Genetic variants influencing smoking behavior and efficacy of smoking cessation therapies

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Abstract

Literature data showed that smoking initiation and maintenance of smoking habit are strongly influenced by the genetic individual background which is also influencing the success rate of smoking cessation therapies. In addition, the level of nicotine dependence was found to be determined by the combination of specific genetic variants in smoking related genes. The aim of this paper is to provide an overview of the genetic variants in smoking related genes influencing smoking behavior on one side and efficacy of smoking cessation therapies on the other side. The smoking related genes include the genes involved in the responses to nicotine (for example the genes interfering with nicotinic receptors or with nicotine metabolism) and the genes affecting the neurotransmitter pathways that may lead to addictive behavior (like dopamine or serotonin). Personalized treatment strategies might be developed based on individual genetic background in order to increase the efficacy of smoking cessation treatment.

Keywords: nicotine, nicotine dependence, smoking related genes

1. Introduction

Smoking is a major health problem associated with high morbidity and mortality all over the world that continues to be difficult to fight with despite intensive efforts of healthcare providers, pharmaceutical industry and also of the smokers. In January 2014, the Institute for Health Metrics and Evaluation at the University of Seattle in Washington reported that 967 millions of people smoked cigarettes every day throughout 2012 all over the world. Even though the health hazards associated with smoking are well recognized by the general population, still a high number of persons start smoking and then continue smoking. Furthermore, for many smokers it is difficult or even impossible to quit smoking despite the desire, the efforts and the attempts made. Due to nicotine dependence, 70% of smokers do not succeed to quit smoking. There is a very high relapse rate and generally definitive smoking cessation occurs after several attempts [1]. The results from genetic studies showed that nicotinic receptor subtypes and also genes involved in neuroplasticity and learning are involved in the development of nicotine dependence [2]. It is known that nicotine is primarily metabolized by CYP2A6 and variability in rate of metabolism contributes to vulnerability to tobacco dependence, smoking cessation treatment response, and also to lung cancer risk [2]. The frequency of nicotine dependence is higher in patients with mental illness and substance abuse disorders, a high proportion of the current smokers being represented by this category.
Smoking initiation, development of addiction and the level of nicotine dependence were found to be dependent on genetic factors. In addition, the efficacy of smoking cessation therapies is influenced by the genetic factors [4, 5]. Therefore, understanding the genetic role in smoking behaviour and in efficacy of smoking cessation therapies will provide a justification for initiating smoking, a self-harming behaviour, and also the difficulty in stopping it.

**Discussion:** Nicotine dependence was found to be highly heritable. Substantial evidences from twins, adoptions and family studies are supporting the heritability of nicotine addiction which was estimated at 50-75%. There is an increased interest in studying the genetic basis of the smoking behavior and nicotine addiction which provides an explanation for the high number of persons that start and then continue smoking and also for the low success rates of smoking cessation therapies. The results of various studies showed that the genetic factors have an important contribution to both the initiation and maintenance of the smoking habit and also to the efficacy of smoking cessation therapies. Genetic factors were demonstrated to be responsible for about 40 to 75% of the variation in smoking initiation, 70 to 80% of the variation in maintenance of smoking habit, for 30 to 50% of the variation in withdrawal symptoms risk and also for 50% of the variance in smoking cessation success [6-10]. Therefore individual smoking profile is strongly influenced by the genetic determinants a summary of which is provided under table 1.

![Table 1: Influences of genetic determinants on the individual smoking profile](image)

In this paper, an overview of the genetic variants in smoking related genes influencing smoking behavior and efficacy of smoking related therapies is presented.

**Genetic variants which can influence the smoking behavior**

Variants in two distinct classes of genes were described in the literature as being involved in the smoking behavior [11]:

1. genes which can influence the response to nicotine (like gene interfering with nicotinic receptors and nicotine metabolism)
2. genes which can predispose to addictive behavior as a result on their effects on key neurotransmitter pathways (like dopamine and serotonin)

Genes involved in nicotine metabolism determine both persistence and the level of nicotine in the body and therefore they are assumed to influence the smoking behavior. CYP2A6 is responsible for approximately 90% of metabolic inactivation of nicotine and thus it is considered more predictive for the rate of nicotine metabolism [12]. Genetic polymorphism in
Genes influencing CYP2A6 might lead to variability in the rate of nicotine metabolism that contributes to nicotine dependence and response to smoking cessation therapies. Nicotine’s pharmacological effects are initiated by the activation of nicotinic acetylcholine receptors (nAChRs) resulting in the release of various neurotransmitters and hormones which can predispose to addictive behaviour (like dopamine, acetylcholine, serotonin, glutamate, GABA, norepinephrine, and β-endorphin). Smoking behavior is mediated by the release of these neuro-chemicals. Therefore, genetic polymorphism in nAChR subunit genes or genes affecting the key neurotransmitter pathways may influence the smoking behavior.

