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Polymorphisms in genes involved in neurotransmission in relation to smoking

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Abstract

Smoking behavior is influenced by both genetic and environmental factors. The genetic contribution to smoking behavior is at least as great as its contribution to alcoholism. Much progress has been achieved in genomic research related to cigarette-smoking within recent years. Linkage studies indicate that there are several loci linked to smoking, and candidate genes that are related to neurotransmission have been examined. Possible associated genes include cytochrome P450 subfamily polypeptide 6 (CYP2A6), dopamine D_1, D_2, and D_4 receptors, dopamine transporter, and serotonin transporter genes. There are other important candidate genes but studies evaluating the link with smoking have not been reported. These include genes encoding the dopamine D_3 and D_5 receptors, serotonin receptors, tyrosine hydroxylase, trytophan 2,3-dioxygenase, opioid receptors, and cannabinoid receptors. Since smoking-related factors are extremely complex, studies of diverse populations and of many aspects of smoking behavior including initiation, maintenance, cessation, relapse, and influence of environmental factors are needed to identify smoking-associated genes. We now review genetic polymorphisms reported to be involved in neurotransmission in relation to smoking.

Keywords: Smoking; Genetic polymorphism; Neurotransmitter; Association; Linkage

1. Genetic influence on cigarette smoking

Cigarette smoke contains more than 4000 different compounds, the major ones of which are carbon monoxide, nicotine, and tar (Miller and Cocores, 1991). L-Nicotine, which is the major constituent of tobacco, is the most pharmacologically active form of nicotine and is thought to be responsible for tobacco dependence. Smoking has rewarding effects such as decreasing irritability and heightening attention and psychomotor function (Sherwood, 1995). Individuals smoke cigarettes habitually to maintain their blood nicotine levels. When smoking is stopped, smokers may suffer from withdrawal syndromes, which include weariness, nausea, constipation/diarrhea, insomnia, and depressed concentration and psychomotor activity. These symptoms of withdrawal are improved by administration of nicotine. The pharmacological and behavioral bases for nicotine dependence are similar to those for cocaine and heroin dependence.

It is known that smoking behavior is influenced by both genetic and environmental factors (Carmelli et al., 1992; Edwards et al., 1995; True et al., 1997). Twin studies strongly support the notion that genetic factors are involved in the initiation, continuation, and cessation of smoking. Estimated inheritability rates are 47–76% for smoking initiation and 62% for persistence (Heath et al., 1995; Hughes et al., 1997). Smoking behavior is as inheritable as alcohol consumption behavior, and the genetic effect on smoking is at least as great as that on alcoholism (Hughes et al., 1997). Monozygotic twins were more likely than dizygotic twins to be concordant for quitting smoking. A recent study showed the odds ratios for nicotine-dependence in second siblings in families in which the first sibling was nicotine-dependent to be 2.13 and 3.50 according to two different criteria (Niu et al., 2000).

2. Genome-wide overview of cigarette smoking-related loci by linkage analyses

Genome-wide linkage analysis is an important tool for localization of genes that contribute to phenotypes. Link-

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age findings can support the candidacy of known genes and hint at the identities of unknown phenotype-related genes. Three linkage analyses of smoking behavior have been reported. Two used COGA (Collaborative Study on the Genetics of Alcoholism) families. Bergen et al. (1999) carried out a sib-pair linkage analysis and reported some evidence for linkage of smoking behavior to chromosomes 6, 9, and 14. Duggirala et al. (1999) reported linkage of smoking behavior to marker D5S1354 on chromosome 5q and weak linkages to the loci between D4S244 and D4S2393 on chromosome 4q, D15S642 on chromosome 15q, as well as GATA193 on chromosome 17p. It is interesting that D5S1354 is located close to DRD1 and that genotypic association between a DRD1 polymorphism and smoking has been reported (Comings et al., 1997). Straub et al. (1999) examined families from New Zealand and Richmond in the USA. Regions on chromosomes 2, 4, 10, 16, 17, and 18 were suggested to be linked to nicotine dependence. Among them, D2S1326 showed the highest lod score in the New Zealand families. These linkage findings were not replicated in the Richmond families. These data indicate that the effects of genes on smoking behavior are weak, or that gene alleles that influence smoking behavior occur in only a small proportion of families.

