Drug-induced interstitial lung disease: role of pharmacogenetics in predicting cytotoxic mechanisms and risks of side effects

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Purpose of review
The diagnosis of drug-induced interstitial lung disease (DI-ILD) is challenging and mainly made by exclusion of other possible causes. Toxicity can occur as a cause of drug(s) or drug–drug interactions. In this review, we summarize the possible role of pharmacogenetics of metabolizing enzymes in DI-ILD.

Recent findings
Knowledge of the genetic predispositions of enzymes involved in drug metabolization and their relation with proposed cytotoxic mechanisms of DI-ILD, in particular direct cell toxicity and free oxygen radical production is increasing. The cytochrome P450 enzyme family and other enzymes play an important role in the metabolism of all sorts of ingested, injected, or inhaled xenobiotic substances. The liver is the major site for metabolism. Metabolic cytotoxic mechanisms have however also been detected in lung tissue. Polymorphisms in genes coding for enzymes that influence metabolic activity may lead to localized (toxic) reactions and tissue damage. This knowledge may be helpful in preventing the risk of DI-ILD.

Summary
Drug toxicity can be the consequence of absence or very poor enzyme activity, especially if no other metabolic route is available. In the case of reduced enzyme activity, it is recommended to reduce the dose or to prescribe an alternative drug, which is metabolized by a different, unaffected enzyme system to prevent toxic side effects. However, enhanced enzyme activity may lead to excessive formation of toxic and sometimes reactive metabolites. Therefore, knowing a patient's drug-metabolizing profile before drug prescription is a promising way to prevent or explain DI-ILD.

Keywords
adverse drug reactions, cytochrome P450, cytotoxic mechanisms, drug metabolizing enzymes, drug-induced pneumonitis, glucose-6-phosphate dehydrogenase, polymorphisms, thiopurine S-methyltransferase, xenobiotics

INTRODUCTION

Diffuse or interstitial lung diseases (ILD) can involve various patterns and the causes vary [1▪▪,2▪▪]. An ever increasing number of drugs can produce variegated patterns of ILD, virtually all histopathologic patterns of interstitial pneumonia, including cellular and fibrotic nonspecific interstitial pneumonia, pulmonary infiltrates, and eosinophilia (PIE), organizing pneumonia, lymphocytic interstitial pneumonia, desquamative interstitial pneumonia (a condition in which both the interstitium and the alveolar space are involved), a pulmonary granulomatosis-like reaction, and a common interstitial pneumonia-like pattern [3]. Moreover, the presentation can be more or less subclinical, with only an alveolitis pattern in the

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KEY POINTS

- Drugs are underestimated serious causative agents of interstitial lung disease.
- The variability in drug response among patients is multifactorial.
- Genetic variations in metabolizing enzymes are able to enhance the drivers of drug-induced interstitial lung disease.
- Both clinical and genetic risk stratification (pharmacogenomics) may lead to a more accurate prevention of drug-induced lung damage in the future.
- Current and future reports regarding the association of certain gene variants with progression and/or deterioration in interstitial pneumonias should be validated before utilization in patients' management.

cellular profile of bronchoalveolar lavage fluid (see also Fig. 1) [4]. Moreover, drug-induced pulmonary toxicity can present with varying patterns on chest computed tomography imaging (see also Fig. 2). Drugs in one therapeutic class may collectively produce the same pattern of involvement. Few drugs are known to produce more than one pattern of ILD [5]. The diagnosis of drug-induced ILD (DI-ILD) essentially rests on the temporal association between exposure to the drug and the development of pulmonary infiltrates. Thus, the diagnosis of DI-ILD is mainly made by the meticulous exclusion of all other possible causes [4,6]. The striking individual susceptibility for drug-induced lung injury, however, suggests a genetic background. Increased understanding