As there is an increased interest in this area, several studies investigated the genes involved in nicotine metabolism with more studies investigating the CYP2A6 polymorphism. Studies using the measurement of the ratio of cotinine / nicotine or trans-3′-hydroxicotinine/cotinine in blood or urine showed that persons carrying CYP2A6 variants reducing the enzyme activity are less tobacco dependent, smoke significantly fewer cigarettes/day and have an increased likelihood of quitting smoking [13-18]. The results of the study of Saarikoski [19] showed that there are higher chances for ultrametabolisers to be heavy smokers.

Genetic studies on nicotinic acetylcholine receptors were directed at several subunit genes (like CHRNA4, CHRNA5, CHRNA7, and CHRN B1, CHRN B2 and CHRN B3). Until now a subgroup of smokers with CHRNA4 variants that have massive withdrawal symptoms and also affective vulnerability has been identified [20].

Nicotine is known to stimulate the release of dopamine in accumbens nucleus, and thus DRD2 receptor was intensively studied because it is associated with addictive behaviors. Studies investigating the genetic variation in the dopamine pathways identified certain polymorphisms in DRD2 alleles more frequently in smokers than in nonsmokers. Individuals caring this certain polymorphisms in DRD2 alleles have less dopaminergic receptors and were shown to start smoking earlier, to consume higher quantities of cigarettes every day and have bigger difficulties in quitting the smoking habit. Furthermore, polymorphism in the DRD4 gene is considered possibly related to smoking initiation and in African population it was associated with a higher predisposition for smoking [21]. As for dopamine transport, it was found that individuals with SLC6A3-9 polymorphism have a lower predisposition to become smokers, and that they consume lower quantities of cigarettes every day and do not have difficulties in quitting smoking [22].

The studies investigating the genetic variation in the serotonergic pathway showed that in case of polymorphisms of the 5-HT2A serotonin gene receptor, individuals with CC alleles have higher chances of maintenance of smoking habit when compared with those with TT alleles [23]. Moreover, a polymorphism in the serotonin transporter gene is highly associated with smoking status (nonsmoker versus smoker) which suggested that this gene is influencing smoking initiation [24].

With regards to noradrenaline pathways, polymorphisms of the monoamine oxidase (MAO) genes (MAO-A and MAO-B) is associated with the quantity of cigarettes consumed [25]. Lerman [26] suggested that the risk of drug dependence (including nicotine) is influenced by the A118G polymorphism of the μ -opioid receptor (OPRM1). A summary of genetic variants in various genes involved in smoking behavior and their influences on smoking behavior described in the literature are presented in the table below.

Table 2: Influences of various genetic variants on smoking behavior described in the literature

<table>
<thead>
<tr>
<th>Genetic characteristics</th>
<th>Influences on smoking behavior</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>nicotine metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>polymorphism in CYP2A6</td>
<td>Individuals are less addicted to</td>
<td>Pianezza [13]; Rao [14];</td>
</tr>
<tr>
<td>associated</td>
<td>smoking,</td>
<td></td>
</tr>
</tbody>
</table>
Genetic variants influencing the efficacy of smoking cessation therapies

Lately there is an increased interest for pharmacogenetic studies which are allowing us to investigate the variability of the individual response to the medication, the efficacy and also the rate of side effects registered for a specific drug. Smoking cessation therapies have recently started to be investigated, and out the currently available therapies only nicotine replacement treatments and bupropion have been studied more. Important inter-individual differences were reported in the therapeutic responses to smoking cessation treatments. In addition, even though there are several efficient therapies available and smokers are motivated to quit, the results from clinical studies showed that the overall success rate is low irrespective of the treatment (about 30% successful rate) (Fulga et al., 2014). In order to increase the efficacy of available smoking cessation methods, the potential for individually tailored pharmacotherapies started to be investigated [28]. The efficacy of pharmacological therapies used for the cessation of smoking was found to be influenced by genetic polymorphisms through different mechanisms. For example, genetic variation in genes affecting the smoking behaviour will influence the efficacy of the therapies directed at modulation of the smoking behaviour pathways; genetic variants in genes influencing the metabolism or elimination of a specific smoking cessation drug will influence its plasmatic concentration and also its duration of the effect which in the end will influence the treatment efficacy and safety [29]. The effects of the genetic variants are frequently distinctive for different pharmacotherapy
classes with different mechanisms of action. A difference in the pathways involved in the mechanism of action or in the metabolism or elimination of any of the drug used as a smoking cessation therapy can make one class more efficient than another or can result in a better safety profile in a certain smoker subgroup. Therefore, the high inter-individual differences in the therapeutic responses to smoking cessation therapies can be explained by the fact that the efficacy of each therapy is influenced by individual genetic variants in smoking-related and treatment-related genes. In this paper the genetic variants in smoking related genes will be addressed.

