

## Novel Therapeutic concepts

# Drug-induced arrhythmia: pharmacogenomic prescribing?

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Drug-induced Torsades de Pointes is a rare, unpredictable, and life-threatening serious adverse event. It can be caused by both cardiac and non-cardiac drugs and has become a major issue in novel drug development and for the regulatory authorities. This review describes the problem, predisposing factors, and the underlying genetic predisposition as it is understood currently. The future potential for pharmacogenomic-guided and personalized prescription to prevent drug-induced Torsades de Pointes is discussed. Database searches utilized reports from [www.qtdrugs.org](http://www.qtdrugs.org) up to January 2012, case reports and articles from [www.pubmed.com](http://www.pubmed.com) up to January 2012, and the British National Formulary edition at [www.bnf.org](http://www.bnf.org).

### Keywords

Torsades de pointes • Serious adverse events • Anti-arrhythmic drugs • Pharmacogenomics • Drug-induced arrhythmia • Acquired long QT syndrome

## Drug-induced arrhythmia: pharmacogenomic prescribing?

### The problem

Drug-induced ventricular arrhythmias and sudden deaths are uncommon events that occur in an unpredictable or idiosyncratic fashion. Their epidemiological importance has been poorly understood due to reliance upon spontaneous reports and anecdotal accounts. In addition, the clinical complexity of retrospective diagnosis has hampered the accurate ascertainment of cases and the attribution of suspicious events to drug therapy.<sup>1</sup>

The majority of recognized drug-induced ventricular arrhythmia is related to medications that affect cardiac repolarization and consequently prolong the QT interval causing drug-induced Torsades de Pointes (DITdP). A recent Phenotype Standardization Project sponsored by the international Serious Adverse Events Consortium (ISAEC) has aimed to establish a universally acceptable definition of the phenotype for DITdP to support research into pharmacogenomic markers of risk.<sup>2</sup> The minimum proposed requirements for a case are as follows:

- (i) The DITdP event must have occurred during treatment with a known QT-prolonging drug, including amiodarone, and/or a drug suspected as causing QT prolongation.

- (ii) Upon drug withdrawal, arrhythmias and symptoms abate and there is at least partial resolution of QT prolongation that is clinically significant in the opinion of an arrhythmia specialist.
- (iii) Arrhythmia documentation must be reviewed by an appropriately experienced physician or electrophysiologist.

Three clinical sub-phenotypes for suspected DITdP were also defined to cover all potential presentations:

- (i) 'Classical DITdP' where the pause-dependent onset of polymorphic VT (at least five beats) with associated QT prolongation is documented with or without resuscitation and/or subsequent VF and cardiac arrest.
- (ii) 'Probable DITdP' where polymorphic VT and/or VF have been documented but the typical onset of TdP has not been seen. QT prolongation must nonetheless have been documented.
- (iii) 'Possible DITdP' where ventricular arrhythmia has not been documented but a history of unexplained syncope without vagal or neurological features has been elicited with severe QT prolongation on the ECG (QTc >550 ms).

Most of the burden of DITdP has been due to anti-arrhythmic drug therapy. Early studies estimated risks of DITdP in up to 1–3% of patients receiving quinidine and sotalol, as well as newer drugs such as ibutilide and dofetilide.<sup>3–5</sup> A multitude of medications

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**Table 1** Drugs reported to be associated with QT prolongation and/or Torsades de Pointes with postulated levels of risk based upon reports and the literature