3. Polymorphisms in cytochrome P450 genes involved in nicotine metabolism

Genes involved in metabolizing nicotine are considered important to smoking-related behaviors. Nicotine is absorbed through the lung epithelium and travels directly to the brain, where it readily crosses the blood–brain barrier. Nicotine is metabolized in three different ways: by C-oxidation, N-oxidation, and N-methylation, and there are important and interesting inter-individual differences in nicotine metabolism among humans.

Cytochrome P450s (CYPs) are central nervous system (CNS) enzymes that metabolize a number of exogenous and endogenous compounds. In humans, 60–80% of nicotine is metabolized to cotinine by CYP2A6 via formation of the $\Delta 1'(5')$-iminium ion. The gene for CYP2A6 is located on chromosome 19q12–13.2 (Miles et al., 1989), and is adjacent to the CYP2A7 gene, which encodes an inactive enzyme, and is close to the CYP2A13 gene and two CYP2A7 pseudogenes (Hoffman et al., 1995). Large inter-individual differences exist in the CYP2A6 protein levels and activities (Nakajima et al., 1996; Nunoya et al., 1998), and the variability is as great as several 10-folds. There are defectively functioning polymorphisms. The wild type is denoted as CYP2A6*1. CYP2A6*2 contains a Leu to His substitution at codon 160, which yields an inactive enzyme (Yamano et al., 1990). One individual homozygous for this inactive allele has been reported to lack coumarin 7-hydroxylation capacity (Hadidi et al., 1997). The rare CYP2A6*3 allele, generated through a gene conversion between CYP2A6 and CYP2A7, is also thought to be inactive (Fernandez-Salguero et al., 1995). Partial deletion of the CYP2A6 gene (CYP2A6*4) was reported in a Japanese population. Subjects homozygous for this allele exhibited the poor metabolizer phenotype (Nunoya et al., 1998). Recently, two novel inactive CYP2A6 alleles have been reported. The CYP2A6*5 allele carries a G479L substitution in exon 9, and the CYP2A6*4D has a deletion caused by a crossover in a region located in either intron 8 or exon 9, resulting in an allele where exons 1–8 are consistent with CYP2A7 and the 3′ flanking region has the CYP2A6 sequence (Oscarson et al., 1999).

These CYP2A6 variants may affect nicotine inactivation rates and, possibly, smoking patterns (Pianezza et al., 1998). CYP2A6*2 and *3 were reported to be associated with smoking. However, due to improved genotyping methods (Oscarson et al., 1998; Sabol and Hamer, 1999), this association has become controversial (London et al., 1999; Sabol and Hamer, 1999). Studies thus far have shown that the system for metabolism of nicotine may be a critical factor for the prevention of smoking addiction. However, strong evidence for this is not available.

4. Polymorphisms in dopamine receptors and transporters

The mesolimbic dopaminergic system has been implicated in the reinforcement of the effects of nicotine (Nisell et al., 1995). The behavioral and neurobiological effects of nicotine are similar to those of other drugs known to be addictive (Henningfield and Heishman, 1995; Pontieri et al., 1996). In experimental animals, nicotine causes the release of dopamine and stimulates energy metabolism in the basal ganglia, especially in the ventral tegmental area and nucleus accumbens, as do other addictive drugs such as cocaine, amphetamine, and morphine (Pontieri et al., 1996). The habit-forming action of nicotine appears to be triggered primarily at acetylcholine receptors on dopaminergic neurons in the ventral tegmental area. Injections of acetylcholine receptor agonists into the ventral tegmental area are “rewarding”, and both the ventral tegmental area and systemic injection of dopamine antagonists reduce the intravenous self-administration of nicotine (Nisell et al., 1995; Rose and Corrigall, 1997; Wise, 1996a,b). Nicotine-induced dopamine release is significantly reduced by mecamylamine, an antagonist of CNS acetylcholine receptors, but not of peripheral acetylcholine receptors (Di Chiara and Imperato, 1988; Imperato et al., 1986).

