

# Role of Cytochrome P450 Polymorphisms in the Development of Pulmonary Drug Toxicity

## A Case-Control Study in the Netherlands

*Petal A.H.M. Wijnen*<sup>1,2</sup> *Marjolein Drent*<sup>2,3</sup> *Patty J. Nelemans*<sup>4</sup>  
*Petra M.J.C. Kuijpers*<sup>2,5</sup> *Ger H. Koek*<sup>2,6</sup> *Cees Neef*<sup>2,7</sup> *Guido R.M.M. Haenen*<sup>2,7</sup> and  
*Otto Bekers*<sup>1,2</sup>

- 1 Department of Clinical Chemistry, Maastricht University Medical Centre, Maastricht, the Netherlands
- 2 Ild care center, Maastricht University Medical Centre, Maastricht, the Netherlands
- 3 Department of Respiratory Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
- 4 Department of Epidemiology, University Maastricht, Maastricht, the Netherlands
- 5 Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands
- 6 Department of Gastroenterology/Hepatology, Maastricht University Medical Centre, Maastricht, the Netherlands
- 7 Department of Pharmacology and Toxicology, University Maastricht, Maastricht, the Netherlands

### Abstract

**Background:** Drug-induced pulmonary toxicity is a serious and expanding problem with often unknown aetiology. Many drugs are metabolized by cytochrome P450 (CYP) enzymes.

**Objective:** To establish whether allelic variation in *CYP* polymorphic genes contributes to variability in drug response and unexpected toxicity.

**Methods:** A case-control study was conducted. The cases consisted of patients with drug-induced interstitial lung disease (DI-ILD; n = 59). Two control groups were used: one group of healthy volunteers (n = 173) and one group of patients with idiopathic pulmonary fibrosis (IPF; n = 110).

**Results:** Of the patients with DI-ILD 91.5% (54/59) had at least one of the studied variant genes compared with 70.5% (122/173, p < 0.001) of the healthy volunteers and 69.1% (76/110, p < 0.001) of the IPF patients. The percentage of individuals with one or more variant *CYP* genes was higher in the DI-ILD group. Odds ratios were significantly increased and ranged from 3.25 to 40.8, indicating a significant association between the development of DI-ILD and the presence of one or more variant *CYP* genes.

**Conclusion:** DI-ILD appeared to be associated with the presence of at least one variant *CYP* allele. This study supports the potential usefulness of personalized medicine by genotyping aiming to improve efficacy, tolerability and drug safety.

## Background

One may view the lung as bathed in two dissimilar environments: inhaled air and circulating blood. Both can carry noxious substances that may inflict damage to the lung. Air can deliver noxious particles and blood is the main supplier of most drugs, independent of the route of administration, and adverse respiratory reactions may follow by the most unlikely routes. Drugs can induce specific respiratory reactions, or the lungs may be affected as part of a generalized response. The most common form of drug-induced respiratory disease is diffuse interstitial lung disease (ILD). The drugs involved not only comprise prescribed and over-the-counter drugs, but also illicit drugs, herbs, alcohol and ingredients of the diet. The list of compounds involved has grown rapidly over the last decades.<sup>[1,2]</sup> Although drugs have been unequivocally identified as the cause in only a limited number of cases, it is important to acknowledge the potential role of medication in the development of ILD. This is due to the severity of the potentially irreversible damage to the lungs and the improvement that is often easily brought about by stopping administration of the drug involved.

The diagnosis of drug-induced ILD (DI-ILD) primarily rests on the link between drug intake and the subsequent development of respiratory symptoms. In some cases, the evidence that reactions in the lung are drug-induced is circumstantial. A straightforward interpretation is hampered when the damage is irreversible or when the symptoms are aggravated after stopping drug administration. Re-challenging the patient with the drug involved is frequently unethical and dangerous. Sensitive and specific tests are lacking. The key to diagnosis is a

high clinical acuity.<sup>[2]</sup> All medication needs to be recorded and reviewed meticulously.