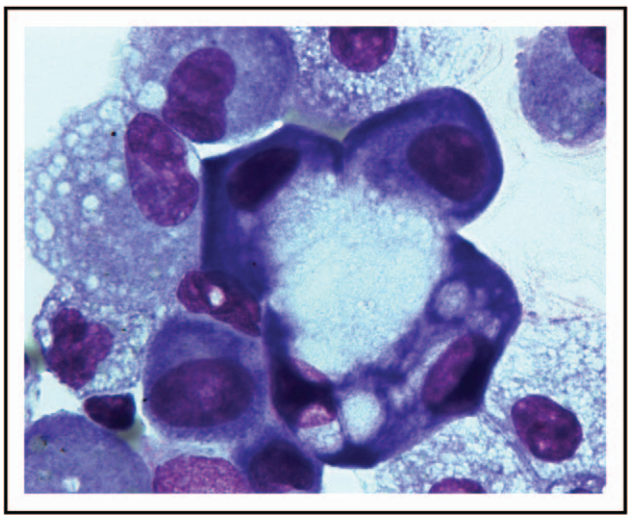

FIGURE 1. Reactive pneumocyte type II cell (central) present in bronchoalveolar lavage fluid of a patient with cocaine DI-ILD (see also Figure 2).

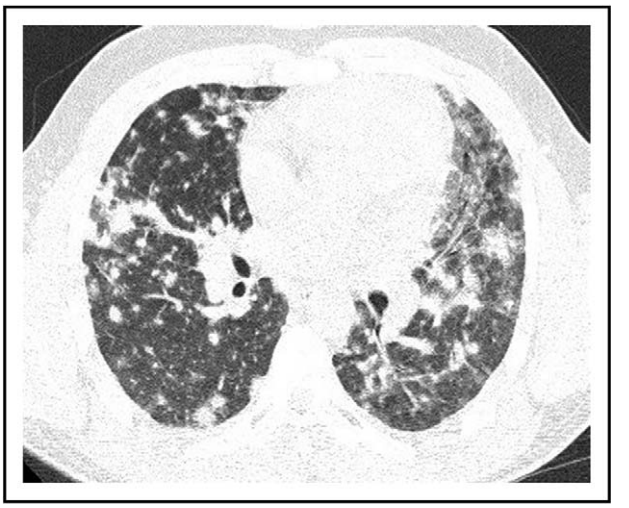

FIGURE 2. High-resolution computed tomography scan through the midlung zones shows scattered ill-defined nodulas and ground-glass opacity in the lingular segment of a patient with cocaine-induced ILD (a carrier of CYP2C and VKORC1 variant alleles).

of the genetic predispositions of enzymes involved in drug metabolization and their relation with proposed cytotoxic mechanisms of drug-induced lung injury, in particular direct cell toxicity and free oxygen radical production, offers the possibility to prevent the frequently serious DI-ILD from occurring [7].

MECHANISMS OF DRUG-INDUCED LUNG INJURY

Both cytotoxic and immune mechanisms may be involved independently or in combination, in the initiation and propagation of DI-ILD [8]. The lungs have the potential of metabolizing many foreign compounds, including pharmaceutical products. The so-called biotransformation is the process by which cells modify xenobiotics with the ultimate goal of facilitating the elimination of lipophilic substances. To increase the water solubility of xenobiotics, a broad set of enzymes capable of introducing new functional groups (phase I) or conjugating with internal cell's molecules (phase II) is involved. Sometimes, however, these enzymes transform an otherwise harmless product in a reactive intermediate, a process called bioactivation (Fig. 3). Biotransformation can result in the formation of reactive electrophilic species such as epoxides, quinones, quinone-imines, methylene-imines, and acyl radicals which react with cell biomolecules, modifying them or forming covalent adducts and causing direct cell toxicity [9]. In addition to this mechanism, the production of free oxygen radicals and alteration of the oxidant-antioxidant balance is one of the mechanisms (Fig. 3) of iatrogenic pneumonitis [10]. Redox