In case of nicotine replacement therapies, results from genetic studies investigating the nicotinic acetylcholine receptors showed smokers carrying TC genotype (genetic polymorphisms associated with increased α4β2 binding in the nucleus accumbens leading to bigger sensitivity to the acute effects of smoking) experience better benefits from nicotine spray due to the greater rewarding effects [30]. Smokers with increased nicotine metabolism (CYP2A6 genotype) have lowers quit rates with transdermal nicotine patches [31] while smokers with reduced nicotine metabolism (CYP2A6) have better results for extended transdermal nicotine therapy [32]. Smokers having increased activity variants in the μ-opioid receptor (OPRM1 Asp40 variant) may have better success rates with transdermal nicotine patches due to higher levels of nicotine delivered [33]. When investigating the polymorphism in dopamine D2 receptor (DRD2 C/T and DRD2 A/G) and in dopamine beta-hydroxylase (DBH A/G) (both implicated in modulation of smoking), it was found that there are better quit rates for nicotine replacement patches in smokers with DRD2 CT/TT genotype (polymorphism in Dopamine D2 receptors) compared with CC genotype. And also higher efficacy was registered in smokers with both DRD2 CT/TT and DBH GA/A4 genotypes [34]. Studies with bupropion showed that higher efficacy for bupropion compared with placebo are registered in fast nicotine metabolisers while in slow nicotine metabolisers there are equivalent quit rates reported with placebo and bupropion [35]. Preliminary results suggested that DRD2-Taq1A polymorphism can influence bupropion efficacy considering that David [36] indentified a significant DRD2 x bupropion interaction and a three-way DRD2 x bupropion x craving interaction. Smokers with A2/A2 genotype had the biggest craving reduction and also the highest abstinence rates with bupropion. In addition a significant DRD2 x CYP2B6 interaction was identified based on the fact that individuals with the DRD2-Taq1 A2/A2 genotype had higher odds of abstinence only if they possessed CYP2B6 1459 T/T or C/T genotype [36].

A summary of genetic genotypes and their influences on nicotine replacement treatments and bupropion as described in the literature is presented in the table below.

Table 3: Influences of different genotypes on nicotine replacement treatments and bupropion

<table>
<thead>
<tr>
<th>Genetic characteristics</th>
<th>Influences on smoking cessation treatment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>reduced nicotinic receptor activity</td>
<td>Better rewarding effects from nicotine spray</td>
<td>Hutchison [30]</td>
</tr>
<tr>
<td>reduced nicotine metabolism (CYP2A6)</td>
<td>Better results for extended transdermal nicotine therapy</td>
<td>Lerman [32]</td>
</tr>
<tr>
<td>increased nicotine metabolism</td>
<td>Lower efficacy with transdermal nicotine patches</td>
<td>Schnoll [31]</td>
</tr>
<tr>
<td>increased activity in the μ opioid receptor (OPRM1 Asp40 variant)</td>
<td>Better success with transdermal nicotine patches</td>
<td>Lerman 33]</td>
</tr>
<tr>
<td>polymorphisms in the dopamine D2</td>
<td>Better-quit rates in smokers with DRD2 CT/TT genotype</td>
<td>Johnstone [34]</td>
</tr>
</tbody>
</table>
Overall, understanding the genetic contributions to smoking behavior might lead to increased efficacy of smoking cessation treatment as personalized treatment strategies can be developed. Therefore, the genetic background should also be considered when deciding on the most effective treatment for an individual smoker.

**Conclusion:**
- Smoking behavior, including smoking initiation, development of addiction to nicotine, and maintenance of smoking habit, as well as the levels of nicotine addiction, are strongly influenced by the genetic individual background.
- The efficacy of smoking cessation therapies is also determined by various genetic polymorphisms. Individual genetic background should be considered when selecting the anti-smoking therapy.
- Therefore determination of the individual genetic background could allow determination of the individual smoking profile (as described in table 1 and 2) on one side and on the other side, it could help in optimizing the response to smoking cessation therapies, at least in case of nicotine replacement therapies and bupropion (as shown in table 3).
- Furthermore, it can be hypothesized that based on genetic analysis and determination of the genetic profile, it is possible to personalize the anti-smoking therapy which is expected to result in a more efficient use of anti-smoking treatments, increased cessation rates, and ultimately, in reduced morbidity and mortality from smoking.

**References**