The molecular mechanism involved in the development of DI-ILD is still enigmatic. Inflammation initiated by drugs, drug metabolites or drug-induced free radical generation processes has been implicated.<sup>[3]</sup> There is also emerging evidence for a role of genetic factors in the development of ILD such as differences in gene expression profiles between idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis.<sup>[4,5]</sup>

Cytochrome P450 (CYP) single nucleotide polymorphisms (SNPs) are one of the key factors known to cause variation in drug response between individuals.<sup>[3,6-9]</sup> CYP is a super family of microsomal enzymes that metabolize various endogenous compounds and xenobiotics, including most drugs. Through CYP metabolism the chemical structure of drugs is changed, in general facilitating elimination of the drug from the body.<sup>[3,7]</sup>

The risk for development of DI-ILD and clinical patterns vary depending on a variety of host and drug factors.<sup>[2]</sup> Several different phase I xenobiotic-metabolizing CYP and phase II enzymes (i.e. conjugation enzymes including several transferases) are present in the human lung, possibly contributing to *in situ* activation.<sup>[10-14]</sup> Metabolism also affects the biological activity of the drug. The biological activity of the parent drug is usually superior to that of the metabolite, but there are several exceptions. Sometimes CYP metabolism yields very toxic metabolites, for example, with paracetamol (acetaminophen), benzo[a]pyrene and carbamazepine.<sup>[14]</sup> Occasionally, drugs may cause the formation of reactive oxygen species by uncoupling of the electron transport of the CYP system.<sup>[15]</sup> These metabolites or

reactive oxygen species may damage vital cellular components, such as proteins, lipids or DNA.<sup>[16]</sup> This might be the cause of clinically relevant, drug-induced pulmonary toxicity.<sup>[12,17,18]</sup>

Recently, we reported two cases of patients with interstitial pneumonia who developed cardiac failure following treatment with venlafaxine.<sup>[19]</sup> In both cases, a strong relationship between the development of the patients' illness and the initiation of venlafaxine treatment was identified. Furthermore, members of the CYP family are involved in the metabolism of venlafaxine. Therefore, we hypothesized that genetically or environmentally induced inter-individual differences in the expression of pulmonary biotransformation enzymes such as CYP may form the basis for, or contribute to, the risk of DI-ILD.<sup>[2,10,13,14]</sup>

The aim of this study was to establish whether variation in *CYP* genes contributes to variability in individual drug response and toxicity. Therefore, the presence of the most clinically relevant variants of *CYP* genes (*CYP2D6*, *CYP2C9* and *CYP2C19* variants) was compared in a population of patients with DI-ILD with the presence of these variant genes in a population of patients with IPF and one of healthy volunteers.

## Methods

### Setting and Study Population

The study was conducted as a case-control study. Between 2002 and 2006, 575 bronchoalveolar lavages (BAL) were performed on patients referred to the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC), Maastricht, the Netherlands, suspected of a non-infectious or infectious disorder. Of these 575 cases, 51.1% appeared to have an infectious disorder, 17.8% had diffuse alveolar haemorrhage and 31.1% an ILD. Of this latter group, 59 (10.2%) met the criteria of DI-ILD. All of the 59 patients were Cau-

casian, used multiple drugs for various indications and did not have a history of any pulmonary disorder. The clinical presentation of drug-induced pulmonary toxicity varied. Besides pulmonary symptoms, some patients (n = 7; 12%) showed signs of other toxicities such as skin, cardiac and gastrointestinal involvement. The diagnosis of DI-ILD was established by clinical presentation including dyspnoea and hypoxia, diffuse interstitial features on chest x-ray and a high-resolution CT scan as well as a BAL fluid (BALF) profile compatible with DI-ILD, excluding an infectious cause.<sup>[2,20,21]</sup> A lung biopsy was performed in 20% (n = 12) of the patients. Clinical records were reviewed carefully and present and past drug use was documented. After reviewing the drug use of all DI-ILD patients, the most important groups appeared to be antihypertensive medication,  $\beta$ -adrenergic receptor antagonists, anti-arrhythmic agents, antidepressants and anticoagulants. Every DI-ILD patient used a combination of at least two or more of these drugs. Withdrawal of the suspected causative drug(s) led to a favourable outcome in 75% of the patients, including an improvement of the respiratory symptoms, lung function test results, especially the diffusing capacity, and chest x-ray abnormalities. In 25% of patients the damage was irreversible. Subjects were genotyped retrospectively for *CYP* polymorphisms and the drug(s) which are metabolized by the CYP enzymes that show genetic polymorphisms were identified.

