Assessment of genetic variation as a predictor of smoking cessation success: a review

M Quaak¹,²*, FJ van Schooten¹, CP van Schayck²

Abstract

Introduction
Recent research strongly suggests that a specific genetic background influences smoking behaviour and may also determine the efficacy of pharmacotherapies used for smoking cessation. The aim of this critical review was to provide an overview of the developments in the pharmacogenetics of smoking cessation treatment.

Discussion
Several (combinations of) genetic variants in smoking-related genes (e.g. genes influencing the response to nicotine (e.g. nicotine metabolism, nicotinic receptors) and genes that may predispose to addictive behaviour due to their effects on key neurotransmitter pathways (e.g. dopamine, serotonin, opioid)) have been found to influence the level of nicotine dependence. Furthermore, the different aspects of nicotine dependence seem to be influenced by genetic variants in different pathways; ‘morning smoking’ by genes that may influence the response to nicotine, but ‘smoking pattern’ by genes that influence key neurotransmitter pathways. Moreover, several variants in smoking- and treatment-related genes influence the efficacy of smoking cessation therapies, which are often distinctive for the different forms of pharmacotherapy, especially when they have a different mechanism-of-action.

Conclusion
Much progress has been made in unravelling the effects of genetic variants on smoking behaviour and smoking cessation treatment, but much research still remains to be done and prospective trials should be set up to fully confirm the effect of the variants before genetically tailored smoking cessation therapy can be implemented in standard clinical practice.

Introduction
Although the risk of smoking is well documented, tobacco smoking continues to be the largest preventable cause of disease and premature death throughout the world. It is estimated that there are currently still over 1.5 billion smokers world-wide and this is expected to reach about 2 billion by 2025. Smoking results in many of the most common diseases: cancers, cardiovascular diseases, and chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Moreover, about half of all the smokers who continue to smoke will eventually die from a smoking-related disease, resulting in over 6 million deaths per year world-wide. Smoking cessation can reverse many of the adverse effects of smoking. However, although the majority of smokers are highly motivated to quit and much progress has been made in the (pharmacological) treatment of nicotine dependence (ND), the efficacy of available treatments is limited; only ~15%–30% continue to abstain from smoking (see Table 1).

Recent research strongly suggests that a specific genetic background influences smoking behaviour. Since pharmacological therapies used for smoking cessation are directed at the modulation of the pathways involved in smoking behaviour, genetic variation in candidate genes for smoking behaviour will probably also influence the efficacy of smoking cessation therapies. Furthermore, genetic variants in genes influencing the metabolism and/or secretion of smoking cessation pharmacotherapies, thereby determining the level and duration of the medication in the body, might also influence the efficacy of smoking cessation treatment. Therefore, the overall effectiveness of smoking cessation therapy could be increased if the therapy is matched with the smoker’s genetic background. This is expected to result in a more efficient use of anti-smoking therapies, increased cessation rates, and ultimately, in reduced morbidity and mortality deaths from smoking.

In this paper we present an overview of the developments in the assessment of genetic variation as a predictor of smoking cessation success. For this, we first shortly discuss the biological pathways associated with smoking. This is followed by an overview of the influence of genetic variants on smoking behaviour and smoking cessation treatments (for more extensive reviews see 67).

Discussion
The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

For citation purposes: Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.
Table 1  Efficacy of smoking cessation treatments

| Treatment type           | Standard dose and duration                        | Quit rate (range) | 6–12 Months follow-up OR (95% CI) |
|-------------------------|--------------------------------------------------|-------------------|-----------------------------------|
| Placebo                 | 1.2% (0–46)                                       | 1.00             |
| Behavioural counselling |                                                  |                   |
| Individual therapy      | Weekly sessions of 10–60 min for 2–16 weeks       | 15.3% (0–43)      | 1.65 (1.35–2.01)                  |
| Group therapy           | 1–3 Sessions/week of 45 min–2 h for 2–14 weeks    | 15.1% (0–38)      | 2.17 (1.37–3.45)                  |
| Antidepressant therapy  |                                                  |                   |
| Bupropion               | 150 mg/day for 3 days + 300 mg/day for 7–12 weeks | 20.2% (3–43)      | 1.94 (1.72–2.19)                  |
| Nortriptyline           | 75–100 mg/day for 10–12 weeks                    | 22.6% (9–31)      | 2.34 (1.61–3.41)                  |
| SSRIs                   | Dependent on type of SSRI used                   | 15.1% (10–27)     | 0.90 (0.69–1.18)                  |
| Venlafaxine             | 225 mg/day for 8 weeks                           | 23.0%             | 1.29 (0.58–2.88)                  |
| Nicotine replacement therapy |                                      |                   |
| Gum                     | 2–4 mg (recommended 10–15/day) for 1–4 months    | 23.7% (3–60)      | 1.66 (1.52–1.81)                  |
| Transdermal patch       | 21 mg for 4–6 weeks + 14 mg for 2 weeks + 7 mg for 2 weeks | 15.8% (7–38) | 1.84 (1.65–2.06)                  |
| Inhaler/inhalator       | 6–16 cartridges/day for 12 weeks (4 mg)          | 20.2% (11–28)     | 2.14 (1.44–3.18)                  |
| Spray                   | 8–40 doses/day (0.5 mg/nos-tril) for 8 weeks     | 24.5% (18–27)     | 2.35 (1.63–3.38)                  |
| Tablets/lozenges        | 9 Lozenges/day for 6 weeks + 6 week tapering     | 17.1% (12–23)     | 2.05 (1.62–2.59)                  |
| Nicotine receptor partial agonists |                                  |                   |
| Varenicline             | 0.5–1 mg 1–2/day for 6–12 weeks                  | 21.8% (14–23)     | 3.22 (2.43–4.27)                  |
| Cytisine                | 1.5 mg tabs: days 1–3, 6/day; days 4–12, 5/day; days 13–16, 4/day; days 17–20, 3/day | 21.0%             | 1.77 (1.30–2.40)                  |
| Opioid antagonists      |                                                  |                   |
| Naltrexone              | 25–100 mg/day for 4–12 weeks                     | 17.0% (9–20)      | 1.34 (0.49–3.69)                  |
| Naloxone                | Subcutaneous: 10 mg/day or intravenous: 0.1–1.6 mg | –                 | –                                 |
| Buprenorphine           | 4–8 mg/day with ascending dosage for 10–14 days  | –                 | –                                 |

Biological pathways associated with smoking
Nicotine is the primary reward component which is associated with the addictive effects of smoking. The level of ND has been shown to depend on the amount and the way in which nicotine is delivered.

The amount and the duration of nicotine in the body are determined by the rate the nicotine is metabolised. The major genes responsible for the nicotine metabolism are the hepatic enzymes cytochrome P450 2A6 (CYP2A6) and 2D6 (CYP2D6). of these, CYP2A6 is believed to be the most important predictor of the rate of nicotine metabolism, because it is responsible for roughly 90% of the metabolic inactivation of nicotine to cotinine.