Drug group	High risk: frequent reports of DITdP	Moderate risk: reported to cause DITdP	Low risk: DITdP only likely if associated with overdose, other culpable drugs, or concomitant risk factors	Low risk: associated with QT prolongation only or rarely with DITdP usually with other risk factors
Anti-arrhythmics				
Class I	Quinidine <sup>a</sup> , procainamide <sup>a</sup> , Disopyramide, dihydroquinidine <sup>a</sup>	Flecainide, propafenone, pirmenol <sup>a</sup> , cibenzoline <sup>a</sup> , ajmaline <sup>a</sup>		
Class III	Sotalol, d-sotalol <sup>a</sup> , dofetilide <sup>a</sup> , azimilide <sup>a</sup> , Ibutilide <sup>a</sup> , sematilide <sup>a</sup> , ersentilide <sup>a</sup> , almokalant <sup>a</sup> , nifekalant <sup>a</sup> , terikalant <sup>a</sup>	Amiodarone	Dronedarone	
Anti-anginals and vasodilators	Prenylamine <sup>a</sup> , terodiline <sup>a</sup> , lidoflazine <sup>a</sup> , bepridil <sup>a</sup>			Vardenafil, ranolazine
Anti-hypertensives		Indapamide		Nicardipine, isradipine, moexipril/hydrochlorothiazide
Anti-histamines	Terfenadine <sup>a</sup> , astemizole <sup>a</sup>	Ebastine <sup>a</sup>	Diphenhydramine	Mizolastine, bilastine
Serotonin agonists and antagonists	Cisapride <sup>a</sup> , ketanserin <sup>a</sup>	Dolasetron		Ondansetron, granisetron
Anti-microbials				
Macrolides	Erythromycin, spiramycin	Azithromycin, clarithromycin	Roxithromycin <sup>a</sup>	Telithromycin
Fluoroquinolones		Gatifloxacin <sup>a</sup> , levofloxacin, Sparfloxacin <sup>a</sup> , moxifloxacin, grepafloxacin <sup>a</sup>	Ciprofloxacin	Gemifloxacin <sup>a</sup> , ofloxacin, gatifloxacin, Posaconazole
Anti-fungals			Ketoconazole, fluconazole, itraconazole, voriconazole	
Anti-malarials	Halofantrine <sup>a</sup>	Chloroquine	Quinine	artemether with lumefantrine,
Others	Pentamidine		Amantadine, cotrimoxazole, Trimethoprim, ritonavir	Foscarnet, atazanavir, Saquinavir, telaprevir
Psychiatric				
Tricyclic anti-depressants			Amitriptyline, nortriptyline, desipramine <sup>a</sup> , clomipramine, imipramine, trimipramine, doxepin, protriptyline <sup>a</sup>	
Serotonin re-uptake inhibitors		Citalopram	Fluoxetine, paroxetine, sertraline, zimeldine <sup>a</sup> , amoxapine <sup>a</sup>	Venlafaxine, escitalopram
Anti-psychotics	Thioridazine <sup>a</sup> , chlorpromazine, haloperidol, droperidol <sup>a</sup>	Pimozide, mesoridazine, sertindole	Amisulpiride, ziprasidone, risperidone	Trifluoperazine, prochlorperazine, Paliperidone, quetiapine, flepenthixol, fluphenazine, zuclopenthixol
Others			Maprotiline, trazodone	Lithium
Anti-cancer	Arsenic trioxide	Tacrolimus, geldanamycin <sup>a</sup> , vandetanib		Nilotinib, tamoxifen, sunitib, lapatinib, vinflunine, erubilin, pazopanib, fingolimob, capecitabine

Continued

**Table 1** Continued

Drug group	High risk: frequent reports of DITdP	Moderate risk: reported to cause DITdP	Low risk: DITdP only likely if associated with overdose, other culpable drugs, or concomitant risk factors	Low risk: associated with QT prolongation only or rarely with DITdP usually with other risk factors
Others	Probucof, domperidone, cisapride, methadone	Vasopressin, tizanidine, alfuzosin, amantadine, levomethadyl <sup>a</sup> , lofexidine	Organophosphates <sup>a</sup> , galantamine, solifenacin, clobutinol <sup>a</sup> , chloral hydrate, sevoflurane	Felbamate <sup>a</sup> , fosphenytoin, degarelix, perflutren, octreotide, oxytocin, galantamine, retigabine, tizanidine, tolterodine, alfuzosin, isoflurane

Derived from Yap *et al.*,<sup>24</sup> reports from [www.qtdrugs.org](http://www.qtdrugs.org) up to January 2012, case reports from [www.pubmed.com](http://www.pubmed.com) up to January 2012, the British National Formulary edition 63 at [www.bnf.org](http://www.bnf.org). Adapted from 'Acquired Repolarisation Disorders'.<sup>20</sup>

<sup>a</sup>Unlicensed, withdrawn, or suspended in UK.