Imaging studies of the human brain have revealed an association between dopamine and smoking. Functional magnetic resonance imaging has shown that intravenous administration of nicotine induces a dose-dependent increase in neuronal activity in brain regions including the nucleus accumbens, amygdala, cingulate, and frontal lobes

(Stein et al., 1998). Positron emission tomography has shown that an increase in L-DOPA uptake occurs in both putamen and caudate of smokers in comparison to uptakes in non-smokers (Salokangas et al., 2000). Levels of homovanillic acid (HVA), a metabolite of dopamine, in cerebral spinal fluid (CSF) are lower in smokers who abstain from tobacco for 11 to 17 h than in non-smokers (Geracioti et al., 1999). The lower CSF concentrations of HVA in smokers may be associated with either chronic inhalation of nicotine, of other constituents of tobacco smoke or with acute abstinence.

These findings give priority to polymorphisms affecting the function of the dopaminergic system as candidate genes for smoking-related behaviors. In fact, associations of smoking with polymorphisms in the dopamine D_2 and D_4 receptor genes and dopamine transporter gene have been reported (Shields et al., 1998; Spitz et al., 1998).

4.1. Dopamine D_1 receptor gene (DRD1)

At present, no missense polymorphisms in the coding of the DRD1 gene have been identified (Liu et al., 1995). Comings et al. (1997) reported an association between homozygosity for either allele of a *Dde*I polymorphism (−48A/G) and smoking in individuals attending a smoking cessation clinic. They considered the association to be a negative heterosis for smoking addiction (Comings et al., 1997). The functional significance of this polymorphism has not yet been clarified.

4.2. Dopamine D_2 receptor gene (DRD2)

Of the many polymorphic sites in the DRD2 gene, the *Taq*I A polymorphism has been the most extensively studied. Although the polymorphism is not thought to be functional, *Taq*I A1 allele is associated with reduced dopamine D_2 receptor availability in the striatum (Jonsson et al., 1999; Pohjalainen et al., 1998; Thompson et al., 1997). It was reported that there is a significant inverse association between the prevalence of the *Taq*I AI allele and the age of smoking onset and the maximum period of time for which smokers were able to abstain from smoking (Comings et al., 1996a; Noble et al., 1994). An association between smoking and the DRD2 gene polymorphisms in lung cancer patients was reported (Spitz et al., 1998). An association between the A1 allele and novelty-seeking personality trait has been reported (Noble et al., 1998). Smokers showed higher novelty-seeking scores than did the general population (Pomerleau et al., 1992; Zuckerman et al., 1990). These findings indicate an association between the *Taq*I A1 allele, which is associated with reduced dopamine D_2 receptor availability in the striatum, and smoking. However, the results of a transmission-disequilibrium test study did not support an association between the *Taq*I A1 allele and habitual smoking (Bierut et al., 2000).

Recently, a unique study investigating the genetic association of the *Taq*I A polymorphism with smoking, and also with brain event-related potentials, was reported. Smoking effected a reduction in P300 in the presence of the *Taq*I A1 allele, and association between the polymorphism and smoking was detectable in individuals with relatively low P300 amplitudes. Therefore, it is possible that the A1 allele increases the risk of addiction to nicotine. In other words, sensitivity of CNS to the effects of smoking may depend on the *Taq*I A genotype (Anokhin et al., 1999).

Other polymorphisms in the DRD2 gene such as the Ser311Cys (Cravchik et al., 1996; Itokawa et al., 1993) and -141C Ins/Del (Arinami et al., 1997) polymorphisms, that may cause functional differences in dopamine D_2 receptors, remain to be examined for association with smoking.