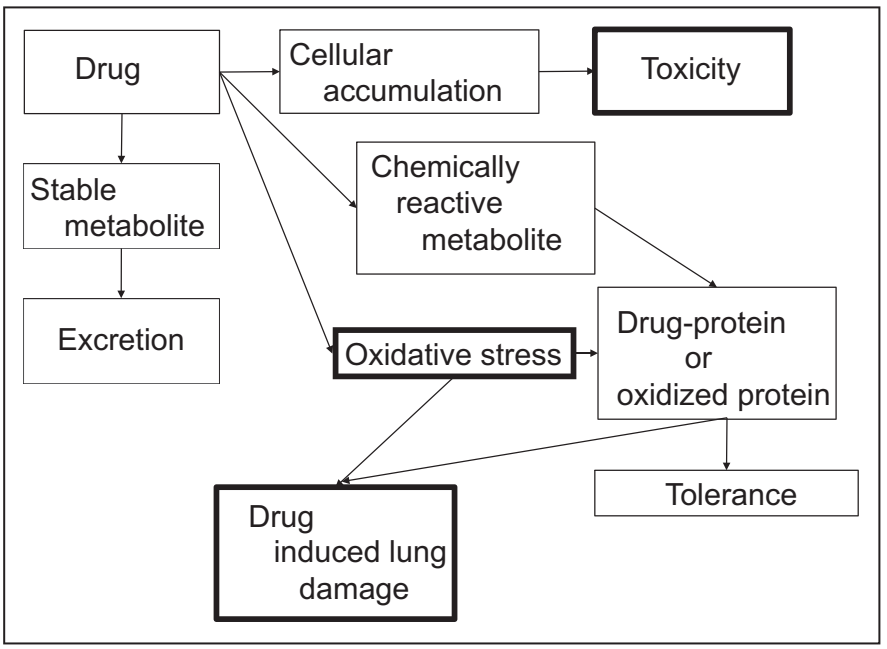

FIGURE 3. Overview of molecular mechanisms leading to drug-induced lung damage. Drugs are enzymatically degraded to stable metabolites (e.g. via cytochrome P450) and excreted. A decreased metabolic activity may cause accumulation of drugs, which may lead to toxicity. Biotransformation may also lead to the formation of chemically reactive metabolites. These metabolites (haptens) can form an adduct with proteins. This leads to tolerance or (sometimes), in combination with a costimulatory signals (e.g. oxidative stress, or a viral or bacterial infection) to a toxic immune reaction and subsequent lung damage [15▪]. Finally, there are strong indications that oxidative stress, for example via redox cycling of drugs, is involved in drug-induced lung damage.

cycling leads to the formation of superoxide anion free radicals ($O_2^{\bullet -}$), which may transform into other reactive oxygen species (ROS) such as H_2O_2 and •OH (Fig. 3) [8,11]. These ROS may directly or indirectly lead to lung damage. Interestingly, direct activation of lung fibroblasts is initiated via the influx of superoxide anion radicals through chloride channels. Activated fibroblasts result in the production of transforming growth factor beta-1 and collagen [12]. This finding makes it conceivable that redox cycling drugs lead to lung fibrosis. A similar mechanism has been suggested to occur in hepatic stellate cells, which has led to the suggestion that this may lead to liver fibrosis [13]. The noncommercial website Pneumotox provides a list of drugs that have shown or suggested to cause lung damage [14]. The website ranks the reported cases by 1–5 stars ranging, indicating the degree of plausibility that the drug is causative for lung damage.

ENZYMES WITH GENETIC VARIATION AND INVOLVEMENT IN DRUG METABOLIZATION POSSIBLY LEADING TO INTERSTITIAL LUNG DISEASE

There are more than 30 families of drug-metabolizing enzymes in humans. Essentially all of the major human enzymes responsible for modifications of functional groups (phase I) or conjugation with endogenous substituents (phase II) exhibit common polymorphisms at the genomic level, many of which translate into functional changes in the encoded proteins and thereby determine the efficacy and toxicity of medications. In many cases, a polymorphism is associated with reduced activity of the encoded protein (e.g. glucose-6-phosphate dehydrogenase, G6PD), but there are also examples where the allelic variant encodes proteins with enhanced activity (e.g. CYP iso-enzyme *2C19*17) [16,17]. It is now well recognized that adverse drug reactions may be caused by specific drug-metabolizer phenotypes, such as severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard dose of the thiopurines, azathioprine or 6-mercaptopurine [18]. Another example is dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity leading to hematological and gastrointestinal toxicities [19]. A large number of associations have been identified between drug-induced toxicity and genetic variations in their metabolizing enzymes [20]. The focus in this review, however, is on drug-genetic variant enzyme combinations, which are most important for the causation of DI-ILD.