**Table 2** Common clinical risk factors for drug-induced QT prolongation and Torsades de Pointes

Female gender
Conditions predisposing to heightened QT prolongation and risk of arrhythmia
Heart disease
Congestive heart failure
Left-ventricular hypertrophy
Hours following conversion of atrial fibrillation to sinus rhythm
Congenital long-QT syndrome (may be clinically unrecognized)
Bradycardia and conduction disease
Increased drug bioavailability
Altered function of specific cytochrome P450 (CYP450) isoforms (for liver metabolized drugs)
Genetic variants
Concomitant inhibitory drugs
Liver disease
Altered renal or liver function (for renally or hepatically excreted drugs)
Electrolyte imbalance
Hypokalaemia
Hypomagnesaemia
Hypocalcaemia (possible)

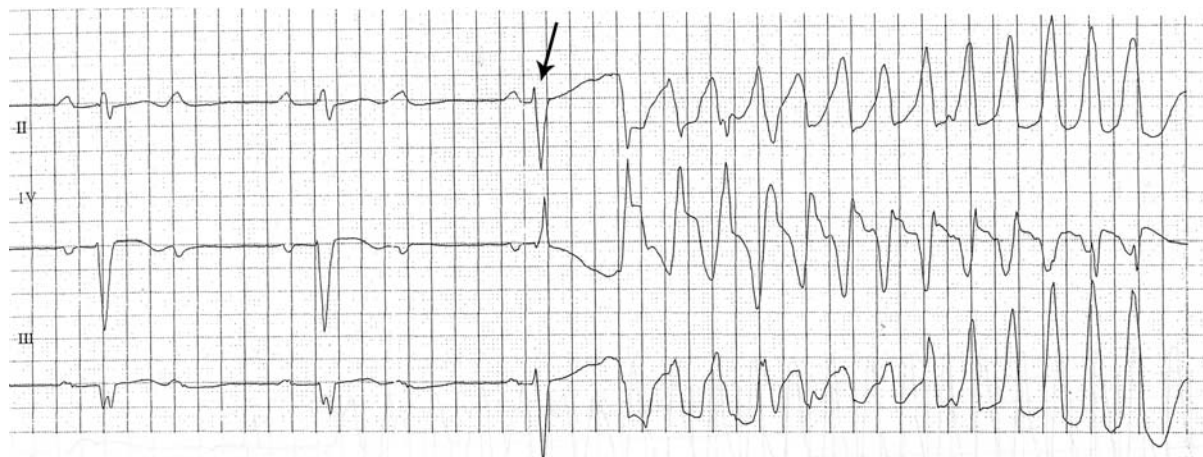
(Table 1), including non-cardiac drugs, have since been described as prolonging the QT interval, although only a proportion have been associated with the development of TdP.<sup>6,7</sup> Non-cardiac drugs culpable for DITdP include anti-psychotics (e.g. thioridazine, chlorpromazine, and haloperidol),<sup>8–10</sup> anti-histamines (e.g. terfenadine and astemizole),<sup>11,12</sup> anti-infectives (e.g. some macrolides, quinolones, imidazole anti-fungals),<sup>13</sup> and gastrointestinal drugs (e.g. cisapride and domperidone).<sup>13</sup> The estimated incidence of DITdP and sudden death with non-cardiac drugs is much lower than that for anti-arrhythmics, 1–10 per 100 000.<sup>14–17</sup> Nonetheless, the absolute numbers of individuals exposed to risk are significant, as up to 3% of all prescriptions world-wide are of potentially pro-arrhythmic agents.<sup>18</sup> DITdP has, therefore, become an