Upon entering the brain, nicotine binds to nicotinic acetylcholine receptors (nAChRs), which activates them and results in the release of several types of neurotransmitters and hormones. Release of these neurochemicals induces the behavioural effects associated with smoking. Release of dopamine is the most important neurotransmitter released by nicotine; it is responsible for the pleasurable (rewarding) effects of nicotine and is therefore critical for its reinforcing effects. Furthermore, dopamine is responsible for compelling urges such as eating. Nicotine also seems to mediate the release of glutamate, which is believed to play a role in learning and memory, and facilitates the release of dopamine. It also stimulates the release of γ-aminobutyric acid (GABA), associated with a reduction in anxiety and tension, and inhibits dopamine release. Furthermore, nicotine has been shown to increase the secretion of serotonin in the brain, which is involved in mood regulation, impulse control, appetite and aggression. Increased serotonin levels have been associated with decreased food intake and weight gain.
and have an antidepressant effect, and lower serotonin re-uptake with several behavioural traits (e.g. novelty seeking and anxiety-related personality traits) that are related to an increased incidence of smoking, increased ND, and difficulty quitting smoking\(^{13-15}\).

With chronic exposure to nicotine, tolerance develops to the release of many of these neurochemicals\(^5\). In the absence of nicotine, this results in a relative deficiency state, which is generally characterised by symptoms that are opposite to the acute effects of nicotine\(^6\). Furthermore, with long-term exposure to nicotine, some nicotinic cholinergic receptors become desensitised but some do not. As a result, GABA-mediated inhibitory tone diminishes while glutamate-mediated excitation persists, thereby increasing excitation of dopaminergic neurons and enhancing responsiveness to nicotine\(^12\).

### Figure 1: Neurochemical and related psychological effects of nicotine’s binding to nAChRs (adapted from\(^1\)). N: nicotine; nAChR: nicotinic acetylcholinic receptor; GABA: γ-aminobutyric acid.

and...
present in these genes, approaches analysing single variants or single genes will probably fail to fully determine the influence of genetic variation on smoking behaviour. Therefore, we investigated the effect of multiple genetic variants and their interactions in a large number of smoking-related genes. Several variants were found to influence ND levels and combinations of genetic variants were found to be able to have a significant effect, even if the variants do not show an effect on their own. Moreover, the different aspects of ND seemed to be influenced by genetic variants in different pathways. While ‘morning smoking’ (FTND [Fagerström Test of Nicotine Dependence] items 1, 3 and 5) was found to be associated mainly with genes that influence the response to nicotine, ‘smoking pattern’ (FTND items 2, 4, and 6) was found to be associated mainly with genes that influence key neurotransmitter pathways. These results confirm that ND is multifactorial rather than one common trait.

Therefore, we may conclude that it is important to investigate the effect of multiple genetic variants in smoking-related pathways on both the level and the different aspects of ND. This could help to better understand the underlying biological mechanisms that cause (the different aspects of) ND, which can help direct treatment to the individual needs of smokers who want to quit. Furthermore, it can guide the development of new pharmacotherapies, since these can then be directed at the pathways found to be involved in ND.

Influence of genetic variation on smoking cessation treatments

Since pharmacotherapies used for smoking cessation are directed at the pathways involved in smoking behaviour, variants in candidate genes for smoking behaviour are also expected to influence the efficacy of smoking cessation therapies. Furthermore, genetic variants in genes influencing the metabolism and/or secretion of smoking cessation pharmacotherapy, thereby determining the level and duration of the medication in the body, are also expected to influence the efficacy of smoking cessation therapy.

Most research on the role of genetic variation on smoking cessation pharmacotherapy has been directed to the two most widely accepted and licensed forms of smoking cessation therapy: nicotine replacement therapy (NRT) and the antidepressant bupropion (see Table 2). They include both placebo-controlled studies and studies comparing multiple active medications. The former may be maximally informative to determine the underlying mechanisms of the pharmacogenetic effect, while the latter may help to identify subgroups of patients who will respond optimally to a particular medication given a range of therapeutic options. In most of these studies, the available pharmacotherapies are combined with behavioural interventions. However, since participants in the different treatment groups usually all receive the same behavioural interventions, the effect of the behavioural interventions is comparable in the treatment groups.

Overall it seems that smokers with genotypes associated with reduced dopamine levels achieve better-quit rates with NRT, while genotypes associated with increased dopamine availability predict a better response to bupropion. Furthermore, a decreased metabolism of the used medication seems to increase cessation rates as well. Moreover, smokers who carry genetic polymorphisms associated with reduced nicotinic receptor (and possibly also dopaminergic) activity may experience greater benefit from the greater rewarding effects of nicotine spray (NS), while smokers with increased activity variants in the µ-opioid receptor (MOR) may have better success with the higher levels of nicotine delivered by transdermal nicotine (TN) patches. Variants in the serotonin transporter do not seem to influence the response to NRT.

It has been suggested that variants in the serotonin pathway, mainly the serotonin transporter (SERT), may be associated with the response to pharmacologic treatments for smoking cessation with an antidepressant action. We therefore investigated the influence of three functional genetic variants in the SERT gene (SLC6A4 5-HTTLPR, STin2 and rs25531) on smoking cessation rates using the antidepressants bupropion and nortriptyline. Both bupropion and nortriptyline seemed to increase, possibly even double, smoking cessation rates, but only among the carriers of serotonin transporter high-activity variants. This is probably because they block the increased serotonin transporter activity, thereby increasing serotonin levels. In addition, several other variants in smoking- and treatment-related genes were found to influence cessation rates using bupropion and nortriptyline.

Some of these variants had comparable effects for both bupropion and nortriptyline treatment, but some genetic variants were also identified that had distinct effects depending on the type of antidepressant that was used. Genetic variants associated with a dopamine or serotonin deficiency resulted in increased cessation rates using both antidepressants. Furthermore, both seemed to attenuate the decreased cessation rates among individuals with a higher nicotine metabolism (CYP2D6), although this was not significant for nortriptyline, possibly because this variant also results in an increased nortriptyline metabolism. Moreover, cessation rates using bupropion were found to be decreased among individuals with a lower bupropion metabolism, while a variant in the acetylcholine pathway was found to be associated with nortriptyline only. Finally, variants in nicotinic receptor subunits also seemed to play