The first control group consisted of 173 healthy Caucasian volunteers, recruited for method validation, who did not use medication nor had any relevant medical history, especially no history of pulmonary complaints.<sup>[22]</sup> All healthy volunteers were hospital employees. This healthy volunteer control group was also used to establish the distribution of allele variants in the general population.

The second control group consisted of 110 Caucasian patients with IPF, known at our out-patient clinic and collected during the timeframe of this

study, who also used medication for various indications. This group was selected as a control group, for it was expected that drug use did not play a substantial role in the pathogenesis of this disease. The diagnosis of IPF was based on consistent clinical features, radiographic findings and BALF analysis results. According to the international consensus, a biopsy was obtained from 50% of the IPF group, which confirmed the diagnosis histologically as being usual interstitial pneumonia.<sup>[23]</sup> Clinical records were reviewed carefully and present and past drug use was documented. All IPF patients used one or more drug(s). For the DI-ILD group as well as for the IPF group it was checked whether the drugs used were metabolized by polymorphic CYP enzymes. The study was performed in accordance with the Declaration of Helsinki and its amendments. The protocol was approved by the local Medical Ethics Board of the MUMC. Written informed consent for participation in this study was obtained from all patients.

### Genotyping

DNA was obtained from all subjects by using venous EDTA anti-coagulated blood and isolating with a High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions.

In this study, genotyping was carried out for the following CYP allelic variants: *CYP2C9*\*2 C430T/\*3 A1075C, *CYP2C19*\*2 G681A/\*3 G636A and *CYP2D6*\*3 2549delA/\*4 G1846A. For genotyping the *CYP2C9*\*1,\*2,\*3 and *CYP2C19*\*1,\*2,\*3 SNPs, real-time PCR Fluorescence Resonance Energy Transfer (FRET) assays (TIB MOLBIOL, Berlin, Germany) were performed using the *CYP2C9* and *CYP2C19* Mutation Detection Kits (Roche Diagnostics, Mannheim, Germany). The *CYP2D6*\*1,\*3 and \*4 SNPs were genotyped using FRET assays as described by Stamer et al.<sup>[24]</sup> and Muller et al.<sup>[25]</sup> on

the LightCycler® (Roche Diagnostics, Mannheim, Germany).

### Statistical Analysis

Statistical analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA) for Windows. In order to evaluate the association between the presence of pulmonary disease and the presence of CYP polymorphisms, odds ratios (ORs) with corresponding 95% confidence intervals were calculated. Actual allele distributions were compared against the expected frequencies calculated, using the Hardy-Weinberg equilibrium. Deviations from the Hardy-Weinberg equilibrium were analysed using the chi-square test. A p-value of <0.05 (two sided) was considered to indicate statistical significance. A Bonferroni correction, to adjust for multiple comparisons, was applied where it was appropriate (p < 0.01, indicating statistical significance).

### Results

A summary of the characteristics of the DI-ILD, IPF and healthy volunteer populations is shown in table I.

The subjects in the healthy volunteers group were younger than the subjects in the other two populations and used no medication. The age difference had no influence on the distribution of genetically variant genes; however, it does indicate that (multiple) drug use increases with age. The IPF control patients did use (multiple) drugs, but to a lesser extent than the DI-ILD patients. Table I also shows that of the patients in the DI-ILD group, substantially larger percentages were receiving drugs that are metabolized by a polymorphic CYP enzyme system. For example, of the 43 patients who received a drug that should be metabolized by CYP2D6, 73% had a genetic polymorphism that would be likely to influence their ability to metabolize drugs efficiently.

The percentages of individuals having one of the studied individual polymorphisms (*CYP2D6*,

**Table I.** Baseline characteristics of the drug-induced interstitial lung disease (DI-ILD), idiopathic pulmonary fibrosis (IPF) and healthy volunteer (HV) populations

Characteristic	DI-ILD	IPF	HV
Subjects (no.)	59	110	173
Male/female (no.)	28/31	62/48	78/95
Age (mean/range [y])	65.4/21–87	63.3/27–89	38.5/19–59
Percentages of above populations taking one or more drugs metabolized by CYP polymorphic enzymes:			
CYP2D6	73	18	0
CYP2C9	52	19	0
CYP2C19	88	17	0