important public health and regulatory issue leading to market withdrawal of a number of highly prescribed drugs (for example, thioridazine, astemizole, cisapride, grepafloxacin, terfenadine) and to restriction of use of several others (for example, droperidol, haloperidol, sertindole, citalopram).<sup>19,20</sup> Unfortunately, there are proarrhythmic drugs that are essential to medical practice and cannot be withdrawn: for example, halofantrine for drug-resistant malaria and macrolide antibiotics for penicillin-sensitive individuals. Most neuroleptics are associated with at least some risk of QT prolongation and DITdP but are vital for the treatment of psychotic illnesses. New-drug development has also been complicated by the need to ensure minimal risk of DITdP.<sup>18–21</sup>

QT-prolonging agents have also been reported to cause DITdP in combinations with each other or with other medications affecting drug elimination, such as inhibitors of specific cytochrome P450 isoforms,<sup>7,10,13,17,22,23</sup> discussed further below. They are commonly prescribed to individuals with other predisposing risk factors known to increase the risk of DITdP (Table 2): female gender, structural cardiac disease, metabolic abnormalities (hypokalaemia, hypomagnesaemia, and hypocalcaemia), specific conditions (liver disease, diabetes mellitus, obesity, and anorexia nervosa), and ECG abnormalities (bradycardia and conduction disease).<sup>24</sup> Indeed, a very common feature of DITdP is acute bradycardia and/or pauses leading to pause-dependent initiation of tachycardia (Figure 1).<sup>25</sup>

## Mechanisms and predispositions

The known clinical risk factors for DITdP (Table 2) serve to segregate patients into high- or low-risk subgroups, but do not identify risk in an individual subject. This unpredictable nature provides one rationale for pursuing a genomic contribution to risk. Another is that TdP is an unusual arrhythmia and is also characteristic of the congenital long-QT syndrome. Finally, small studies have suggested increased susceptibility to QT prolongation among first-degree relatives of patients with DITdP exposed to QT-prolonging drug challenge.<sup>26</sup> An understanding of the pharmacokinetic and electrophysiological mechanisms predisposing to DITdP is one starting point for genetically informed studies of risk.



**Figure 1** An example of second-degree heart block (Mobitz type 2) with severe QT prolongation associated with sotalol therapy. A probable ventricular ectopic occurs (arrowed) with associated severe QT prolongation and a bizarre T-wave followed by a late coupled initiation of Torsades de Pointes.

## Variable plasma concentrations and DITdP

For most drugs, the risk of DITdP is plasma concentration-related. Thus, genetic or other mechanisms that contribute to high-plasma concentrations for specific drugs are also risk factors for DITdP. Sotalol and dofetilide are renally excreted, and failure to decrease the dose in patients with renal dysfunction receiving these drugs will increase plasma levels and the associated risk of DITdP.<sup>3,4</sup> Similarly, overdose with QT-prolonging drugs such as sotalol or terfenadine,<sup>27–29</sup> leads to high plasma concentrations and increased risk. Terfenadine is a potent QT-prolonging/ $I_{Kr}$  blocking compound, but is ordinarily very rapidly eliminated by metabolism accomplished by a specific hepatic cytochrome P450, CYP3A4; CYP3A4-mediated terfenadine metabolism results in a metabolite fexofenadine that retains the anti-histamine activity in the parent drug, but lacks its QT-prolonging liability. In patients receiving terfenadine and strong CYP3A4 inhibitors such as ketoconazole or erythromycin, risk for DITdP was markedly increased.<sup>29–31</sup> Indeed, it was the risk for DITdP and the availability of the downstream metabolite that retains the desired pharmacological effect, but largely lacks the toxicity that led to terfenadine's withdrawal from the market. The biological activity of CYP3A4 and related enzymes (CYP3A5, CYP3A7) vary substantially among individuals, and genetic variants mediating this variability in enzymatic activity have been identified. However, to date, none have been clearly linked to increased risk for DITdP. The anti-psychotic agent thioridazine is bioinactivated by metabolism accomplished by a separate enzyme, CYP2D6. In 5–10% of Caucasian and African subjects, CYP2D6 activity is absent on a genetic basis; these subjects are homozygotes (or compound heterozygotes) for loss-of-function alleles in the gene. In such poor metabolizers receiving thioridazine, an increased risk for QT prolongation, and perhaps DITdP, has been described.<sup>32</sup>