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

For citation purposes: Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.
Table 2 Influence of genetic variations on cessation rates using nicotine replacement therapy (NRT) or bupropion treatment

| Gene function | Variant | Phenotype | Effect on treatment | References | Bupropion | References |
|---------------|---------|-----------|---------------------|------------|-----------|------------|
| CYP2A6        | *2      | Inactive enzyme (stop codon change) | - NMR SM* lower than NM* (0.45 ± 0.22 vs 0.23 ± 0.017, p < 0.01).  
|               |         |           | - Higher plasma nicotine levels among SM* than NM* using TN (23.2 ± 4.6 vs 15.8 ± 0.6 ng/ml, p = 0.02), but not with NS (p = 0.02).  
|               |         |           | - SM* use fewer NS doses/day than NM* (4.8 ± 0.3 vs 15.5 ± 8.0, p < 0.02) | 28         |           |            |
|               | *4      | Inactive enzyme (gene deletion) | - Reduced metabolisers (with a variant) benefit more from extended TN (6-mo) than standard 8-wk therapy compared to normal metabolisers, but only significant at 6-mo (EOT < sub; OR/GxT = 3.2, 1.05–10.05, p = 0.04; OR/NT = 4.78 (1.13–16.83, p = 0.002 vs OR/IT = 1.47 (0.90–2.41), p = 0.13) | 27         |           |            |
|               | *9      | Intermediate activity (decreased transcription) | - Reduced metabolisers (with a variant) benefit more from extended TN (6-mo) than standard 8-wk therapy compared to normal metabolisers, but only significant at 6-mo (EOT < sub; OR/GxT = 3.2, 1.05–10.05, p = 0.04; OR/NT = 4.78 (1.13–16.83, p = 0.002 vs OR/IT = 1.47 (0.90–2.41), p = 0.13) | 27         |           |            |
|               | *12     | Intermediate activity (CYP2A6/2A7 hybrid) | - Lower cessation success among faster metabolisers in TN group (per quartile: OR = 0.72 (0.57–0.90), p = 0.02).  
|               |         |           | - No association in NS group (OR = 1.05 (0.83–1.34), p = 0.68).  
|               |         |           | - Slow metabolisers have higher relapse rates following TN.  
|               |         |           | - Fast metabolisers (Q1) less likely to be abstinent with TN at EOT than slow metabolisers (Q5) (OR = 0.54 (0.36–0.82), p = 0.003).  
|               |         |           | - Extended TN (6-mo) more effective than standard 8-wk therapy among reduced metabolisers (Q2, Q3, Q4) (OR = 2.54 (1.15–5.60, p = 0.02) than normal metabolisers (Q5) (OR = 1.60 (0.95–2.71, p = 0.08), but only at 6-mo (EOT-Tstandard).  
|               |         |           | - No significant interaction effect between treatment and NMR (p = 0.346).  
|               | *3      | Inactive enzyme (stop codon change) | - NMR SM* lower than NM* (0.45 ± 0.22 vs 0.23 ± 0.017, p < 0.01).  
|               | *4      | Inactive enzyme (gene deletion) | - Reduced metabolisers (with a variant) benefit more from extended TN (6-mo) than standard 8-wk therapy compared to normal metabolisers, but only significant at 6-mo (EOT < sub; OR/GxT = 3.2, 1.05–10.05, p = 0.04; OR/NT = 4.78 (1.13–16.83, p = 0.002 vs OR/IT = 1.47 (0.90–2.41), p = 0.13) | 27         |           |            |
|               | *12     | Intermediate activity (CYP2A6/2A7 hybrid) | - No association (OR = 0.89 (0.36–2.20), p = 0.80) | 30         |           |            |

For citation purposes: Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.

Competing interests: declared in the article. Conflict of interests: none declared.

All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
### Table 2 (Continued)

| Gene function | Variant | Phenotype | Effect on treatment | NRT | References | Bupropion | References |
|---------------|---------|-----------|---------------------|-----|------------|----------|------------|
| **CHRNA4** Nicotinic acetylcholine receptor | rs2236196 | Altered mRNA binding site for IRE; higher mRNA stability; 2× more active T-allele | - T/C-genotype associated with abstinence (genotype \times treatment \times timepoint OR = 3.87 (1.36–11.01), \( p = 0.01 \))<br>- No association TN with prolonged abstinence (wk4: OR = 0.89; wk12: OR = 1.19; wk26: OR = 1.27; wk52: OR = 1.36, all \( p > 0.05 \)) | 30 | – | – | – |
| | rs1044396 | ? | - No association TN with prolonged abstinence (wk4: OR = 0.88; wk12: OR = 0.98; wk26: OR = 0.87; wk52: OR = 1.19, all \( p > 0.05 \)) | 31 | – | – | – |
| | rs2273504 | ? | - No association TN with prolonged abstinence (wk4: OR = 1.33; wk12: OR = 1.17; wk26: OR = 0.96; wk52: OR = 1.27, all \( p > 0.05 \)) | 31 | – | – | – |
| | rs2273502 | ? | - Association TN with prolonged abstinence approached significance (wk4: OR = 1.19 (0.76–1.89); wk12: OR = 1.65 (0.97–2.78); wk26: OR = 1.76 (0.99–3.13); wk52: OR = 1.83 (0.96–3.49)). | 31 | – | – | – |
| **CHRNA7** Nicotinic acetylcholine receptor | rs2133965 | ? | - No association TN with prolonged abstinence (wk4: OR = 0.97; wk12: OR = 1.15; wk26: OR = 1.37; wk52: OR = 1.51, all \( p > 0.05 \)) | 31 | – | – | – |
| | rs4779969 | ? | - No association TN with prolonged abstinence (wk4: OR = 1.11; wk12: OR = 1.37; wk26: OR = 1.45; wk52: OR = 1.48, all \( p > 0.05 \)) | 31 | – | – | – |
| **CHRN2** Nicotinic acetylcholine receptor | rs2072661 | ? (3’UTR) | - More days abstinent with TN versus placebo with G/G-genotype (\( p < 0.01 \)).<br>- Increased probability of quitting on TQD with G/G (\( p < 0.01 \)).<br>- Increased probability of quitting on any day with G/G (\( p < 0.05 \)).<br>- No association TN with prolonged abstinence (wk4: OR = 0.92; wk12: OR = 1.06; wk26: OR = 1.04; wk52: OR = 1.03, all \( p > 0.05 \)). | 32 | – | – | – |
| | rs2072660 | ? (in LD with rs2072661) | - No association TN with prolonged abstinence (wk4: OR = 0.93; wk12: OR = 0.99; wk26: OR = 0.98; wk52: OR = 0.99, all \( p > 0.05 \)) | 31 | – | – | – |

**References**
- 30
- 31
- 32
- 33

**Competing interests:** declared in the article. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
| Gene Function | Variant | Phenotype | Effect on treatment |
|---------------|---------|-----------|---------------------|
| Taq1A         | G/C     | Lower receptor density T-allele (A1-allele) |
| DBH           | A/G     | 1.30 (0.5–3.3) |
| DRD2          | C/T+T/T | Comparable results found at later time-points (6 mo, 12 mo, and 8 yr) |
| ANKK1         | C/T+T/T | Slightly lower abstinence rates on TN with ≥1 T-allele (A1) compared to C/C (3 mo: OR = 0.75 (0.48–1.17), p = 0.19); |
|               |         |           | 6 mo: OR = 0.52 (0.24–1.11), p = 0.093; |
|               |         |           | 6 mo: no effect of genotype (BMI: OR = 1.39, p = 0.28; |
|               |         |           | 6 mo: OR = 1.78, p = 0.068; |

References:

1. Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.