4.3. Dopamine D_3 receptor gene (DRD3)

High densities of DRD3 are present in the nucleus accumbens. Lannfelt et al. (1992) identified a Ser9Gly polymorphism in the N-terminal extracellular domain of the DRD3 gene. Receptor binding analysis based on the Ser9Gly variant expressed in the Semliki Forest Virus system showed a significantly high dopamine binding affinity in Gly9 homozygotes, but binding kinetics in heterozygotes did not differ from those of Ser9 homozygotes. The dopamine D_3 receptor-selective ligand, GR99841, showed significantly lower activity in Ser9 homozygotes than in either the Gly9 homo or the heterozygotes. However, differences in the binding affinities are slight, and the relevance of this finding in relation to disease is unclear (Lundstrom and Turpin, 1996). The polymorphism may be associated with schizophrenia (Spurlock et al., 1998), and an association between the homozygosity for the Ser9Gly polymorphism and cocaine abuse has been shown (Comings et al., 1999). Ishiguro et al. (2000a) found the Ala38Thr polymorphism and two additional polymorphisms in the 5′region of the DRD3 gene. Despite these interesting polymorphisms in the DRD3 gene, their association with smoking behavior has not been examined.

4.4. Dopamine D_4 receptor gene (DRD4)

Of the many polymorphisms in the DRD4 gene, an imperfect 48-bp variable number tandem repeat polymorphism in the third exon has been examined the most thoroughly. It involves a 16-amino acid repeat that encodes a proline-rich protein domain. The three cloned receptor variants have properties that differ between the long form (7-repeat allele, L allele) and the short form (2-repeat and 4-repeat alleles, S allele) as found in ligand-binding study (Van Tol et al., 1992). The L allele reduces dopamine affinity. However, the same group continued their study

and could conclude that the polymorphic repeat sequence has little influence on binding profiles (Asghari et al., 1995).

An association between smoking behavior and the L allele has been reported for an African-American population. Shields et al. (1998) found that, after smoking cessation counseling, none of the subjects with an L allele were abstinent at 2 months compared with 35% of the subjects who were homozygous for the S allele. This association, however, was not found in Caucasian subjects.

Reports of an association between the L allele and the novelty-seeking personality trait are the first to indicate associations between specific genes and personality traits (Benjamin et al., 1996; Ebstein et al., 1996). Because smokers showed higher novelty-seeking rates than did the general population (Pomerleau et al., 1992; Zuckerman et al., 1990), it is likely that the L allele is associated with smoking, which is consistent with the findings reported for African-American smokers (Shields et al., 1998). Functional polymorphism in the promoter region of the DRD4 gene was recently found in Japanese subjects and an association between this polymorphism and the novelty-seeking personality trait has been suggested (Okuyama et al., 2000). Although this polymorphism was found not to be associated with alcoholism (Ishiguro et al., 2000b), its association with smoking remains to be examined.

A significant interaction between the DRD4 exon III variable number tandem repeat polymorphism genotypes and depression was also found for stimulation smoking and negative-effect reduction smoking (Lerman et al., 1998a). Specifically, smoking increased significantly in depressed smokers homozygous for the S allele but not in smokers heterozygous or homozygous for the L allele. The authors concluded that the rewarding effects of smoking and the beneficial effects of nicotine replacement therapy for depressed smokers might depend in part on genetic factors involved in dopamine transmission.

4.5. Dopamine D_5 receptor gene (DRD5)

Six polymorphisms have been identified in the DRD5 gene, and functional analyses have shown reduced levels of functional protein (Cravchik and Gejman, 1999; Sobell et al., 1995). Although associations between these polymorphisms and smoking have not been reported, an association between a microsatellite marker of the DRD5 gene and substance abuse has been found (Vanyukov et al., 1998).

4.6. Dopamine transporter gene (SLC6A3)

Lerman et al. (1999) and Sabol et al. (1999) reported an association between smoking behavior and the SLC6A3-9 allele of the 3′ untranslated region of the dopamine transporter gene in their case-control study of non-smokers and current smokers. They found that individuals with the SLC6A3-9 allele are less likely to be smokers than are individuals without SLC6A3-9, and that smokers with SLC6A3-9 started to smoke later and were able to quit for longer periods than were other smokers. Sabol et al. (1999) replicated this study but added more information by including former, current, and non-smokers as phenotypes. They also included a study of the association between personality traits and SLC6A3-9 and/or smoking behavior. They found that SLC6A3-9 was associated with relatively lower novelty-seeking scores and with smoking cessation. Although Lerman et al. (1999) had indicated that SLC6A3 may influence smoking initiation, Sabol et al. (1999) did not observe this association. Jorm et al. (2000) did not find this association in a non-volunteer community sample of 861 Caucasians.