Considering the mechanisms of lung injury and the (by-)products of drug metabolization, it is expected that polymorphism(s) of metabolizing enzymes enhancing or leading to the formation of reactive drug metabolites and ROS, may increase the chances of the occurrence of DI-ILD. In this review, the current state of research on the association between genetic variations in phase I and phase II enzymes involved in drug metabolization and their distinct role in the mechanisms of drug-induced lung damage is assessed and merged. The results of the analysis are summarized in Table 1. Except for the enzymes belonging to the CYP superfamily, most polymorphisms, lead to enzyme deficiencies. In the sections later, involvement of polymorphisms of *G6PD*, *CYP* and thiopurine S-methyltransferase (*TPMT*) in DI-ILD are further explored. Some clinical cases are included as an example.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE

A single genotype seems to play a crucial role in the protection against ROS-induced lung damage, viz. G6PD, a critical enzyme in the pentose phosphate pathway. In this pathway a supply of NADPH is generated via the G6PD catalyzed conversion of glucose-6-phosphate to 6-phosphogluconolactone. NADPH is necessary for adequate generation of protective intracellular thiols, which are needed to protect against the damaging effects of ROS. An important protective thiol is the tripeptide glutathione (GSH). GSH itself is an antioxidant and acts as a cofactor in glutathione dependent antioxidant enzymes [21,22]. A diminished activity of G6PD thus increases the risk of a lack of intracellular antioxidant protection, and increases oxidative stress because it hampers the regeneration of the reduced protective form of GSH (Fig. 4).

In many cases clinical manifestations of G6PD deficiency will not be observed. Other antioxidants such as mitochondrial antioxidant systems will take over the protection against ROS. Erythrocytes lack mitochondria and thus strongly depend on the cytosolic pentose phosphate pathway for NADPH and are therefore particularly vulnerable for oxidative damage in case of G6PD deficiency. Hemolytic anemia may be the result. Other tissues besides erythrocytes may also become damaged more easily in cases of oxidative stress. This can be a direct ROS damage or an indirect damage via the toxicity of iron, which is known to cause a fibrotic interstitial trigger in lung tissue. G6PD deficiency is a very common enzymopathy and is estimated to affect 400 million people especially in areas in Africa [23]. It is thought that G6PD deficiency offered an evolutionary advantage because it weakens the erythrocyte membrane, the host cell of the malaria parasite (*Plasmodium falciparum*). This makes it difficult for the parasite to have productive growth in the erythrocyte. Numerous medications and some oxidative food products like fava beans (*Vicia faba*) should be avoided by G6PD-deficient patients.

Redox cycling compounds generate superoxide anion radicals and subsequently various other ROS. Redox cycling compounds include the antibiotic nitrofurantoin, the cytostatic bleomycin (which is even used as model compound in animal or cell research to reliably induce pulmonary fibrosis), cocaine, and the antimalarial drug primaquine (Table 1) [24–27].

ILD induced by redox cycling drugs is based on this mechanism and G6PD deficiency, by increased oxidative stress, could increase the occurrence of ILD. Widely used drugs that should be avoided in G6PD deficiency are associated with DI-ILD (Table 2) [28]. Figure 5a and b show an example of DI-ILD: a case of nitrofurantoin induced pneumonitis.

CYTOCHROME P450 ENZYMES

Members of the CYP family are responsible for the metabolism of endogenous substrates, and for pharmaceuticals. CYP enzymes are involved in the biotransformation of chemicals like drugs. CYP activity frequently (but not always!) reduce or alter the pharmacological activity of many drugs while facilitating their elimination. The CYP enzymes are largely polymorphic and variant alleles together with host and environmental factors result in, normal (extensive metabolizer, EM), increased (ultra-rapid metabolizer), decreased (intermediate metabolizer), or no enzyme activity (poor metabolizer), and thus four possible metabolizing phenotypes. Therefore, an ultra-rapid metabolizer phenotype leads to accelerated drug metabolism of the parent drug resulting in low parent drug serum levels accompanied by sometimes less efficacy and the formation of (in)active and even toxic or reactive metabolites. intermediate metabolizer and poor metabolizer phenotypes lead to the accumulation of the parent drug, or a push to another sometimes less favorable metabolization pathway [29]. Because the various CYP enzymes have different metabolic activity and are not evenly distributed in organs, knowledge on the characteristics of CYP enzymes in the lung and drug metabolism pathways may have value in recognizing the causative agent in patients presenting with DI-ILD [20]. The most important enzymes for drug metabolism are CYP1A2(+), CYP2C9(++), CYP2D6 (++), CYP3A4(+++), and CYP3A5(+++). Their presence in the lung is noted

Table 1. Drug metabolizing enzymes, drugs metabolized by these enzymes and the current state of information of their relation with ILD