2. Bupropion smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.

3. For citation purposes: Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.

4. Lower abstinence rates with A1/A2 versus homozygotes (X = 21.2, p < 0.01).

5. With A2/A2 more likely to be abstinent compared to placebo (EOT: OR = 3.28 (2.00–5.28), 6 mo: OR = 3.81 (1.66–4.77); 12 mo: OR = 1.70 (0.95–3.05). No effect on abstinence compared to placebo with ≥1 A1-allele (EOT: OR = 1.15 (0.58–2.29); 6 mo: OR = 1.91 (0.83–4.28); 12 mo: OR = 1.40 (0.75–2.61).

6. No effect of genotype on smoking cessation at EOT (p = 0.11). With A2/A2 more likely to be abstinent compared to placebo (EOT: OR = 3.28 (2.00–5.28), 6 mo: OR = 3.81 (1.66–4.77); 12 mo: OR = 1.70 (0.95–3.05). No effect on abstinence compared to placebo with ≥1 A1-allele (EOT: OR = 1.15 (0.58–2.29); 6 mo: OR = 1.91 (0.83–4.28); 12 mo: OR = 1.40 (0.75–2.61).

7. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
Table 2 (Continued)

| Gene function | Variant | Phenotype | NRT | References |
|---------------|---------|-----------|-----|------------|
| DRD2 Dopamine receptor (DR) | A22316G rs6276 (exon 8) | Unknown | - No effect genotype on effectiveness TN compared to placebo at EOT (p = 0.54). | 34 |
|                | -141C Ins/Del rs1799732 | Lower transcriptional activity DelC (T) allele | - Lower quit rates with NRT (NS and TN combined) with InsC/InsC compared to ≥1 DelC-allele at EOT (OR = 0.44 (0.25–0.79), p = 0.006). | 43 |
|                | - 34 | - No longer significant at 6mo (OR = 0.71 (0.37–1.37), p = 0.31). | - Better response to NRT (NS and TN combined) with ≥1 DelC-allele and two FREQ rs1054879 A-alleles at EOT OR = 2.32 (1.12–4.79), p = 0.022). |
|                | C957T rs6277 | Lower mRNA stability & protein synthesis T-allele | - Lower response to NRT (NS and TN combined) with ≥1 C-allele compared to T/T at EOT (OR = 0.59 (0.36–0.95), p = 0.03). | 44 |
|                | | | - No effect of genotype at 6mo (OR = 1.02 (0.58–1.82), p = 0.94). | |
| DRD4 Dopamine receptor exon III VNTR | C-521T rs1800955 | Lower receptor activity long variant | - Presence of ≥1 long-allele (≥7-repeats) associated with reduced cessation rates at EOT (independent of treatment) (OR = 0.65 (0.44–0.97), p = 0.034). | 45 |
|                | | | - No effect at 6mo follow-up (p > 0.05). | |
|                | rs3780715 | ? | - Better response to NRT (NS and TN combined) with A/A-genotype and ≥1 DRD2 −141DelC-allele at EOT and 6mo (OR = 2.32 (1.12–4.79), p = 0.022). | 44 |
|                | rs1054879 | ? | - No effect genotype on NRT (NS and TN combined) at EOT and 6mo (OR = 1.06 (0.47–2.39), p = 0.89). | 44 |

For citation purposes: Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.

Competing interests: declared in the article. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
| Gene function | Variant | Phenotype | Effect on treatment |
|---------------|---------|-----------|---------------------|
| SLC6A3 (DAT1) Dopa mine transporter | 3'UTR-VNTR (9 vs. 10 repeat) | Lower transporter levels 9-repeat | - Higher abstinence rates (independent of treatment) with 9 vs 10-repeat in the presence of DRD2-Taq1 A2/A2 at EOT (OR = 1.74 (1.03–2.93), p = 0.03). No effect genotype with ≥1 DRD2-Taq1 A1-allele (OR=0.67 (0.37–1.21), p = 0.18). - Effect of genotype on treatment influenced by DRD2-Taq1A at EOT: - Largest treatment effect among DRD2-A2/SLC6A3-10 repeat group, due to lower abstinence on placebo (OR = 2.80 (1.30–6.00), p < 0.01). - No effect in A1/9, due to high abstinence on placebo (OR = 0.87 (0.37–2.00), p = 0.74). - Intermediate treatment effects in A1/9 (OR = 2.23 (0.92–5.41, p = 0.07), and A2/9 (OR = 1.91 (0.98–4.41), p = 0.10). |
| | | | |
| Intron8-VNTR (2 vs. 3 repeat) | Higher transporter levels 2-repeat | - Higher initial cessation rate (wk1) among carriers 2-repeat versus 3/3 unrelated to treatment (OR = 1.9 (1.1–3.2), p = 0.012), but not later (wk3/4: p > 0.05). |
| | | | |
| G478T rs11564752 (Haplotype tag) | - No effect on cessation unrelated to treatment (wk1: OR_{G<T>TG vs G/G} = 1.0 (0.53–1.8), p > 0.05; wk3/4: OR_{G>T>TG vs G/G} = 0.75 (0.48–1.2), p > 0.05). |

References: 47, 38, 48, 49, 42
Table 2 (Continued)

| Gene function | Variant | Pheno-type | Effect on treatment |
|---------------|---------|------------|---------------------|
|               |         |            | References          | Bupropion | References |
| C1036A        | rs2963238 (Haplotype tag) | - No effect on cessation unrelated to treatment (wk1: $OR_{G/A+A/AvsA/G} = 1.1$ (0.67–1.9), $p > 0.05$; wk3/4: $OR_{A/A+A/AvsA/G} = 1.1$ (0.71–1.5), $p > 0.05$). | - | 48 |
| A2086G        | rs27048 (Haplotype tag) | - No effect on cessation unrelated to treatment (wk1: $OR_{C/A+A/AvsC/C} = 1.0$ (0.99–1.6), $p > 0.05$; wk3/4: $OR_{A/A+A/AvsC/C} = 1.0$ (0.72–1.5), $p > 0.05$). | - | 48 |
| DBH Dopamine metabolism | A1368G rs77905 | Lower enzyme activity (linked to promoter polymorphism) | - Increased cessation rates on TN compared to placebo with both an A-allele and DRD2-Taq1 A1-allele at EOT ($OR_{DRD2C/T+T/T,DBHG/A+A/A} = 3.59$ (1.66–7.77) vs. $OR_{DRD2C/C,DBHG/G} = 1.41$ (0.87–2.28), $p = 0.04$). | - | 34 |
| COMT Dopamine metabolism | Val108/158Met (L/H) rs165688/rs6580 | 3-4× lower enzyme activity Met-allele (L-allele) | - Probability of smoking cessation with NRT (NS and TN combined) increases with the number of Met-alleles among EA women ($OR_{M/M,V/M} = 1.26$ (0.50–3.22), $OR_{V/V,M/M} = 3.23$ (1.13–9.20), $p = 0.03$). | - | 34 |
| | | | - No effect genotype on abstinence among AA women ($p = 0.98$). | - Higher frequency of Val/Val among abstinent smokers ($\chi^2 = 8.12, p = 0.02$). | 51 |
| | | | - Greater benefit of TN compared to placebo in Met/Met group (33% vs 12%) compared to individuals with ≥1 Val-allele (22% vs 16%) at EOT ($p = 0.05$). | - Higher frequency Val- vs Met-allele among abstinent smokers ($\chi^2 = 63.45, p = 0.00$). | 42 |
| | | | - Shorter times to relapse with the Val-allele compared to Met/Met (HR$_{V/V} = 1.33$ (1.11–1.59), $p = 0.002$; HR$_{V/M} = 1.47$ (1.19–1.82), $p < 0.001$). | - | 52 |
| rs737865      | Unknown | - | - | - | 51 |
| rs165599      | Higher activity with A-allele? | - | - | - | 51 |

