of individual to various cancer of lungs, esophagus, liver, stomach and oral cavity (pre-malignant lesions like oral leukoplakia) [27].

Enzymatic measure activity

Nicotine metabolites ratio (NMR) 3HC/COT is stable in current smokers and functions as a predictor of rate of nicotine metabolism and an CYP2A6 enzyme activity [20, 28]. Further, higher the ratio indicates faster metabolism. This categorizes into slow and fast metabolizer. This NMR ratio has been measured in plasma blood, saliva and urine though plasma measure is more reproducible [29]. Cotinine blood concentrations varies from 250–300ng/ml and can be high as 900ng/ml and measures only short-term exposures. The cut off point for cotinine level for smokers and nonsmokers was 50ng/ml in plasma and saliva and 15ng/ml in urine [30]. In NRT cotinine level is 30-70% as seen in smoking [31]. This measure based on the fact the half-lives of nicotine (1 to 2 hours) less than cotinine (16 to 18 hours) and 3HC (6 to 7 hours) [15]. The elimination of 3HC is formation dependent on cotinine [28]. This ratio is dependent on the puffing behavior also described as smoking topography. West *et al.* [32] reported smokers with fast metabolizers are more likely to benefit from bupropion, while those with slow metabolizers are more benefited from nicotine patches or nicotine gum, but not from nicotine nasal spray. This is also related to possible explanation that fast metabolizer is more addicted and smoking topography than slow metabolizer. Lerman *et al.* [33] reported higher cravings among fast metabolizer than slow metabolizer using nicotine patch which was not seen in those using nasal spray or bupropion but reported no withdrawal. Rubinstein *et al.* [34] reported withdrawal in the fast metabolizer adolescent group than slow metabolizer but reported no craving.

Demographic variability and interaction due to genetic polymorphism

Understanding the genetic polymorphism provides an insight about the increased vulnerability within the given demographic determinants. Cotinine clearance is about 45 ml/min and 3HC is about 82 ml/min. The total clearance is reduced by one fourth and renal clearance is reduced by half in elderly. There is no decrease of CYP2A6 enzymes and steady plasma concentration of nicotine with increasing age but the volume of distribution is reduced due decrease in lean body mass [35-37]. The nicotine concentration is higher in neonates and cotinine level in neonates are comparable to adults which is due to the reduced level of CYP2A6, CYP2D6, and CYP2E1 [38].

There is a greater expression of the main enzyme CYP2A6 oxidative enzymes in females with up regulation of CYP1A1 allele [39]. This up regulation is translated into increased metabolism of nicotine products and bioactive compounds that increases the odds of exposure to the toxins. This is particularly for Polycyclic Aromatic Hydrocarbon (PAH) and their heterocyclic analogue like benzopyrene, naphthalene [40]. The female hormone estrogen is associated with the difference in the metabolism of nicotine. Two estrogen receptors associated with the lungs are α and β [41]. The upregulated CYP1A1 and CYP1B1 expression concerned with the metabolism of PAH is mediated through the less predominant α estrogen receptor [42]. The increased level of estrogen during the proliferative stage of menstrual cycle is

also associated with increased activity of CYP2A6 enzyme [43]. The increased metabolism was reported among women using only estrogen oral contraceptive pills (OCP) and combination pills than those using only progesterone OCP pills and menopausal women [44]. Health professional assisted smoking cessation showed no difference among gender [45]. Further the studies are inconsistent regarding the motivation level among women to quit [46]. Wetter *et al.* [47] reported higher withdrawal symptoms of anxiety, depression and irritability among women compared to men during cessation period. Studies report that NRT are not successful among females and they have more behavioral dependence than pharmacological dependence which is common in men [46, 48]. This variability is also attributable to difference in the metabolism of nicotine which is the function of genetic polymorphism. Allen *et al.* [49] reported that relapse was higher during estrogen proliferative phase than progesterone luteal phase of menstrual cycle. Further genetic factors have larger role in initiation than continuation in females which is opposite to the males [1, 4].

There are 31 allelic variant that affect the enzymatic activity. [38] Studies report that Asian, European and African are fast metabolizer due to genetic polymorphism in CHRNA5 and CYP2A6 genes [50]. This is associated with increased risk for smoking, better success in smoking treatment and development of disease [51-54]. The ethnic variability is due to the distribution of some allele in specific ethnic group. Studies report different allele of CYP2A6 distributed in different ethnic group but the impact in all ethnic group remains the same [51]. Asian and African American have higher metabolic activity of CYP2A6 than the White population [51, 55, 56]. This was also low for Asians adolescent than White as determined by salivary NMR [57]. There is variability in the activity of enzyme of CYP2A6 among the ethnical and region is due the increased presence of specific allele among these groups. The impact due to allele on the enzymatic activity among ethnical and racial has been reported to be same.

Other interactions

Other factors like drug increases the enzyme activity like Phenobarbitone, Rifampicin and dexamethasone and drugs like 8 Methoxypsoralen, selegiline and ketoconazole are the CYP2A6 enzyme inhibitor [58-61]. Menthol, grapefruit juice, caffeic acid, p-coumaric acid, quercetin and cinnamaldehyde are substances present in dietary products that inhibit CYP2A6 enzyme activity [62-64]. Caffeic acid, p-coumaric acid, quercetin is present in coffee, cinnamaldehyde is present in cinnamon. Tyrosol is present in olive, olive oil and red wine is metabolized by CYP2A6 enzyme leading to formation of hydroxytyrosol which is a potent anti-oxidant than tyrosol [65].

Public Health Perspective

Correlation and the interaction in genetic epidemiological studies have been able to interpret genetic and environment (GE) interplay concept in public health. This interaction of GE has led to the reporting of tobacco as a modifiable risk factor in tobacco related literature. Genetic based nicotine addiction studies have helped to understand the various reasons cited for the normal cultural acceptance of different types of tobacco use among various ethnic and regional groups. Public health researchers have reported such variability of risk factors of tobacco for given determinants, markers and indicators through various epidemiological studies. Molecular genetic studies in tobacco have further

enhanced our understanding in modifying tobacco cessation therapy effectively in clinical setup. This has led to the concept of modifying the risk factors in public health. The various biomarkers are important predictor tools in monitoring of tobacco use, harm and cessation therapy in public health. Public health researchers have tried to understand the risk factor of tobacco for given determinants of age, sex/gender and ethnicity. For age they have focused on the mean age of initiation of tobacco, as long exposure tends to modify the genetic expression. The variability in gender and ethnicity still shows variation due to the interactions based on up and down regulation and gradual changes in micro social ecosystem. Understanding these interactions have led to the emphasis of tailor-made cessation therapy. Public health experts can overcome their weaknesses and threat in tobacco cessation through their strength and opportunities of scientific understanding of genetic and genetic polymorphism in tobacco cessation.

Conclusion

Genetics is an important aspect in tobacco cessation. Many epidemiological genetic studies have identified the predictive genetic factors that interact with given determinants to control an important risk factor of tobacco use. Further these studies provide information of heritable risk factor attributable to gene. Higher the population prevalence greater is the gene attributable risk for the disease. It is important to understand that the given determinants just help in characterizing the risk and modifying risk factors still remains the best priorities in public health.

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