Nicotine clearance: genetic and environmental influences

The renal clearances of nicotine and cotinine, its proximate metabolite, vary considerably between individuals. This twin study looked at the influences of genetic and environmental factors on renal clearance.

One hundred and ten monozygotic and 29 dizygotic healthy twin pairs with a mean age of 37.7 years were recruited. The group was predominantly female (69.9%) and Caucasian (76.1%). An intravenous infusion of deuterium-labelled nicotine and cotinine was administered after an overnight fast. In smokers, the dose was dependent upon their plasma cotinine concentration. Blood samples were taken at intervals and urine was collected over 8 h. These compounds demonstrate minimal protein binding, so their glomerular filtration was estimated by the glomerular filtration rate (GFR).

Analysis using twin methods revealed the presence of non-additive genetic effects on GFR and net secretory/reabsorptive clearance. Additive genetic effects seemed to be more important in the renal clearance of cotinine. The study was not powered sufficiently to allow biometric models to separate additive genetic effects from non-additive genetic effects and shared environmental factors.

Renal clearance comprises passive glomerular filtration/reabsorption, previously shown to be largely under environmental control, and active secretion which has been found to be heritable. This study showed that, at uncontrolled urine pH, there was net reabsorption of both compounds in most subjects. Therefore, there may be an overriding genetically-controlled active secretory process despite net reabsorption or, in this case, reabsorption may be genetically influenced. Furthermore, the results suggest that nicotine and cotinine are cleared in slightly different ways and are likely to be influenced by different factors.

Future studies to determine the factors influencing renal drug clearance may make it possible to individualise drug prescribing, increasing effectiveness and safety.

► Benowitz NL, Lessov-Schlaggar CN, *et al*. Genetic influences in the variation in renal clearance of nicotine and cotinine. *Clin Pharmacol Ther* 2008;**84**:243–7.

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Mutations in the LKBI tumour suppressor gene linked to non-small cell lung cancer in Caucasians

Lung cancer remains the most common cause of cancer-related death in the UK. However, patients with non-small cell lung cancer (NSCLC) may benefit from surgery or radiotherapy, providing a cure in a small proportion. Mutations in the LKBI tumour suppressor gene have been found in several human cancers including NSCLC. This study explores the incidence of LKBI mutations in patients with NSCLC, the frequency in different ethnic groups and associations with other clinicopathological characteristics (sex, smoking, tumour stage, histology and outcome).

Tumour tissue collected from 310 patients at curative surgical resections was screened for LKBI mutations. These were present in 11% of the tumours, which was more than other common solid malignancies (0–4%). Mutations were more prevalent in the Caucasian group (17%) than the Asian group (5%), with an association between smoking (>10 pack-years) and the presence of mutations. Despite this, the study fails to address fully the fact that smokers were predominantly Caucasian, confounding the ethnic divide. Surprisingly, LKBI mutations were more common in adenocarcinomas (13%) as, histologically, this is the most frequent lung cancer in non-smokers. Statistically, LKBI mutation status was not found to affect outcomes in patients with stage I and II NSCLC treated with surgery alone, although the study showed shorter survival rates.

The complexity of this study and numerous influencing factors highlight the multifactorial aetiology of NSCLC and an important genetic link, raising the question whether genetic screening in the future could help detect those at risk of developing a potentially curable cancer.

► Koivunen JP, Kim J, Lee J, *et al*. Mutations in the LKBI tumour suppressor are frequently detected in tumours from Caucasian but not Asian lung cancer patients. *Br J Cancer* 2008;**99**:245–52.

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PF-3512676 may enhance the clinical activity of taxane/platinum chemotherapy in advanced non-small cell lung cancer

Current first-line therapy for stage IIIB–IV non-small-cell lung cancer (NSCLC) is taxane plus platinum-based chemotherapy. With this regime the 1-year survival rate is less than 40%. Toll-like receptors (TLR) can stimulate innate and antigen-specific acquired immunity. PF-3512676 is a TLR9-activating oligodeoxynucleotide and has confirmed antitumour activity against a variety of cancers.

This randomised phase II study examined the safety and antitumour action of the combination of PF-3512676 and taxane/platinum chemotherapy in stage IIIB–IV NSCLC. One hundred and twelve patients were included from 26 centres. All patients had adequate blood counts, renal and hepatic function and had received no previous chemotherapy. Patients with autoimmune diseases or brain metastasis were excluded.