**Competing interests:** declared in the article. Conflict of interests: none declared.

All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
| Gene function | Variant | Phenotype | Effect on treatment | References | Bupropion | References |
|---------------|---------|-----------|---------------------|------------|-----------|------------|
| 5-HTT Sero- | 5-HTTLPR (long | Higher transciptional activity for short form | - No effect genotype on treatment response at EOT (SL: $p = 0.53$; SS: $p = 0.54$) or 6mo (SL: $p = 0.89$; SS: $p = 0.40$). | 54 | - Higher abstinence rates with L-allele but sample size too small (SS: 37.1%; SL: 40.5%; LL: 66.7%). | 42 |
| tonin receptor | vs. short) | | - No effect genotype on treatment response at EOT (SL: $p = 0.47$; SS: $p = 0.59$) or wk24 (SL: $p = 0.48$; SS: $p = 0.46$). | 55 | - Increased abstinence rates compared to placebo with ≥1 L-allele compared to SS-genotype from EOT to 12mo (OR = 1.23 (1.06–1.43), $p < 0.01$). | 22 |
| STin2 (intron 2 VNTR) | Higher transcriptional activity 12-allele | | - No effect genotype on treatment response from EOT to 12mo ($p = 0.57$). | 22 |
| rs25531 | Higher transcriptional activity G-allele | | - No effect genotype on treatment response from EOT to 12mo ($p = 0.39$). | 22 |

**OPRM1** μ-opioid receptor (MOR)  
Asn40Asp/A118G  
rs1799971/rs1799971  
rs516720  
3× Increased binding affinity of β-endorphin Asp40 (G) allele  
- Higher abstinence with ≥1 Asp40-allele compared to Asn40/Asn40 at EOT (OR = 1.79 (1.05–3.06), $p = 0.03$); no effect at 6mo ($p = 0.34$); Significant in TN group (OR = 2.4 (1.14–5.06), $p = 0.02$); Not significant in NS group (OR = 1.28 (0.58–2.94), $p > 0.05$).  
- Possible lower abstinence rates with Asp40-allele when treated with placebo (OR = 0.75 (0.33–1.72), $p = 0.50$).  
- Effect genotype on abstinence with TN different compared to placebo (OR = 3.18 (1.05–9.63), $p = 0.04$).  
- Higher benefit from TN compared to placebo with Asn40/Asn40, but not with ≥1 Asp40-allele at EOT (OR = 0.47 (0.23–0.99), $p = 0.048$) only among men and reverse among women.  
- Higher cessation rates (TN and NS combined) with ≥1 Asp40-allele compared to Asn40/Asn40 at EOT (OR = 1.71 (1.05–2.80), $p = 0.032$) and at 6mo (OR = 2.60 (1.12–6.00), $p = 0.026$).  
- 56  
- 57  
- 58  

**Competing interests:** declared in the article. Conflict of interests: none declared.

All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
### Table 2 (Continued)

| Gene function | Variant | Phenotype | Effect on treatment |
|---------------|---------|-----------|---------------------|
| ARRB2         | rs1045280 | ?         | - Highly correlated (all $r > 0.96$). |
|               | rs2036657 | ?         | - High quit rates with OPRM1 Asp40-allele probably only maintained after 6mo among ARRB2 homozygous wild-type smokers (6mo: $p = 0.055$). |
|               | rs3786047 | ?         | - No interaction with OPRM1 Asn40Asp variant (all $p ≥ 0.18$). |
| HINT1         | rs3852209 | ?         | - Higher quit rates (TN and NS combined) with ≥1 C-allele vs A/A (EOT: OR = 1.46 (0.93–2.28), $p = 0.099$; 6mo: OR = 1.96 (1.6–3.34), $p = 0.013$). |
|               | rs2036657 | ?         | - No effect genotype on cessation rates or treatment response (all $p > 0.05$). |
| CYP2B6        | C1459T CYP2A6? | Lower brain levels carriers T-allele | - No differences in abstinence rates overall or after stratification for CYP2A6 metabolism for TN, NS, or combined at EOT and 6mo ($\chi^2 = 6.68, \ p = 0.01$; 6mo: $\chi^2 = 7.06, \ p = 0.008$). |
| Bupropion metabo- lapse Nicotine metabolism? (in the absence of functional CYP2A6?) | rs3211371 | ? | - Increased abstinence rates compared to placebo with *6 (EOT: $\chi^2 = 6.68, \ p = 0.01$; 6mo: $\chi^2 = 7.06, \ p = 0.008$). |
|               | rs3745274 | A785G (rs2279343) | - Does not improve outcome with normal bupropion metabolism (EOT: $p = 0.93$; 6mo: $p = 0.94$). |

| References | Bupropion | References |
|------------|-----------|------------|
| 58         |           |            |
| 58         |           |            |
| 59         |           |            |
| 38         |           |            |
| 60         |           |            |
| 29         |           |            |

1NM: normal metaboliser (100% activity); IM: intermediate metaboliser (75% activity), one *9A or one *12A; SM: slow metaboliser (<50% activity), one/two *2/*4 or two *9A and/or *12A.

3-HC: 3-hydroxycotinine; AA: African-American; COT: cotinine; EA: European-American; MD: mean difference (standard error); mo: month; NRT: nicotine replacement therapy; NS: nicotine spray; OR odds ratio (95%CI); TN: transdermal NRT (patches); Q1: 1st quartile; Q4: 4th quartile; wk: week; yr: year.
a role, but the nature of this association is not yet clear.