Enzymes involved in drug metabolism	Polymorphisms phenotype	Drugs metabolized by the particular enzymes	Proposed mechanism of causing pulmonary toxicity	All if available: Rating in Pneumotox [14] *<10 cases; **10–50 cases; ***50–100 cases; ****100–200 cases; *****>200 cases	Quality of the studies (very low – high) n/a = not included in the latest systematic review [1▪▪]
Phase I enzymes					
Glucose-6-phosphate dehydrogenase (G6PD)	Decreased activity	Nitrofurantoin	Generation of free oxygen radicals [11]	*****	Low
		Cocaine		*****	n/a
		Primaquine		*	n/a
		Flutamide		*	n/a
		Dapsone		**	n/a
		Sulfacetamide		*	n/a
Cytochrome P450			Release of toxic oxygen radicals and reactive metabolites [7]		
CYP2D6	Decreased (poor and intermediate metabolizer) Increased function (rapid metabolizer)	Tamoxifen		*	n/a
CYP3A		Acetaminophen		***	n/a
		Amiodaron		*****	Very low – low
		Dasatinib		****	n/a
		Fentanyl		*****	n/a
		Fluticasone		****	n/a
		Imatinib		***	Low
		Sirolimus		****	Very low
		Everolimus		*****	Very low – moderate
		Erlotinib		***	Low-moderate
		Gefitinib		*****	Low-moderate
		Methadone		*****	n/a
CYP2C8	Decreased activity	Amiodaron		*****	Very low – low
CYP2C9	Decreased activity	Paclitaxel		*****	n/a
CYP2C19	Decreased activity	Cyclophosphamide		****	n/a
		Warfarine		**	n/a
Dihydropyrimidine dehydrogenase (DPD)	Decreased activity	5-FU capecitabine	Decreased detoxification of pyrimidine-based antimetabolite analogues [15▪]	*** *	n/a
Phase II enzymes					
N-Acetyltransferases	Decreased activity				
NAT2	Decreased activity	Isoniazid	Increased oxidative stress [16]	**	n/a
Thiopurine S-methyltransferase (TPMT)	Decreased activity	Azathioprine	ROS generation, causing oxidative DNA damage and mitochondrial dysfunction [15▪]	***	n/a
		Mesalazine		***	n/a
		6-Mercaptopurine		*	n/a
		6-Thioguanine		No results	n/a
UDP Glucuronyltransferases (UGTs)					
UGT1	Decreased activity Increased activity	Irinotecan	Less scavenging of toxic and reactive metabolites [9] Instable acyl derivatives leading chemical protein adducts with electrophilic chemical reactivity [9]	**	low
UGT2					