There are exceptions to the general rule that increasing plasma concentrations confers increased risk for DITdP. For example,

quinidine markedly prolongs action potentials *in vitro* at low concentrations but at higher ones this action potential effect is blunted. It is thought that block of outward current, notably outward  $I_{Kr}$  (discussed subsequently), accounts for action-potential prolongation at low concentrations while block of peak inward current, mediated by sodium channels, accounts for action-potential shortening at higher concentrations. Similarly, the calcium-channel blocker verapamil is a potent  $I_{Kr}$  blocker *in vitro*, but QT prolongation is virtually never seen since the drug's major clinical effect is to block calcium channels and thereby limit QT prolongation by  $I_{Kr}$  block.

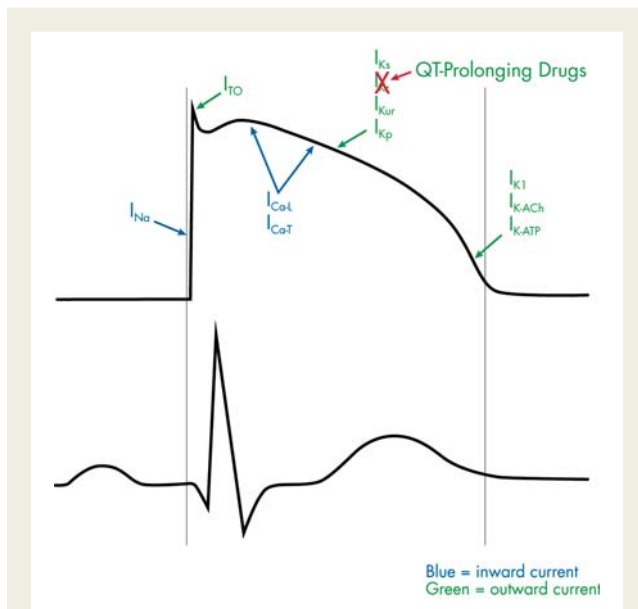
## Electrophysiological mechanisms in DITdP

Prolongation of the QT interval on the surface electrocardiogram directly indicates that action potentials in at least some portion of the ventricle must be prolonged. There is an abundant literature that has implicated dispersion of action-potential durations in the ventricle as a key component of QT-interval morphology (e.g. time from the peak of the T-wave to the end of the T-wave) as well as susceptibility to TdP and perhaps other arrhythmias. One school of thought contends that such dispersion is transmural, with marked prolongation of action-potential durations in the mid-myocardium (M cell) layer,<sup>33</sup> while others maintain that normal cell-to-cell coupling cannot generate large transmural heterogeneities and rather, if heterogeneities exist, they must be apical to basal.<sup>34</sup> In either case, any effort to understand the molecular and cellular basis of QT-interval prolongation must start with a consideration of repolarization of Purkinje and ventricular action potentials.