Thus it seems that several genetic variants in smoking- and treatment-related genes influence the efficacy of smoking cessation therapy and that these effects are often distinctive for the different forms of pharmacotherapy, especially when they have a different mechanism-of-action. Therefore, genotyping smokers before a cessation attempt may give directions in determining at forehand which treatment would be most effective for an individual smoker. In Figure 2 it is hypothesised how smoking cessation therapy might be genetically tailored based on the present knowledge. Smokers with variants resulting in a dopamine or serotonin deficiency (e.g. decreased synthesis, increased re-uptake or increased metabolism) seem to achieve better-quit rates with antidepressant therapies, such as bupropion and nortriptyline. On the other hand, smokers with an effective neurotransmitter response and nicotinic receptors (e.g. increased/normal number and activity receptors), and a decreased nicotine metabolism (determined primarily by CYP2A6 genotype) achieve better-quit rates with NRT. Since varenicline is a (partial) nicotinic receptor agonist, like NRT, it is expected to be more effective among smokers with genotypes associated with an effective neurotransmitter response and nicotinic receptors as well. However, differences in the metabolism or elimination of these drugs and pathways involved in their mechanism-of-action could make one drug within these categories (e.g. nicotinic receptor agonists and antidepressants) more effective than the other, or result in less side-effects in certain subgroups of smokers. For instance, bupropion has been found to be more effective in the presence of a high bupropion metabolism and high-expression nicotinic receptors, but nortriptyline among carriers of variants resulting in a low nortriptyline metabolism and differences in the acetylcholine pathway. Furthermore, since NRT has been found to be less effective among smokers with a high nicotine metabolism, varenicline might be indicated for these smokers. In contrast, since varenicline is eliminated

![Figure 2: Hypothetical model for genetically tailored smoking cessation therapy. NRT: nicotine replacement therapy; CYP2A6: cytochrome P450 2A6; CYP2B6: cytochrome P450 2B6; CYP2D6: cytochrome P450 2D6; OCT2: organic cation transporter 2; TN: transdermal nicotine patch; NS: nicotine nasal spray.](image)

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

For citation purposes: Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.
by the organic cation transporter 2 (OCT2), carriers of variants resulting in a high transporter activity might benefit more from NRT. Moreover, smokers carrying genetic polymorphisms associated with reduced nicotinic receptor (and possibly also dopaminergic) activity may experience greater benefits from the greater rewarding effects of NS, while smokers with increased activity variants in the MOR may have better success with the higher levels of nicotine delivered by TN.

Conclusion
Much progress has been made in unravelling the effect of genetic variants on smoking behaviour and smoking cessation treatment, and promising results have been found. It seems that several genetic variants in smoking-related (e.g., influencing the response to nicotine and influencing key neurotransmitter pathways activated by nicotine) and treatment-related (e.g., metabolism and/or secretion) genes influence the efficacy of smoking cessation therapy and that these effects are often distinctive for the different forms of pharmacotherapy, especially when they have a different mechanism-of-action. Therefore, genotyping smokers before a cessation attempt may give directions in determining at forehand which treatment would be the most effective for an individual smoker. However, much research still remains to be done before genetically tailored smoking cessation therapy can be implemented in standard clinical practice.

Firstly, and most importantly, although many genetic variants have been reported to influence smoking cessation rates using NRT or bupropion, most have not yet been replicated in other studies or inconsistent results have been found. Only a few genetic variants have been investigated in more than one trial, and only a very few variants have been investigated in more than two trials. Therefore, findings of the previous studies should be validated across independent trials and prospective studies should be set up to fully confirm the effect of the variants.

Secondly, multiple genes (and environmental factors) are likely to influence the response to smoking cessation therapies. However, so far most studies investigated only single genes. This approach will fail to fully determine the role of genetic variation in the individual susceptibility towards smoking cessation therapies. The commonly occurring alleles have only relatively small effect (ORs in the range of 1.1–2.0) and explain only a minor proportion of the observed phenotypic variance. Combinations of genetic variants have been found to have a significant effect even if the variants do not have an effect on their own. Thus it is important to investigate the combined effect of multiple genetic variants in smoking- and treatment-related genes. However, this will require larger scale genetic trials, of hundreds to thousands of participants, to achieve significant statistical power to evaluate these gene–gene and gene–environment interactions.

Thirdly, until now the pharmacogenetics of only a couple of smoking cessation therapies has been investigated extensively (e.g., NRT and bupropion). Newer compounds (e.g. varenicline), as well as current second-line medications for smoking cessation (e.g. nortriptyline), will also require investigation.

Fourthly, genetic associations with tolerability and side-effects should also be examined. It is likely that some individuals are predisposed to have unusual reactions to drugs due to the presence of certain genetic defects. Certain subgroups of individuals may also exist who respond well to certain medications that are normally not well tolerated. For instance, individuals with a high nicotine metabolism may benefit from high-dose nicotine patches without experiencing the generally occurring side-effects.

Fifthly, a marked racial/ethnic diversity exists in smoking behaviour (e.g., age of initiation, smoking rate, level of dependence) and in the frequency of functional polymorphisms. To date, the vast majority of studies have been conducted with Caucasians only to avoid population stratification. Thus, the effect of genetic variants in other racial/ethnic groups should be investigated as well.

Furthermore, some researches suggest that pharmacotherapies might work through different processes and/or are subject to different genetic influences in men and women. Therefore, the effect of genetic variations should be assessed for men and women separately.

And finally, several practical, policy and ethical considerations have to be addressed. Additional research should be conducted to examine the benefits, risks, and challenges of conveying genetic information about smoking predisposition to the patients, clinicians and the public. Economic analyses of the cost-effectiveness of using genotype information to tailor smoking treatment would also be necessary and appropriate legal and regulatory frameworks should be set up to ensure privacy and to protect against genetic discrimination.

In order to make it possible to implement genetically tailored smoking cessation therapy in general medical practice, future studies should thus investigate the effect of multiple susceptibility genes as well as their mutual interactions on several smoking cessation therapies in large-scale, comparable trials in different ethnic/racial and gender groups. Furthermore, prospective trials should be set up to fully confirm the effect of the variants. Finally, several practical, policy and ethical considerations will

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

For citation purposes: Quaak M, van Schooten FJ, van Schayck CP. Assessment of genetic variation as a predictor of smoking cessation success: a review. OA Epidemiology 2013 Jul 22;1(1):8.
have to be addressed. When these steps are taken, genetically tailored smoking cessation therapy will likely become available in general medical practice in the next decades, which will result in a more efficient use of anti-smoking therapies, increased cessation rates, and ultimately, in reduced morbidity and mortality deaths from smoking.

**Competing interests**
Quaak and Van Schooten declare no financial relationship with any organisations that might have an interest in the submitted work in the previous five years; Van Schayck has received financing (grant and/or travel/accommodation costs) from AstraZeneca, Boehringer Ingelheim and Pfizer, unrelated to this study.

**Funding**
School for Public Health and Primary Care (CAPHRI) and the Netherlands Organization for Health Research and Development (ZonMW), The Hague (50-50101-96-404).