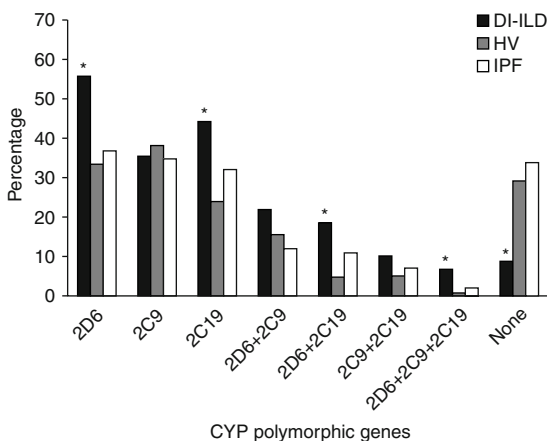
CYP = cytochrome P450.

*CYP2C9* and *CYP2C19*) or combinations in the DI-ILD, healthy volunteer and IPF control patient groups, respectively, are shown in figure 1.

The genotype distribution for the three groups in this study showed that all results were generally consistent with the Hardy-Weinberg equilibrium (table II, upper panel, expected values not shown).<sup>[26–29]</sup> One exception was the *CYP2D6* polymorphism of the healthy volunteer group, in which a small but significant deviation from the Hardy-Weinberg equilibrium was observed ( $p < 0.01$ ). Fewer heterozygotes (45 actually present in the healthy volunteer group vs 56 expected, calculated using the Hardy-Weinberg equilibrium) and more

homozygotes (13 vs 7) were found. However, the allele frequencies in both control groups (healthy volunteers and IPF patients) were comparable with those in the reference populations from the literature (table II, lower panel).<sup>[26,27,29]</sup>

Table III presents the results from the analyses that compared the proportions of persons with one or more variant genes that express the polymorphic CYP enzymes between DI-ILD patients and both control groups. The proportion of persons without any allelic variants was only 8.5% among DI-ILD patients versus 30.9% and 29.5% in IPF patients and healthy volunteers. Furthermore, it appeared that there was a higher prevalence of combinations of variant genes within the DI-ILD patients compared with the IPF patients and healthy volunteers (table III, upper panel). Subjects without any *CYP* variant genes within the DI-ILD group and healthy volunteer group were used as a reference group for the calculation of ORs associated with the presence of one or more of the studied genetic polymorphisms. Strong and significant associations were found comparing the prevalence of *CYP2D6* and *CYP2C19* genetic variants in DI-ILD patients with those of the healthy volunteers. The ORs calculated were 5.80 (95% CI 2.17, 15.4;  $p < 0.001$ ) for *CYP2D6*, 3.25 (95% CI 1.18, 8.86;  $p = 0.026$ ) for *CYP2C9* and 6.47 (95% CI 2.35, 17.7;  $p < 0.001$ ) for *CYP2C19*, respectively (table III). For the combined genotypes with variant *CYP* alleles, significant ORs were found of 4.91, 14.0, 6.80 and 40.8 (table III).



**Fig. 1.** Percentage of individual and combinations of cytochrome P450 (*CYP*) polymorphic genes in individuals with drug-induced interstitial lung disease (DI-ILD,  $n = 59$ ), idiopathic pulmonary fibrosis (IPF,  $n = 110$ ) and healthy volunteer (HV,  $n = 173$ ) groups. \*  $p < 0.05$ .