Systematic screening of DNA sequence variations in the coding region of SLC6A3 was recently completed (Grunhage et al., 2000; Vandenbergh et al., 2000). Thus, associations between the polymorphisms of SLC6A3 and smoking still remain to be explored thoroughly.

5. Polymorphisms in serotonin receptors and transporters

The serotonergic system is involved in a variety of neuropsychiatric phenotypes including mood, sleep, appetite, aggression, and sexual behavior. The serotonergic system may be implicated in habitual smoking, since nicotine increases brain serotonin secretion and nicotine withdrawal reduces it (Mihailescu et al., 1998; Ribeiro et al., 1993). These findings have led to the hypothesis that appetite and mood disturbances associated with nicotine withdrawal may be mediated through a diminished serotonergic transmission. Clinical data have shown that fluoxetine hydrochloride, a serotonin re-uptake inhibitor, might promote smoking cessation. Fluoxetine treatment effectively prevents the increased food intake and weight gain in smokers who have reduced their nicotine intake (Hitsman et al., 1999).

The serotonergic system is hypothesized to contribute to the harm-avoidance personality trait. A previous study has shown that the neurotic personality, which broadly includes anxiety, depression, impulsiveness and vulnerability, increases the risk of smoking, primarily because of the difficulty of quitting (Hu et al., 2000).

5.1. Serotonin receptor genes

Previous studies have demonstrated that nicotine affects serotonin release in the rat hippocampus. In the hippocampus, smoking clearly reduced serotonin binding to serotonin receptors 1 (5-HT_1) and 5-HT_{1A}, whereas the effects of smoking on binding to 5-HT_{2A} were controversial (Dursun and Kutcher, 1999). 5-HT_{5A} falls into the 5-HT_1-like class according to pharmacological criteria (Hoyer et al., 1994; Rees et al., 1994).

There are no reports of association studies between serotonin receptor gene polymorphisms and smoking behavior. However, many subtypes of serotonin receptor genes have been examined for associations with other addictions. The Cys23Ser polymorphism in the 5-HT_{2C} gene contributes to CSF levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of norepinephrine, but not to 5-hydroxyindoleacetic acid (5-HIAA) or HVA (Lappalainen et al., 1999). In the 5-HT_{2A} gene, functional His452Tyr polymorphism has been described (Ozaki et al., 1997). Neither of these polymorphisms is associated with alcoholism. The Pro15Ser polymorphism in the 5-HT_{5A} gene is also not associated with alcoholism (Iwata et al., 1998). Studies of the genetics of personality have shown that the effect of the Cys23Ser polymorphism in the 5-HT_{2C} gene on the reward dependence trait is markedly accentuated in individuals who have the long allele of the DRD4 exon III variable number tandem repeat polymorphism (Benjamin et al., 1997; Ebstein et al., 1997b).

Moreover, there is an association between the harm-avoidance personality trait and platelet 5-HT_2 sensitivity (Peirson et al., 1999). When serotonergic activity was assessed based on the prolactin response to a highly potent and selective 5-HT_{1A} agonist, there was a positive relation between the harm-avoidance trait and this response (Hansenne and Ansseau, 1999). These findings indicate that associations between serotonin receptor gene polymorphisms and smoking should be explored.

5.2. Serotonin transporter gene (SLC6A4)

There are two variable number tandem repeat polymorphisms in the SLC6A4 gene, one in the transcriptional control region upstream of the coding region [the 5-hydroxytryptamine transporter-linked polymorphic region (5-HTTLPR)] and one in the second intron. There are two common alleles of the 5-HTTLPR polymorphism: the 44-bp insertion (L type) allele and the deletion (S type) allele. The S allele shows decreased transcriptional activity when compared with the L allele, resulting in decreased function in the S/S genotype compared with the L/S and L/L genotypes (Heils et al., 1996). The 5-HTTLPR has been associated with anxiety-related and harm-avoidance personality traits in some studies (Lesch et al., 1994; Murakami et al., 1999; Ohara et al., 1998b), but not in others (Ebstein et al., 1997a; Jorm et al., 1998). Association of depression with the 9-repeat allele of the second intron variable number tandem repeat polymorphism (Ogilvie et al., 1996) or with the S allele of 5-HTTLPR (Collier et al., 1996) has also been reported.