There are two major repolarizing potassium currents in heart,  $I_{Kr}$  and  $I_{Ks}$ . The two currents are the products of separate genes, and display different activation and deactivation kinetics and sensitivities to activation by intracellular signalling systems and to block

by drugs. Normal cardiac repolarization is accomplished by a time-dependent increase in net outward current during the action potential, and this, in turn, is generated by increasing outward potassium currents ( $I_{Kr}$  and  $I_{Ks}$ ) as well as waning inward current through calcium, and to some extent sodium, channels. This is a first approximation: other channels contribute directly or indirectly by contributing inward or outward current to the repolarization process or by modulating these currents, e.g. by changing diastolic and systolic intracellular calcium concentration mediated predominantly by altered calcium influx and efflux and thereby affecting second messenger-related signalling for repolarizing currents. With unusual exceptions, the common mechanism underlying action potential and QT prolongation seen in DITdP is drug block of  $I_{Kr}$ , the rapid component of the delayed rectifier current (Figure 2).<sup>35</sup> Recent studies have implicated reduced PI3K (phosphoinositide 3-kinase) signalling as a modulator of multiple ion currents to prolong action potentials.<sup>36</sup>

Importantly, simple action potential prolongation cannot explain the development of TdP. Experimental studies have suggested that the heterogeneities of repolarization presented earlier predispose to unstable re-entry.<sup>37</sup> A second possibility is raised by *in vitro* studies<sup>38</sup> that demonstrate that when action potentials are markedly prolonged, notably in conduction tissue (such as Purkinje fibers), secondary upstrokes, termed early afterdepolarizations (EADs), often result. Early afterdepolarizations are generated *in vitro* by factors very similar to the risk factors for TdP *in vivo*: hypokalaemia, bradycardia, drug exposure. Thus, the initiation of TdP, or perhaps even its maintenance, may be due to this form of abnormal automaticity.<sup>39</sup>



**Figure 2** The diagram illustrates the timing of the ventricular myocyte action potential and the surface ECG with associated inward and outward currents. Blockade of the rapid rectifier current ( $I_{Kr}$ ) is the most common mechanism for drug-induced QT prolongation and Torsades de Pointes.

The complexity of cardiac repolarization, and the interaction among the various components that control it, suggests that alteration in function of individual components, through genetic or acquired mechanisms (e.g. due to disease) can modulate the QT interval and, in turn, risk for DITdP. On the other hand, the very complexity of the system may allow changes in the function of its individual components to be well-buffered, allowing the entire repolarization process to display some 'reserve'. The concept of 'repolarization reserve'<sup>40</sup> thus suggests that lesions in the individual components of the complex repolarization process may themselves be well tolerated, but that multiple lesions (e.g. a loss-of-function in one component combined with drug block of a second) may be sufficient to elicit marked QT prolongation and susceptibility to TdP.<sup>41,42</sup>

## Identification of genetic variants increasing the risk for DITdP

### Congenital long-QT syndrome disease genes

The accumulation of case series of DITdP identified small numbers of subjects in whom the diagnosis of congenital long-QT syndrome was only made after the culprit drug exposure and arrhythmia.<sup>43,44</sup> This observation is consistent with the current concept that some patients with congenital long-QT syndrome display little QT-interval prolongation at baseline<sup>45</sup> but may be more susceptible to developing marked QT interval prolongation upon challenge with a QT-prolonging drug. The identification of disease genes for the congenital long-QT syndrome has allowed systematic surveys of the extent to which unrecognized congenital long-QT syndrome is a risk factor for DITdP cases.<sup>46–50</sup> On average, around 10% of subjects with DITdP have rare variants in the congenital long-QT syndrome disease genes and thus are thought to represent incompletely penetrant congenital long-QT syndrome (Table 3). These studies have focussed on commoner disease genes for the congenital syndrome and have not surveyed rarer, newly reported ones.<sup>51</sup>