**Table II.** Genotype distributions and allele frequencies of cytochrome P450 (CYP) isoforms

Population <sup>a</sup>	2D6				2C9				2C19			
	DI-ILD	IPF	HV	C	DI-ILD	IPF	HV	C	DI-ILD	IPF	HV	C
No.	59	110	173	765	59	110	173	121	59	110	173	736
Wild type <sup>b</sup> [n (%)]	26 (44.1)	73 (66.4)	115 (66.4)	490 (64.2)	38 (64.4)	75 (68.2)	107 (61.8)	82 (67.8)	33 (55.9)	78 (70.9)	132 (76.3)	554 (75.3)
Heterozygous <sup>c</sup> [n (%)]	26 (44.1)	30 (27.3)	45 (26.0)	233 (30.3)	17 (28.8)	33 (30.0)	62 (35.8)	36 (29.8)	22 (37.3)	26 (23.6)	35 (20.2)	163 (22.1)
Homozygous <sup>d</sup> [n (%)]	7 (11.9)	7 (6.4)	13 (7.5)	42 (5.5)	4 (6.8)	2 (1.8)	4 (2.3)	3 (2.5)	4 (6.8)	6 (5.5)	6 (3.5)	19 (2.6)
Allele (%)												
*1	66.1	80.0	79.5	79.3	78.8	83.2	79.8	82.2	74.6	82.7	86.4	86.5
*2	NA	NA	NA	NA	12.7	8.2	13.9	10.0	25.4	17.3	13.6	13.3
*3	5.1	1.4	1.4	1.8	8.5	8.6	6.4	7.4	0	0	0	0.2
*4	28.8	18.6	19.1	18.4	NA	NA	NA	NA	NA	NA	NA	NA

<sup>a</sup> CYP2D6, CYP2C9 and CYP2C19 genetic polymorphisms in DI-ILD patients (n = 59), IPF control patients (n = 110), healthy volunteers (n = 173) and C populations as a. as reference. For CYP2D6 and CYP2C19, allele frequencies from Tamminga et al.<sup>[26]</sup> and Sachse et al.<sup>[29]</sup> were used and for CYP2C9, allele frequencies from Allabi et al.<sup>[27]</sup> were used.

<sup>b</sup> Wild type (fully functional enzyme).

<sup>c</sup> Heterozygote variant (partially functional enzyme).

<sup>d</sup> Homozygote variant (severely compromised or non-functional enzyme).

**C** = Caucasian populations from literature; **DI-ILD** = drug-induced interstitial lung disease; **HV** = healthy volunteers; **IPF** = idiopathic pulmonary fibrosis; **NA** = not applicable.

Similar results were found comparing the prevalence of variant CYP genes in DI-ILD patients with the IPF control patients. These analyses, as shown in table III, also resulted in significant associations between the development of DI-ILD and the presence of CYP genetic variants.

The percentage of DI-ILD patients having a CYP variant gene and receiving one or more drug(s) metabolized by a polymorphic CYP enzyme was 87% (47/54), compared with only 16% (12/76) of the IPF patients.

Table IV lists the (suspected) causative drugs, the CYP enzymes involved in the metabolism of the mentioned drugs, the number of DI-ILD patients involved (with and without variant CYP genes) and also shows which of the variant forms of CYP genes were found. The last column lists the number of literature references mentioned on www.pneumotox.com concerning the stated causative drug in relation to lung disease.

### Discussion

To the best of our knowledge, this is the first study indicating that DI-ILD may be attributable to a reduced metabolic capacity by CYP enzymes. According to our results, there seems to be an association between having one or more CYP genetic variants that may lead to reduced metabolism, receiving drugs that are metabolized inadequately by the affected system and the development of DI-ILD. Looking at the ORs, ranging from 3.25 to 40.8, patients with variant CYP enzymes appear to be at a substantially greater risk of developing a DI-ILD when prescribed multiple drugs. These findings strengthened our presumption that inadequate drug metabolism predisposes an individual for the development of DI-ILD. In 91.5% of the studied DI-ILD patients at least one CYP variant gene was present, whereas this percentage was about 70% in the control populations. In the DI-ILD group the prevalence of having more than one CYP variant gene was also



**Table III.** Comparison of the percentages of subjects with one or more variant cytochrome P450 (CYP) genes between drug-induced interstitial lung disease (DI-ILD) patients (n = 59), healthy volunteers (HV) [n = 173] and idiopathic pulmonary fibrosis (IPF) control patients (n = 110), using individuals without any CYP variants as a reference group