An association between 5-HTTLPR and smoking was reported (Ishikawa et al., 1999). Because clinical data show that serotonin re-uptake inhibitors effectively prevent nicotine withdrawal symptoms, it can be hypothesized that the low function S genotype of 5-HTTLPR would be protective against smoking. This hypothesis is compatible with results of a study that indicated an association between the 5-HTTLPR L allele and smoking in a Japanese population (Ishikawa et al., 1999). However, comorbidity between depression and smoking shows an opposite trend (Lerman et al., 1996, 1998a). Furthermore, Lerman et al. (1998b) have reported no association between this polymorphism and cigarette smoking in Caucasians and African-Americans.

The prevalence of major depressive disorders in individuals who have smoked habitually is more than double that in non-smokers (Aubin et al., 1996). Moreover, it has been suggested that both anxiety and depression are linked with nicotine dependence (Lerman et al., 1996). Therefore, the serotonin transporter gene is likely to play a role in smoking behavior. Neuroticism was positively associated with smoking habits among smokers with 5-HTTLPR S genotypes (S/S or S/L) but not among smokers with the L genotype (L/L). The 5-HTTLPR may modify the effects of neuroticism on smoking motivation and nicotine dependence (Lerman et al., 2000). Data suggest that smoking behavior is more strongly influenced by the combination of 5-HTTLPR S and neuroticism than by either factor alone; therefore, it is more difficult for smokers with the 5-HTTLPR S allele to quit smoking (Hu et al., 2000). In addition, the serotonin transporter gene has been suggested to affect novelty-seeking in close relatives (Benjamin et al., 2000).

Many complicated factors, including racial differences in the genotype distributions of 5-HTTLPR, sex, and methods for recruiting smoking subjects may influence the study of the data.

6. Polymorphisms in genes encoding enzymes involved in synthesis of neurotransmitters

6.1. Tyrosine hydroxylase gene (TH)

Tyrosine hydroxylase is the rate-limiting enzyme that catalyzes the hydroxylation of L-tyrosine to L-DOPA. Nicotine increases the expression of tyrosine hydroxylase in cell culture systems (Hiremagalur et al., 1993). The TH gene may be regulated by a nicotine-related signaling pathway. Transgenic mice that overexpress the TH gene are relatively less sensitive to nicotine (Nabeshima et al., 1994). The human TH gene has two missense polymorphisms (Ishiguro et al., 1998; Ludecke and Bartholome, 1995), a single nucleotide polymorphism in the 5′ region (Ishiguro et al., 1998), and a (TCAT)*n* repeat polymorphism in intron 1 (HUMTH01-variable number tandem repeat polymorphism) (Polymeropoulos et al., 1991). The functional consequences of the missense polymorphisms and the single nucleotide polymorphism in the 5′ region have not been examined. The HUMTH01-variable number tandem repeat polymorphism has been suggested to affect HVA concentration in the CSF (Jonsson et al., 1996).

The HUMTH01-variable tandem repeat polymorphism was found to be associated with bipolar disorder in one study (Meloni et al., 1995), but not in others (Ishiguro et al., 1998; Korner et al., 1994). No association between the HUMTH01-variable number tandem repeat polymorphism and alcoholism (Ishiguro et al., 1998) or smoking (Lerman et al., 1997) was found.