**References**
1. Guindon GE, Boisclair D. Past, current and future trends in tobacco use. HNP discussion paper no. 6. Economics of tobacco control paper no. 6; 2003.
2. The World Bank. Curbing the epidemic: governments and the economics of tobacco control. Tob Control. 1999;8(2):196–201.
3. Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. Lancet. 2003 Sep 13;362(9387):847–52.
4. Mucha L, Stepheenson J, Morandi N, Dirani R. Meta-analysis of disease risk associated with smoking, by gender and intensity of smoking. Gend Med. 2006 Dec;3(4):279–91.
5. Taylor DH Jr, Hasselblad V, Henley SJ, Thun MJ, Sloan FA. Benefits of smoking cessation for longevity. Am J Public Health. 2002 Jun;92(6):990–6.
6. Quaak M, van Schayck CP, Knaapen AM, van Schooten FJ. Genetic variation as a predictor of smoking cessation success. A promising preventive and intervention tool for chronic respiratory diseases? Eur Respir J. 2009 Mar;33(3):468–80.
7. Quaak M, van Schayck CP, Knaapen AM, van Schooten FJ. Implications of gene–drug interactions in smoking cessation for improving the prevention of chronic degenerative diseases. Mutat Res. 2009 Jul 10;667(1,2):44–57.
8. Benowtiz NL. The biology of nicotine dependence: from the 1988 Surgeon General's Report to the present and into the future. Nicotine Tob Res. 1999;1(Suppl 2):S15–63.
9. Henningfield JE, Keenan RM. Nicotine delivery kinetics and abstinence liability. J Consult Clin Psychol. 1993 Oct;61(5):743–50.
10. Messina ES, Tyndale RF, Sellers EM. A major role for CYP2A6 in nicotine C-oxidation by human liver microsomes. J Pharmacol Exp Ther. 1997 Sep;282(3):1608–14.
11. Balfour DJ. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens [corrected]. Nicotine Tob Res. 2004 Dec;6(6):899–912.
12. Mansvelder HD, McGhee DS. Cellular and synaptic mechanisms of nicotine addiction. J Neurobiol. 2002 Dec;53:606–17.
13. Ribeiro EB, Bettiker RL, Bogdanov M, Wurtman RJ. Effects of systemic nicotine on serotonin release in rat brain. Brain Res. 1993 Sep 10;621(2):311–8.
14. Hu S, Brody CL, Fisher C, Gunzerath L, Nelson ML, Sabol SZ, et al. Interaction between the serotonin transporter gene and neuroticism in cigarette smoking behavior. Mol Psychiatry. 2000 Mar;5(2):181–8.
15. Lerman C, Caporaso NE, Audrain J, Main D, Boyd NR, Shields PG. Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependence. Mol Psychiatry. 2000 Mar;5(2):189–92.
16. True WR, Heath AC, Scherrer JF, Waterman B, Goldberg J, Lin N, et al. Genetic and environmental contributions to smoking. Addiction. 1997 Oct;92(10):1277–87.
17. Sullivan PM, Kendler K. The genetic epidemiology of smoking. Nicotine Tob Res. 1999;1(Suppl 2):S51–7.
18. Batra V, Patkar AA, Berrettini WH, Weinstein SP, Klein DL. The genetic determinants of smoking. Chest. 2003 May;123(5):1730–9.
19. Xian H, Scherrer JF, Madden PA, Lyons MJ, Tsuang M, True WR, et al. The heritability of failed smoking cessation and nicotine withdrawal in twins who smoked and attempted to quit. Nicotine Tob Res. 2003 Apr;5(2):245–54.
20. Berrettini WH, Doyle GA. The CHR-NAS-A3-B4 gene cluster in nicotine addiction. Mol Psychiatry. 2012 Sep;17(9):856–66.
21. Quaak M. Assessment of genetic variation as a predictor of smoking cessation success: a promising preventive and intervention tool? 2012.
22. Quaak M, van Schayck CP, Postma DS, Wagena EJ, van Schooten FJ. Genetic variants in the serotonin transporter influence the efficacy of bupropion and nortriptyline in smoking cessation. Addiction. 2012 Jan;107(1):178–87.
23. Lerman C, Tyndale RF, Patterson F, Wileyto EP, Shields PG, Pinto A, et al. Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. Clin Pharmacol Ther. 2006 Jun;79(6):600–8.
24. Patterson F, Schnoll RA, Wileyto EP, Pinto A, Epstein LH, Shields PG, et al. Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. Clin Pharmacol Ther. 2008 Sep;84(3):320–5.
25. Ozaki S, Oyama T, Isse T, Kagawa N, Uramoto H, Sugio K, et al. Smoking cessation program and CYP2A6 polymorphism. Front Biosci. 2006 Sep 11;11:2590–7.
26. Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N, Lerman C. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: a validation study. Pharmacol Biochem Behav. 2009 Mar;92(1):6–11.
27. Lerman C, Jepson C, Wileyto EP, Patterson F, Schnoll R, Morezwiej M, et al. Genetic variation in nicotine metabolism predicts the efficacy of extended-duration transdermal nicotine therapy. Clin Pharmacol Ther. 2010 May;87(5):553–7.
28. Malaiyandi V, Lerman C, Benowitz NL, Jepson C, Patterson F, Tyndale RF. Impact of CYP2A6 genotype on pretreatment smoking behavior and nicotine levels from and usage of nicotine replacement therapy. Mol Psychiatry. 2006 Apr;11(4):400–9.
29. Lee AM, Jepson C, Hoffmann E, Epstein L, Hawk LW, Lerman C, et al. CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial.
Critical review