CYP gene	2D6	2C9	2C19	2D6+2C9	2D6+2C19	2C9+2C19	2D6+2C9+2C19	None
DI-ILD [no. (%)]	33 (55.9)	21 (35.6)	26 (44.1)	13 (22.0)	11 (18.6)	6 (10.2)	4 (6.8)	5 (8.5)
IPF [no. (%)]	37 (33.6)	35 (31.8)	32 (29.1)	12 (10.9)	11 (10.0)	7 (6.4)	2 (1.8)	34 (30.9)
HV [no. (%)]	58 (33.5)	66 (38.2)	41 (23.7)	27 (15.6)	8 (4.6)	9 (5.2)	1 (0.6)	51 (29.5)
DI-ILD vs HV								
OR	5.80	3.25	6.47	4.91	14.0	6.80	40.8	1.00
95% CI	2.17, 15.4	1.18, 8.86	2.35, 17.7	1.63, 14.6	3.96, 46.6	1.79, 26.0	4.82, 318.4	NA
p-value	<0.001*	0.026	<0.001*	0.007*	<0.001*	0.008*	0.001*	NA
DI-ILD vs IPF								
OR	6.07	4.08	5.53	7.37	6.80	5.83	13.6	1.00
95% CI	2.18, 16.7	1.42, 11.6	1.94, 15.6	2.23, 24.2	1.99, 23.1	1.45, 23.6	2.22, 82.1	NA
p-value	<0.001*	0.010	0.001*	0.001*	0.002*	0.019	0.010	NA

NA = not applicable; OR = odds ratio; \* significantly different ( $p < 0.01$ ) – a Bonferroni correction was applied.

substantially higher. The results support the potential usefulness of CYP genotyping in selecting appropriate drugs or dosages of drugs and avoiding subsequent serious adverse effects.

CYP isoenzymes have been detected in animal as well as in human lung tissues.<sup>[30]</sup> It is generally agreed that the CYP super family of enzymes forms the first step in the inactivation and elimination of numerous drugs by oxidation and reduction. Considering the fact that bio-activation by CYP enzymes plays an important role in human drug toxicity, polymorphisms in the CYP enzyme system may result in large inter-individual variations in the metabolism and toxicity of xenobiotics.

Given the ever-increasing number of patients, especially seriously ill and/or elderly, who take more than one drug, also often metabolized by the same CYP enzyme, the inherent problems of drug-induced toxicity are alarming.<sup>[31]</sup> Physicians should therefore be alert to the possibility that a drug-induced pulmonary reaction may originate from an inappropriate metabolism, especially in the case of multiple drug use. The results in this study corroborate that genotyping a patient before drug initiation could lead to a more tailor-made dosing schedule that might protect the patient from the development of serious adverse effects at the start of the pharma-

cotherapy. Trial-and-error approaches could be reduced this way.<sup>[32]</sup>

In the present study, we focused on CYP polymorphisms. The total 'genetic profile' of an individual patient should include genes expressing further polymorphic enzymes and other proteins involved in drug metabolism and response. For example, in the case of azathioprine indication, also used as treatment for IPF, testing for thiopurine methyltransferase variants involved in azathioprine metabolism is advised before starting treatment.<sup>[33-35]</sup> In the US, drug labels for azathioprine now include information on thiopurine methyltransferase (TPMT) polymorphisms and recommend determining a patient's phenotype or genotype prior to drug treatment.<sup>[36]</sup>

The finding that 87% of the studied DI-ILD patients received one or more drug(s) metabolized by an affected CYP metabolism route is consistent with the assumption that the interstitial lung reactions were drug-induced and that the case group in this study was well defined. In the other cases drug-drug interactions may have been responsible for the toxic drug effects or other pharmacogenetic factors might be involved, such as reduced TPMT activity involved in methotrexate metabolism.<sup>[37,38]</sup>

**Table IV.** List of potentially causative drugs and the cytochrome P450 (CYP) genes and variant genotypes expressing enzymes involved in their metabolism