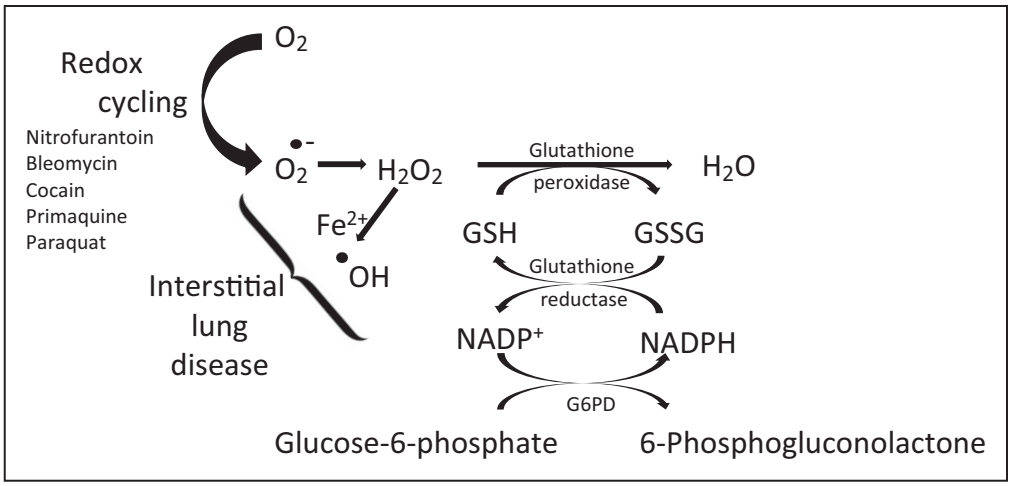

FIGURE 4. Redox cycling compounds generate superoxide anion-free radicals ($O_2^{\bullet-}$). Upon dismutation $O_2^{\bullet-}$ is converted into hydrogen peroxide (H_2O_2). In the presence of Fe^{2+} (which may originate from haem, upon red blood cell hemolysis) H_2O_2 can be transformed into the very reactive damaging hydroxyl radical (•OH). H_2O_2 reduces to water H_2O by glutathione peroxidase. In this reaction glutathione (GSH) provides the reducing equivalents and glutathione disulphide (GSSG) is formed. GSSG is reduced to GSH by glutathione reductase, which obtains its reducing equivalents from NADPH originating from the pentose phosphate pathway. In this pathway glucose-6-phospate dehydrogenase (G6PD) plays a crucial role.

with + for low, ++ for intermediate, and +++ for high presence [30]. Review of www.pneumotox.com and the latest literature review show (Table 1) that drugs associated with pulmonary toxicity are more often metabolized by CYP enzymes that have high presence or activity in the lung compared to drugs that are solely metabolized by CYPs with low presence in the lungs [1▪▪,14].

Acetaminophen / paracetamol

Although acetaminophen (APAP) is mostly known for causing hepatotoxicity, the wide use of this drug justifies drawing the attention for its rare pulmonary toxicity. It is a commonly used medicine for relieving pain and reducing fever in adults and children [31]. The majority of APAP is metabolized in the liver and after glucuronidation and sulfation safely excreted. However, a fraction of APAP is metabolically activated in the liver by CYP2E1, CYP3A4, and CYP1A2, to the pro-oxidant metabolite N-acetyl-p-benzoquinone-imine (NAPQI) [32]. These CYPs are expressed in the respiratory tract, suggesting that similar metabolic activation as in the liver may also occur in the lungs [33]. Polymorphisms that accelerate the forming of NAPQI may lead to enhanced toxicity [34]. There are two hypotheses for the mechanisms of lung injury by NPAQI. The first one suggests that because of NAPQI is highly reactive, it causes cellular oxidative stress, and may covalently bind to cellular macromolecules [35]. The second hypothesis suggests a more specific mechanism of APAP-induced lung disease and proposes neurogenic inflammation. Nassini *et al.* [36–40] suggested that inflammation develops in the lungs after APAP treatment because of activation of the transient receptor potential ankyrin 1 (TRPA1) channel in peptidergic neurons by NAPQI. The TRPA1 hypothesis may be more biologically plausible; however, the evidence for this hypothesis is also preliminary and both models should be further explored.

Table 2. Drugs to be avoided by G6PD-deficient patients [17]

Drugs	Indication
Diaminodiphenyl sulfone (Dapsone)	Leprosy
Flutamide	Prostate cancer
Furazolidone	Largely forbidden as human antibiotic
Methylene blue	Methemoglobinemia
Nitrofurantoin	Urinary tract infections (among others)
Phenazopyridine	Analgesic
Primaquine	Malaria
Rasburicase	Excess uric acid
Sulfacetamide	Infections
Sulfanilamide	Infections

THIOPURINE S-METHYLTRANSFERASE

TPMT polymorphisms lead to an almost 50-fold variation in enzyme activity between individuals. TPMT