### Common polymorphisms in ion-channel genes

The identification of congenital long-QT syndrome disease genes led to a catalog of genetic variation across these genes. Most variants studied to date have been 'non-synonymous' (i.e. they change an amino acid) and often data relating function of variant channels to those of wild-type channels can be generated *in vitro*, e.g. in heterologous expression systems. One variant, resulting in S1103Y (i.e. substitution of a tyrosine for a serine at position 1103 in the cardiac sodium channel) is relatively common in African subjects, with a minor allele frequency of ~13%, but very unusual in subjects of other ethnicities. Functional expression of S1103Y has demonstrated increased late sodium current especially under acidotic conditions.<sup>52</sup> It has been implicated as a risk factor for DITdP and other arrhythmias, including sudden infant death syndrome, in African-Americans.<sup>53</sup> A survey of a large collection of patients with DITdP compared with drug exposed patients



**Table 3** Long QT-syndrome mutations detected in drug-induced Torsades de Pointes cases

Study	Wei et al. <sup>49</sup> Sesti et al. <sup>50</sup> Yang et al. <sup>48</sup>	Paulussen et al. <sup>47</sup>	Mank-Seymour et al. <sup>70</sup>	Itoh et al. <sup>46</sup>	Overall
Ethnicity	White	White	White	Japanese	
KCNQ1, %	1 (0.5)	0	1 (1.5)	2 (10)	4 (2.2)
KCNH2, %	1 (0.5)	1 (1.5)	0	5 (25)	7 (3.9)
KCNE2, %	3 (1.6)	0	0	0	3 (1.7)
SCN5A, %	3 (1.6)	0	1 (1.5)	1 (5)	5 (2.8)
Total mutation carriers, %	8 (8.7)	1 (3.1)	2 (5.9)	8 (40)	<b>19 (10.7)</b>
Total cases	92	32	34	20	178

The overall frequency of long QT syndrome associated mutations is given in bold.

with minimal QT interval prolongation and to population controls implicated the polymorphism resulting in D85N in KCNE1, an important subunit for  $I_{Ks}$  function, as a risk factor.<sup>54</sup> The allele frequency of D85N was ~8% among subjects with DITdP, and 1–2% in the controls, and this confers an odds ratio of 9–12.

## Genome-wide association studies and DITdP

The genome-wide association studies (GWAS) paradigm searches for genetic loci, tagged by common single-nucleotide polymorphisms, associated with human phenotypes. While most GWAS studies include thousands, or tens of thousands, of patients, those focussing on rare adverse drug events do not (by definition) study very large numbers of cases but nevertheless have sometimes been successful in identifying associated genomic variation with only a few (several dozen) cases and controls; the most notable examples have been immunologically mediated adverse reactions (such as Stevens–Johnson syndrome or drug-induced liver injury).<sup>55,56</sup> Preliminary reports of a DITdP GWAS suggest that very large signals are unlikely,<sup>57</sup> suggesting that common variants do not strongly modulate risk across a population.

The GWAS paradigm has also been used to study variability in baseline QT interval.<sup>58–60</sup> These studies, encompassing tens of thousands of individuals, have identified multiple loci at which common variation influences variability in the QT interval. Some of these are in ion-channel genes, suggesting that rare variants in these genes can cause diseases like the congenital long-QT syndrome, whereas common variants modulate the baseline QT interval. One of the strongest signals to emerge from GWAS analysis of baseline QT interval is variation at the *NOS1AP* locus in chromosome 1. The gene encodes an ancillary protein for neuronal nitric oxide synthase, and *in vitro* and *in vivo* studies suggest that it modulates both potassium- and calcium-current function.<sup>61</sup> These results are the starting point for the exploration of the role of QT-modulating genes in DITdP and other traits. *NOS1AP* variants have been implicated as modulators of arrhythmia risk in congenital long-QT syndrome,<sup>62,63</sup> and in sudden death in the general population.<sup>64</sup> Most recently, variation in the *NOS1AP* locus was strongly associated with a roughly five-fold increased

risk of DITdP among patients in whom amiodarone was the culprit drug.<sup>65</sup>