Biol Psychiatry. 2007 Sep 15;62(6): 635–41.
30. Hutchison KE, Allen DL, Filbey FM, Jepson C, Lerman C, Benowitz NL, et al. CHRNA4 and tobacco dependence: from gene regulation to treatment outcome. Arch Gen Psychiatry. 2007 Sep;64(9):1078–86.
31. Spruell T, Calavita G, Donegan T, Egawhary M, Hurley M, Aveyard P, et al. Association between nicotinic acetylcholine receptor single nucleotide polymorphisms and smoking cessation. Nicotine Tob Res. 2012 Aug;14(8):993–7.
32. Perkins KA, Lerman C, Mercincavage M, Fonte CA, Briski JL. Nicotinic acetylcholine receptor beta2 subunit (CHRN2B) gene and short-term ability to quit smoking in response to nicotine patch. Cancer Epidemiol Biomarkers Prev. 2009 Oct;18(10):2608–12.
33. Conti DV, Lee W, Li D, Liu J, Van Den Berg D, Thomas PD, et al. Nicotinic acetylcholine receptor beta2 subunit gene implicated in a systems-based candidate gene study of smoking cessation. Human molecular genetics. 2008 Sep 15;17(18):2834–48.
34. Johnstone EC, Yudkin PL, Hey K, Roberts SJ, Welch SJ, Murphy MF, et al. Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. Pharmacogenetics. 2004 Feb;14(2):83–90.
35. David SP, Naura R, Papandonatos GD, Shadel WG, Burgholder GJ, Britt DM, et al. Does the DRD2-Taq1 A polymorphism influence treatment response to bupropion hydrochloride for reduction of the nicotine withdrawal syndrome? Nicotine Tob Res. 2003 Dec;5(6):935–42.
36. Swan GE, Valdes AM, Ring HZ, Khroyan TV, Jack LM, Ton CC, et al. Dopamine receptor DRD2 genotype and smoking cessation outcome following treatment with bupropion SR. Pharmacogenomics J. 2005;5(1):21–9.
37. Yudkin P, Munafò M, Hey K, Roberts S, Welch S, Johnstone E, et al. Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial. BMJ. 2004 Apr 24;328(7446):989–90.
38. David SP, Brown RA, Papandonatos GD, Kahler CW, Lloyd-Richardson EE, Munafò MR, et al. Pharmacogenetic clinical trial of sustained-release bupropion for smoking cessation. Nicotine Tob Res. 2007 Aug;9(8):821–33.
39. Munafò MR, Johnston EC, Murphy MF, Aveyard P. Lack of association of DRD2 rs1800497 (Taq1A) polymorphism with smoking cessation in a nicotine replacement therapy randomized trial. Nicotine Tob Res. 2009 Apr;11(4):404–7.
40. David SP, Strong DR, Munafò MR, Brown RA, Lloyd-Richardson EE, Wileyto PE, et al. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. Nicotine Tob Res. 2007 Dec;9(12):251–7.
41. Stapleton JA, Sutherland G, O’Gara C, Spirling LJ, Ball D. Association between DRD2/ANKK1 Taq1A genotypes, depression and smoking cessation with nicotine replacement therapy. Pharmacogenomics. 2011 Aug;21(8):447–53.
42. Han DH, Joe KH, Na C, Lee YS. Effect of genetic polymorphisms on smoking cessation: a trial of bupropion in Korean male smokers. Psychiatr Genet. 2008 Feb;18(1):11–6.
43. Lerman C, Jepson C, Wileyto EP, Epstein LH, Rukshtalis M, Patterson E, et al. Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. Neuropsychopharmacology. 2006 Jan;31(1):231–42.
44. Dahl JP, Jepson C, Lervenson R, Wileyto EP, Patterson F, Berrettini WH, et al. Interaction between variation in the D2 dopamine receptor (DRD2) and the neuronal calcium sensor-1 (FREQ) genes in predicting response to nicotine replacement therapy for tobacco dependence. Pharmacogenomics J. 2006 May-Jun;6(3):194–9.
45. David SP, Munafò MR, Murphy MF, Proctor M, Walton RT, Johnstone EC. Genetic variation in the dopamine D4 receptor (DRD4) gene and smoking cessation: follow-up of a randomised clinical trial of transdermal nicotine patch. Pharmacogenomics J. 2008 Apr;8(2):122–8.
46. Munafò MR, Murphy MFG, Johnstone EC. Smoking cessation, weight gain, and DRD4-521 genotype. Am J Med Genet B. 2006 Jun 5;141B(4):398–402.
47. Lerman C, Shields PG, Wileyto EP, Audrain J, Hawk LH Jr, Pinto A, et al. Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. Health Psychol. 2003 Sep;22(5):541–8.
48. O’Gara C, Stapleton J, Sutherland G, Guindalini C, Neale B, Breen G, et al. Dopamine transporter polymorphisms are associated with short-term response to smoking cessation treatment. Pharmacogenet Genomics. 2007 Jan;17(1):61–7.
49. Swan GE, Jack LM, Valdes AM, Ring HZ, Ton CC, Curry SJ, et al. Joint effect of dopaminergic genes on likelihood of smoking following treatment with bupropion SR. Health Psychol. 2007 May;26(3):361–8.
50. Collilla S, Lerman C, Shields PG, Jepson C, Rukshtalis M, Berlin J, et al. Association of catechol-O-methyltransferase with smoking cessation in two independent studies of women. Pharmacogenet Genomics. 2005 Jun;15(6):393–8.
51. Berrettini WH, Wileyto EP, Epstein L, Restine S, Hawk L, Shields P, et al. Catechol-O-methyltransferase (COMT) gene variants predict response to bupropion therapy for tobacco dependence. Biol Psychiatry. 2007 Jan;61(1):111–8.
52. Johnstone EC, Elliot KM, David SP, Murphy MF, Walton RT, Munafò MR. Association of COMT Val108/158Met genotype with smoking cessation in a nicotine replacement therapy randomized trial. Cancer Epidemiol Biomarkers Prev. 2007 Jun;16(6):1065–9.
53. Munafò MR, Johnstone EC, Guo B, Murphy MF, Aveyard P. Association of COMT Val108/158Met genotype with smoking cessation. Pharmacogenomics. 2008 Feb;18(2):121–8.
54. Munafò MR, Johnstone EC, Wileyto EP, Shields PG, Elliot KM, Lerman C. Lack of association of 5-HTTLPR genotype with smoking cessation in a nicotine replacement therapy randomized trial. Cancer Epidemiol Biomarkers Prev. 2006 Feb;15(2):399–400.
55. David SP, Munafò MR, Murphy MFG, Walton RT, Johnstone EC. The serotonin transporter 5-HTTLPR polymorphism and treatment response to nicotine patch: follow-up of a randomised controlled trial. Nicotine Tob Res. 2007 Feb;9(2):225–31.
56. Lerman C, Wileyto EP, Patterson F, Rukshtalis M, Audrain-McGovern J, Restine S, et al. The functional mu opioid receptor (OPRM1) Asn40Asp variant predicts short-term response to nicotine replacement therapy in a clinical trial. Pharmacogenomics J. 2004;4(3):184–92.
57. Munafò MR, Elliot KM, Murphy MF, Walton RT, Johnstone EC. Association of the mu-opioid receptor gene with smoking cessation. Pharmacogenomics J. 2007 Oct;7(5):353–61.
58. Ray R, Jepson C, Wileyto EP, Dahl J, Patterson F, Rukstalis M, et al. Genetic variation in mu-opioid-receptor-interacting proteins and smoking cessation in a nicotine replacement therapy trial. Nicotine Tob Res. 2007 Nov;9(11):1237–41.
59. Lerman C, Shields PG, Wileyto EP, Audrain J, Pinto A, Hawk L, et al. Pharmacogenetic investigation of smoking cessation treatment. Pharmacogenetics. 2002 Nov;12(8):627–34.
60. Lee AM, Jepson C, Shields PG, Benowitz N, Lerman C, Tyndale RF. CYP2B6 genotype does not alter nicotine metabolism, plasma levels, or abstinence with nicotine replacement therapy. Cancer Epidemiol Biomarkers Prev. 2007 Jun;16(6):1312–4.