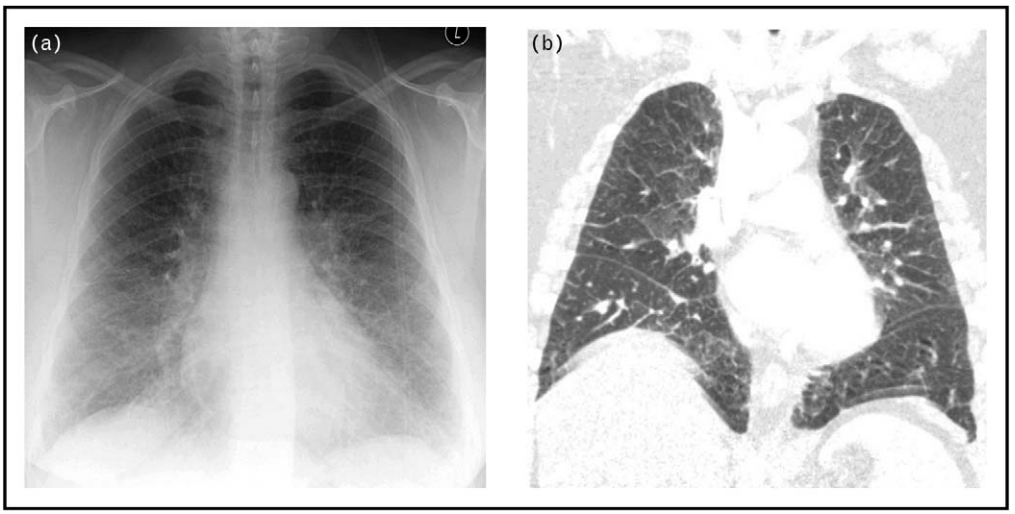

FIGURE 5. An example of nitrofurantoin-induced pneumonitis: (a) chest X-ray shows a diffuse reticular pattern: (b) High-resolution computed tomography (coronal slice) confirms this reticular pattern, which is caused by thickening of the interlobular septa.

catalyzes the transfer of the methyl-group of S-adenosylmethionine to the thiol-group on the thiopurine molecule. Methylation of thiopurines is one of the detoxification reactions in thiopurine metabolism. Variations in response to thiopurine drug therapy are mainly caused by TPMT polymorphism. Adverse effects of the thiopurines, 6-mercaptopurine, and azathioprine include bone marrow suppression, which is of major concern, occurring in 2–5% of inflammatory bowel disease patients. The risk of thiopurine induced myelosuppression is increased in patients with TPMT deficiency. Liver toxicity occurs in 3–10% of azathioprine exposed patients with hypersensitivity, an idiosyncratic cholestatic reaction, or endothelial cell damage and results in drug withdrawal. A number of different factors have been reported to be linked to thiopurine-induced hepatotoxicity including higher concentrations of methylated metabolites and mitochondrial injury associated with glutathione depletion. Thiopurines are known to induce oxidative stress, especially in mitochondria, resulting in mitochondrial dysfunction and activation of stress activated protein kinase pathways. Azathioprine-induced oxidative stress causes tricarboxylic acid cycle dysfunction by depleting crucial mitochondrial enzymes. The metabolite 6-thioguanine nucleotide (6-TGN), a thiopurine metabolite, is also known to incorporate into mitochondrial DNA (mtDNA), where it is rapidly oxidized and inhibits mtDNA replication causing decreased mitochondrial protein concentrations and loss of mitochondrial function. A recent study in cultured human lymphoblasts proposed ROS generation, resulting in oxidative DNA damage and mitochondrial dysfunction as the mechanism responsible for thioguanine induced cytotoxicity. Thiopurine induced alterations in the expression of genes involved in protein and ATP-biosynthesis. When mice were treated with 6-mercaptopurine, significant alterations were observed in the expression of genes associated with abnormal lipid metabolism, inflammatory responses, oxidative stress, ATP depletion, and cell death [41]. Although several cases of azathioprine induced ILD are known, so far, in only one case TPMT deficiency has been associated with pulmonary toxicity [14,42].

In case of an azathioprine indication, also used as treatment for certain ILDs, testing *TPMT* variants involved in azathioprine metabolism is advised before starting treatment [42–44]. In the Unites States of America, drug labels for azathioprine now include information on *TPMT* polymorphisms and recommend determining patients' phenotype or genotype prior to drug treatment [45].

DISCUSSION

Genetic variations in drug metabolizing enzymes may enhance the causation of DI-ILD by inducing the forming of ROS or reactive metabolites (phase I) or by reducing the scavenging of these ROS or reactive metabolites (phase II). We cautiously want to mark that drugs that are solely metabolized by CYP1A (low presence in the lungs), and known for other idiosyncratic adverse drug reactions, such as clozapine, are less associated with DI-ILD than drugs that are metabolized by CYPs with high presence in the lungs such as CYP3A. It was expected that drugs that undergo redox cycling would be well known for causing DI-ILD, but besides nitrofurantoin and cocaine, no other

drugs that should be avoided in G6PD-deficiency had a five-star code in www.pneumotox.com [14]. We must, however, keep in mind that nitrofurantoin and cocaine are far more widely used than the other drugs. Although our findings may point to an association between genetic variation of metabolizing enzymes and the occurrence of DI-ILD it has thus far not been extensively researched, resulting in low grades of evidence and enforcing us to review older publications, however, from a novel perspective.