6.2. Tryptophan hydroxylase gene (TPH)

Tryptophan hydroxylase is the rate-limiting enzyme in the synthesis of serotonin, and it may play a vital role in interindividual variations in serotonergic neurotransmission. All the known polymorphisms in the TPH gene are in non-coding regions (Ishiguro et al., 1999b; Paoloni-Giacobino et al., 2000) or synonymous in codon 365 (Han et al., 1999). There are two closely linked polymorphisms in intron 7 that have been examined for associations with suicidal behavior and alcoholism but with inconsistent results (Abbar et al., 1995; Han et al., 1999; Ishiguro et al., 1999b; Nielsen et al., 1994, 1998). Although aggression was suggested to be associated with the intron 7 polymorphism, no association was found between history of substance abuse and intron 7 polymorphism (Manuck et al., 1999). This polymorphism is not thought to have a functional consequence (Nielsen et al., 1997).

6.3. Trytophan 2,3-dioxygenase gene (TDO2)

Trytophan 2,3-dioxygenase is the rate-limiting enzyme responsible for the catabolism of tryptophan to N-formyl kynurenine and may possibly affect serotonin levels in the brain (Haber et al., 1993). There is a G → A change at position 663 and a G → T transversion at position 666 in intron 6 of the TDO2 gene. The G → T variant has a significant association with platelet serotonin levels (Comings et al., 1996b). These polymorphisms are thought to damage a YY-1 transcription factor binding site in the TDO2 gene (Vasiliev et al., 1999); but no association between these polymorphisms and drug dependence could be shown (Comings et al., 1996b). No association between smoking and any of the TDO2 gene polymorphisms has yet been reported.

7. Polymorphisms in genes encoding enzymes involved in metabolism of neurotransmitters

7.1. Monoamine oxidase genes (MAOA and MAOB)

Monoamine oxidase catalyzes the oxidative deamination of several biogenic amines in the brain and peripheral tissues with the production of hydrogen peroxide (H_2O_2) (Shih, 1991; Thorpe et al., 1987). Two forms of monoamine oxidase have been proposed and are designated monoamine oxidase A and B based on substrate selectivity and inhibitor sensitivity (Johnston, 1968; Knoll and Magyar, 1972). The isoforms are closely linked and are located on chromosome X. Monoamine oxidase A has higher affinities for serotonin, norepinephrine, and dopamine, whereas monoamine oxidase B has higher affinities for phenylethylamine and benzylamine (Shih and Chen, 1999; Shih et al., 1999). Individuals with monoamine oxidase A deficiency due to a point mutation in the gene show abnormal aggressiveness (Brunner et al., 1993). Monoamine oxidase A knockout mice have elevated brain levels of serotonin, norepinephrine, and dopamine and manifest aggressive behavior similar to that of men with deletion of monoamine oxidase A. In contrast, monoamine oxidase B knockout mice do not exhibit aggression and have only phenylethalamine levels increased (Shih and Chen, 1999; Shih et al., 1999).

It has been shown that cigarette smoking reduces the brain levels of both monoamine oxidase A and monoamine oxidase B (Fowler et al., 1996a,b, 1998). Heavy smokers have reduced levels of monoamine oxidase in peripheral tissues (Berlin et al., 1995). Compounds in tobacco other than nicotine may also influence the reward effects of cigarette smoking, because monoamine oxidase A and B are partially inhibited in the brains of smokers by tobacco components other than nicotine (Fowler et al., 1996a,b, 1998). Similarly, the activities of monoamine oxidase A and B are decreased in animals exposed to cigarette smoke (Carr and Rowell, 1990) and in vitro (Yu and Boulton, 1987). However, at physiological concentrations, nicotine does not affect cerebral monoamine oxidase A or monoamine oxidase B activity (Carr and Basham, 1991).

Five polymorphisms have been found in the coding region of the MAOA gene (Tivol et al., 1996). Three polymorphisms in the MAOA gene that do not change the amino acid sequence have been reported to be associated with enzyme activity (Hotamisligil and Breakefield, 1991). A haplotype association was found between Parkinson's disease and MAOA gene polymorphisms (Hotamisligil et al., 1994), but non-association was also reported (Nanko et al., 1996). In addition, the MAOA gene *Eco*RV polymorphism does not alter the effect of smoking on Parkinson's disease (Costa-Mallen et al., 2000). Sabol et al. (1998) reported a functional variable number tandem repeat polymorphism consisting of a 30-bp repeat sequence present in 3, 3.5, 4, or 5 copies that is located 1.2 kb upstream of the MAOA gene coding sequences. This polymorphism is in linkage disequilibrium with previously identified dinucleotide repeat polymorphisms in the MAOA and MAOB loci (Wei and Hemmings, 1999). This polymorphism affects the transcriptional activity of the MAOA gene promoter. A weak association between the polymorphism and depression was found (Sabol et al., 1998). An association between the reduced activity allele and alcoholism with antisocial behavior was reported (Samochowiec et al., 1999).