## Rare variants in ion-channel genes

Newer approaches to sequencing may enable examination of the potential role of rare variants in DITdP. One recent study resequenced 79 candidate arrhythmia genes in a small number of subjects with diLQTS ( $n=26$  Caucasians) and identified a very high proportion of individuals with rare variants, compared with background rates observed in control sets such as the 1000 Genomes project or the Exome Sequencing project.<sup>51</sup>

Identifying the role for genetic variation in DITdP will require further accumulation of well-characterized cases across different ethnic groups receiving different drugs. This is the goal of the iSAEC phenotype standardization project described earlier.<sup>2</sup>

## Approaches to implementation

One goal of studies identifying genomic markers of individuals at increased risk for unusual drug responses is implementation of this information in clinical workflow. One approach is to genotype patients for risk alleles at the time a drug is prescribed. Thus, for example, genotyping for *NOS1AP* variants or for *KCNE1* D85N could be undertaken when a prescription for sotalol or amiodarone is written. A difficulty with this ‘reactive’ approach is that results must be turned around very rapidly and reliably. The cumbersome nature of this genotyping, the associated costs and time involved, and the nuanced nature of the advice (‘this patient is at increased risk for’) all likely contribute to resistance on the part of practitioners to adopt pharmacogenomic testing for DITdP and in many other settings. Exceptions at this point to this generalization are in the uptake of HLA testing for use of drugs such as abacavir or carbamazepine; here, the adverse event is serious and prospective randomized trials have indicated that genetic testing can virtually eliminate the adverse event.<sup>66,67</sup>

An alternate view, propelled by the rapidly decreasing costs of genotyping and resequencing, is to embed information on clinically relevant genomic and pharmacogenomic variation into patients’ electronic medical records, and then to develop informatics-based systems to deliver advice to physicians at the point of care. In this vision, the record of a patient receiving a prescription for sotalol or

amiodarone would be interrogated for variants such as those in *NOS1AP* or *KCNE1*, and if such variants were present, advice would be delivered to the prescriber that the patient may be at increased risk. Adopting this 'preemptive' approach to pharmacogenomic testing has the potential advantage of reducing costs and of exploiting advances in information technology to minimize disruption in the workflow of healthcare.

There are significant issues that must be addressed before such a pre-emptive vision of genotype-based healthcare can start to be implemented. These include: the strength of evidence associating genetic variation with variable drug outcomes; the interaction with non-genetic risk; mechanisms to develop that evidence; the reliability of genotyping assays; the variable effects of genetic variants across ancestries; development of sophisticated informatics-capable electronic medical-record systems; and physicians' and patients' attitudes. Pharmacogenetic data may then be able to influence the clinical management process by either indicating closer monitoring of the patient while receiving medication, an alteration of drug dosage, complete avoidance of therapy in that patient or replacement with a similar drug of lower risk. The experience with other cardiovascular drugs such as warfarin and clopidogrel and genetic variation in drug metabolism indicate that much work is still required to validate promising findings in research before they may have clinical application.<sup>68</sup> Indeed the need for pharmacogenetic stratification may often be removed by developing a new safer drug that will eventually replace old such as prasugrel for clopidogrel or the novel oral anti-coagulants for warfarin. This is less likely to be the case for DITdP as risk transcends individual medication and indication and drugs from certain therapeutic classes such as anti-psychotics and anti-arrhythmics are associated, inevitably, with some degree of risk. While some of the variability in specific drug-associated DITdP risk may relate to genetic variability in metabolism pathways, this remains to be demonstrated. Much relates, however, to the downstream effects of the drug on repolarization reserve, such as  $I_{Kr}$  blockade.

Pilot studies have therefore been initiated to develop and validate these approaches, based on multiplexed genotyping in at-risk patients.<sup>69</sup> As the evidence accumulates implicating genomic variation in DITdP risk, incorporating such risk predictors into preemptive genotyping strategies may become a reality.

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