Both genetic and nongenetic information is important in the susceptibility, development, cause, and treatment response of diseases. The more we know about a patient's genes and context, the better disease management decisions can be made [46]. 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 and the potential to attribute to the patients' safety. Genotyping should be considered to identify patients that might be at risk of severe toxic responses to environmental, pharmacological, herbal remedy, and/or nutritional stimuli, in order to guide appropriate individual dosage(s) [47]. Some patients will continue to react unpredictably to therapy even though, according to obtained test results, problems were not expected. This variability in drug response among patients is multifactorial and include extrinsic factors like environmental aspects, comedication, nutritional status, smoking and alcohol consumption, and intrinsic factors that affect the disposition (absorption, distribution, metabolism, and excretion) of individual drugs.

There are an increasing number of examples where pharmacogenetic studies have indicated that genetic testing prior to treatment may be useful either for setting the individual dose or in choosing a certain drug [48,49,50▪▪]. Genetic screening prior to drug prescription may potentially prevent serious adverse effects such as diffuse alveolar hemorrhage (DAH) or DI-ILD [51▪▪,52▪]. The results obtained by genetic testing appeared to be useful in disease management, because of the prognostic value of the absence or presence of specific polymorphisms. An association with vitamin K epoxide reductase complex 1 (*VKORC1*) and/or *CYP2C9* variant alleles might even be a risk factor for the development or exacerbation of idiopathic pulmonary fibrosis [51▪▪]. Furthermore, it was accentuated that in DAH cases early recognition of the presence of one of the studied polymorphisms is important, because of a potential lethal outcome and the fact that simple vitamin K supplementation can be life-saving [52▪]. Genetic variations are, of course, not limited to drug metabolizing enzymes like the substrates of these enzymes are not limited to drugs. Needless to say, many more substances are associated with the occurrence of ILD. The redox cycling herbicide paraquat is well known and another striking example is 4-ipomeanol, a toxin produced by moldy sweet potatoes (*Ipomoea batatas*) caused by postharvest diseases, the most common is infection with the fungus Fusarium solani. Ingested molded sweet potatoes by livestock causes interstitial pneumonia. The extrahepatic CYP enzyme CYP4B1, present in lung tissue, activates 4-ipomeanol to a reactive intermediate that reacts with nitrogen or sulfur nucleophiles and leads to toxicity [53–55].

It has also been suggested that in the treatment of IPF, clinical meaningful precision medicine might be possible with the antioxidant N-acetylcysteine by taking into account polymorphism within *TOLLIP* [56].

CONCLUSION

Although genetic variations in drug metabolizing enzymes may play an important role in the individual response on drug medication, there are many other factors involved such as age, renal and liver function, concomitant diseases, nutritional status, smoking and alcohol consumption. A 'one-size-fits-all' approach to medicine is based on broad population averages. The advent of personalized medicine is moving us closer to more precise, predictable, and powerful healthcare that is customized for the individual patient. Growing understanding of genetics and genomics provide many advantages in tailoring healthcare to each person's unique genetic make-up which may result in better disease prevention, more accurate diagnoses, safer drug prescriptions, and more effective treatments. It appears that genetic variations in metabolizing enzymes are able to enhance the drivers of DI-ILD. This paves the way for the potential usefulness of personalized medicine by genotyping and aiming to improve efficacy, tolerability, and drug safety. With this, knowledge on pharmacogenetics may finally serve as a predictor of toxicity and clinical response.

There is still a need for well designed prospective clinical trials that measure patient-oriented outcomes of selected genomic applications, and studies that evaluate the role of genomic variations in disease susceptibility, predicting prognosis, treatment response, and in tailoring drug treatment for individual patients. These investigations are aimed to help bridge the gap between 'personalized' and 'evidence-based' medicine.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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This is a recent review about drug-induced interstitial lung diseases (DI-ILD). Overall high-quality evidence in DI-ILD is lacking, and the current review will inform larger prospective studies to investigate the diagnosis and management of DI-ILD.

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In this review, the authors stress the importance that clinicians and pathologists are aware of these potential adverse effects of drugs, radiation, and medical devices and raise the possibility of drug-induced lung toxicity after exclusion of other differential diagnoses. Early intervention to a drug-induced lung toxicity might prevent progression of side effects and permanent changes.

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