Polymorphisms in the coding region of the MAOB gene have not yet been identified. The presence of allelic varia-

tions in the MAOB gene has been suggested to increase the risk of Parkinson's disease (Kurth et al., 1993; Mellick et al., 1999a, 2000; Nanko et al., 1996). It has also been reported that the genetic variation may modify the association between smoking behavior and Parkinson's disease (Checkoway et al., 1998). Mellick et al. (1999b) could not confirm this association but agree with the conclusion that the MAOB gene enhances the protective effects of smoking against Parkinson's disease.

7.2. Catechol-O-methyltransferase gene (COMT)

Catechol-*O*-methyltransferase, which inactivates catecholamine neurotransmitters by an S-adenosylmethionine-dependent methyl transfer reaction, is a key modulator of dopaminergic and noradrenergic neurotransmission. Dopamine is metabolized to HVA by COMT. There is a functional polymorphism, which is a substitution from Val to Met in codons 108 and 158 in the soluble and membrane-bound forms of COMT, respectively. This polymorphism affects enzyme activity and thermal stability (Lundstrom et al., 1995). The isoform with the methionine residue is a low-activity form of COMT, called COMTL, whereas the high-activity isoform with the valine is called COMTH. Homozygotes for the COMTL allele have a three- to fourfold reduction in enzymatic activity compared with that of COMTH (Lundstrom et al., 1995). COMT-deficient mice show region-specific changes in dopamine levels, notably in the frontal cortex; sexually dimorphic changes are also seen. Heterozygous COMT-deficient male mice exhibit increased aggressive behavior (Gogos et al., 1998). In humans, an association between COMTL and violent behavior in schizophrenics has been suggested (Karayiorgou et al., 1997; Strous et al., 1997). Associations of this polymorphism with bipolar disorder in Caucasians (Gutierrez et al., 1997) and with depression in a Japanese population have been reported (Ohara et al., 1998a). No association has been found between this polymorphism and alcoholism (Ishiguro et al., 1999a), Parkinson's disease (Hoda et al., 1996), bipolar disorder (Kunugi et al., 1997), or schizophrenia (Daniels et al., 1996). Additionally, an interaction between the novelty-seeking personality trait and COMT polymorphism has been suggested (Benjamin et al., 2000). Other groups have suggested a possible association between COMTH and substance abuse (Uhl et al., 1998; Vandenbergh et al., 1997), but no association between smoking and the COMT polymorphism has yet been reported.

8. Polymorphisms in other genes

Genes such as those encoding acetylcholine receptors, adrenergic receptors, μ opioid receptors, and cannabinoid receptors are also important candidates for involvement in smoking behavior. Association studies have not yet been reported, however.

9. Future research

To understand smoking behavior, we must consider many aspects of the behavior including initiation, maintenance, cessation, and relapse. Moreover, sensitization to nicotine involves behavioral responses that increase following repeated smoking. Sensitization and some personality traits (or neurological diseases) may play roles in initiation of smoking and their effects may involve neurological actions, alterations in the dopaminergic system. Some smokers may begin smoking for pleasure and/or to escape from depressive or anxious feelings. Maintenance of smoking behavior is affected by both positive and negative reinforcements. The mechanism underlying relapse remains to be investigated. Each aspect of smoking-related behavior could depend on a variety of genetic factors as well as on environmental influences. Therefore, further advances in our understanding of smoking through pharmacology/therapeutic evidence and function/structural analyses of candidate genes may clarify the complicated mechanisms of dependence. In the near future, sequencing of the human genome will be complete. This will facilitate the analyses of associations between candidate genes and smoking. These advances will in turn enable us to investigate functional interactions between smoking and the brain.

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