Causative drug	CYP gene <sup>a</sup>	Allelic variants present	Drug + variant gene <sup>b</sup>	No variant gene + inhibition <sup>c</sup>	Literature <sup>d</sup>
Acenocoumarol	2C9	*1/*2, *2/*3	5	7	4
	2C19	*1/*2, *2/*2	8	2	4
Paracetamol (acetaminophen)	2D6	*1/*4	2	2	11
	2C9	*1/*2, *2/*3	2	1	11
Amiodarone	2D6	*1/*4, *1/*3, *3/*4, *4/*4	8	7	276
	2C19	*1/*2	6	9	276
Amitriptyline	2D6	*1/*4	2		4
	2C19	*1/*2	1		4
Captopril	2D6	*3/*4	1	1	27
Carbamazepine	2C9			1	53
Carvedilol	2D6	*1/*3	1	1	2
Cotrimoxazole	2C9			1	11
Cyclophosphamide	2C19	*1/*2	1		65
Diazepam	2C19	*1/*2	1		
Diclofenac	2C9	*3/*3	1	1	3
	2C19	*1/*2	1		3
Fenfluramine	2D6	*1/*3	1		39
Flecainide	2D6	*1/*3	1		10
Fluoxetine	2D6	*1/*4, *1/*3	2	1	8
	2C19	*1/*2	2		8
Haloperidol	2D6			1	2
Ibuprofen	2C9	*1/*2	1	1	6
	2C19	*1/*2	1		6
Methotrexate				2	117
Metoprolol	2D6	*1/*4, *1/*3, *4/*4	10	1	2
Montelukast	2C9	*1/*2	1		6
Morphine	2D6	*1/*4	1		16
Naproxen	2C9	*1/*2	1	1	14
Omeprazol	2C19	*1/*2	4	5	1
Pantoprazol	2C19	*1/*2, *2/*2	5	2	
Paroxetine	2D6	*1/*4	2	2	2
Propranolol	2D6	*1/*4, *3/*4	1	1	11
Ranitidine	2D6	*1/*4	2	1	
	2C19	*1/*2	2	1	
Risperidone	2D6	*1/*4	1		1
Tamsulosin	2D6	*1/*3, *3/*4	3	1	
Temazepam	2C19	*1/*2, *2/*2	4		
Tramadol	2D6	*1/*4	1		2
Valsartan	2C9	*1/*3, *1/*2, *2/*3	3	1	3
Venlafaxine	2D6	*1/*4	2		5
	2C19	*1/*2	1		5

a Gene expressing CYP enzyme involved in the metabolism of the drug.

b Total number of patients with a variant CYP gene receiving the drug.

c Total number of patients receiving the drug, without a variant CYP gene, but with the drug being associated with an inhibition of the CYP enzyme involved in the metabolism of the drug.

d Total number of articles at www.pneumotox.com referring to the mentioned drug.



There are an increasing number of examples where pharmacogenetic studies have indicated that a genetic test prior to treatment may be useful either for setting the individual dose or making a decision to use a particular drug.<sup>[39]</sup> The ability to identify individuals who are susceptible to adverse drug reactions has the potential to reduce the personal and population costs of drug-related morbidity.<sup>[8]</sup>

In this retrospective study, the healthy volunteers used no medication and among the IPF group patients used fewer drugs compared with the DI-ILD patients. However, this does not imply that the healthy control patients and IPF patients are not at risk of developing a drug-induced pulmonary reaction. Persons with more than one CYP polymorphism and/or other relevant polymorphisms may be especially susceptible to develop DI-ILD when (multiple) drugs are prescribed.<sup>[9,35,37]</sup> To answer the question of whether persons with one or more of these polymorphisms will develop a DI-ILD, whenever future drug prescription is mandatory, needs follow-up. However, since the CYP polymorphisms of these patients are already known, this can be taken into consideration when prescribing, thus avoiding (possible) adverse drug reactions. Moreover, a prospective case-control study deriving both treated patients and control patients from one population source of multi-drug users would be useful, in order to evaluate the cost effectiveness of the introduction of pharmacogenetic testing into routine healthcare. Such studies will help to identify factors that increase the risk of unwanted outcomes from drug therapy. They will also help to establish in which circumstances genotyping should be performed prior to commencing drug treatment and in tailoring drug treatment for individual patients.<sup>[8,9]</sup>

## Conclusion

This study indicates that the presence of *CYP* variant genotypes appeared to be a substantial susceptibility risk factor in the development of drug-

induced pulmonary adverse events. Therefore, genotyping prior to drug prescription may be clinically useful for the prediction and prevention of drug-induced pulmonary toxicity, especially in the case of multiple drug use, where prior genotyping or phenotyping has the potential to contribute to the patients' safety. Both clinical and genetic risk stratification (pharmacogenomics) may lead to more accurate prevention of drug-induced damage in the future.

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Correspondence: Professor *Marjolein Drent*, Department of Respiratory Medicine, ild care center, Maastricht University Medical Centre, PO Box 5800, Maastricht, 6202 AZ, the Netherlands.

E-mail: m.drent@mumc.nl