Risk factors for drug-induced long-QT syndrome

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Congenital long-QT syndrome (cLQTS) is a ventricular arrhythmia that is characterised by a prolonged QT interval on the surface electrocardiogram (ECG). Clinical symptoms include sudden loss of consciousness (syncopes), seizures, cardiac arrest and sudden death. The prevalence of this inherited disease is approximately one in 10,000 in Caucasians. Over the last decade, more than 200 different diseases causing mutations have been identified in five genes that encode ion channels involved in the delicate balance of inward and outward K/Ca currents during the cardiac action potential. A prolonged QT interval accompanied by very similar clinical symptoms as in cLQTS can also occur in otherwise healthy individuals after the intake of specific drug(s). This phenomenon is known as 'acquired' or 'drug-induced' long-QT syndrome. Because the clinical symptoms of the two forms are very similar, the question arises whether a common underlying genetic basis also exists. Several studies indicate that only a minority (approximately 10%) of the drug-induced LQTS cases can be explained by a mutation or polymorphism in one of the known LQTS genes. Even though the disease can often at least partially be explained by environmental factors, mutations or polymorphisms in other genes are also expected to be involved, including genes encoding drug-metabolising enzymes, adrenergic receptors, hormone-related genes and mitochondrial genes. This article reviews the current knowledge on risk factors for drug-induced LQTS, with a special emphasis on the role of genetic determinants. (*Neth Heart J* 2005;13:47-56.)

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Long-QT syndrome is a cardiac disease with clinical features such as sudden loss of consciousness (syncopes), seizures, cardiac arrest or sudden cardiac death. The clinical hallmark of this syndrome is an abnormal prolongation of the QT interval on a surface electrocardiogram (figure 1A). First described in 1856, the inherited forms of the syndrome (dominant Romano Ward and recessive Jervell Lange Nielsen) are now well characterised and more than 2500 scientific articles have since been published on this disorder. The genetic basis of the familial forms of LQTS has been the subject of extensive research, and the first linkage analysis studies led to the location of the first LQTS locus on chromosome 11p in 1991.[1] Additional genetic studies in multiple families subsequently led to the disclosure of seven loci (named LQT1 to LQT7) associated with this syndrome (table 1). Except for one (*AnkB*, LQT4), all of the currently known genes causing LQTS genes code for ion channels located in the cell membrane of cardiac cells. These ion channels are involved in the electrical activity chain that is required for the cardiac action potential that leads to cardiac contraction (figure 1B). The rising phase (phase 0) of the cardiac action potential is mediated by an influx of sodium ions through voltage-gated sodium channels (*SCN5A*, LQT3).[2] After an early transient repolarisation (phase I), calcium ions enter the cell through L- and T-type calcium channels, while potassium ions leave the cell (phase 2 and 3) through I_{Ks} (*KCNQ1*, LQT1 and *KCNE1*, LQT5)[3,4] and I_{Kr} (*KCNH2*, LQT2, *KCNE2*, LQT6).[5,6] A mutation in one of these ion channel genes often leads to a reduction in outward potassium current (LQT1, 2, 5, 6, 7) or an increase in inward

Table 1. Congenital LQTS genes and the encoded proteins.

Form	Chromosomal location	Gene (protein)	Current	Reported mutations in LQTS patients	
				Congenital**	Drug induced***
LQT1	11p15.5	KCNQ1 (KvLQT1)	I_{Ks}	103	3
LQT2	7q35-36	KCNH2 (HERG)	I_{Kr}	140	1
LQT3	3p21-23	SCN5A (SCN5A)	I_{Na}	31	6
LQT4	4q25-27	AnkB (AnkB)	-	1	0
LQT5	21q22.1	KCNE1 (MinK)	β-subunit	13	1
LQT6	21q22.1	KCNE2 (MiRP1)	β-subunit	4	5
LQT7*	17q23-24	KCNJ2 (Kir2.1)	I_{K1}	0	0

* LQT7 is known as Andersen syndrome (AS) which is a rare, inherited disorder characterised by periodic paralysis, long QT (LQT) with ventricular arrhythmias, and skeletal developmental abnormalities.
** For the specific mutations with references see URL http://pc4.fsm.it:81/cardmoc/
*** For details see table 5 and figure 2.

sodium current (LQT3). Both of these scenarios lead to a delay in ventricular repolarisation that is visible as a prolongation of the QT interval on the ECG. In its turn, delayed repolarisation leads to electrical instability that may cause ventricular tachyarrhythmias resulting in a reduced cardiac output and eventually syncopes or sudden death.

Drug-induced long-QT syndrome

Apart from the inherited form of LQTS that typically runs in families, there is another form of LQTS that is induced by the intake of specific drugs, and which can also lead to fatal arrhythmias such as torsades de pointes (TdP). The incidence of drug-induced LQTS is difficult to estimate because the majority of data are based on either individual case reports or clinical trial studies.[7,8] Based on a risk assessment, drugs have been subdivided into one of the following categories: high risk of TdP (group 1), possible risk of TdP (group 2), drugs to be avoided by congenital LQTS patients (group 3) and drugs unlikely to cause TdP (group 4) (www.torsades.org). Several drugs (e.g. astemizole,

Table 2. Case reports involving drugs with a high incidence of torsades de pointes case reports.

Drug class	Drug	Incidence of TdP in treated patients	Reference
Antiarrhythmic drugs	Amiodarone	<1%	42
	Disopyramide	<quinidine	
	Dofetilide	3-4% (intravenous)	43
		0.8-1.5% (oral)	43
	Ibutilide	1.7%	44
	Procainamide	<quinidine	
	Quinidine	1-3%	45
	Sotalol	2-5%	46
Antihistamines	Astemizole	Removed from market	
	Terfenadine	Removed from market	
Antibiotics	Clarithromycin	Rare with single treatment	
		Frequent with drug-drug interaction	47
	Erythromycin	<1%*	48
Antipsychotics	Droperidol	<1%, removed from European market*	49
	Haloperidol	3.6%	50
	Thioridazine		
Cholinergic antagonists	Cisapride	<1%, removed from US and Canadian market*	51

Data based on reports in PubMed until January 2004.
* These drugs are prescribed many millions of times each year. Several case reports have been published over a long period of time. For example, 346 cases of TdP were reported in over 100 million erythromycin prescriptions in a period of 25 years. For droperidol, in 30 years and over 20 million prescriptions a year, 20 cases of TdP, 9 cardiac arrests and 2 deaths at therapeutic dose have been reported.

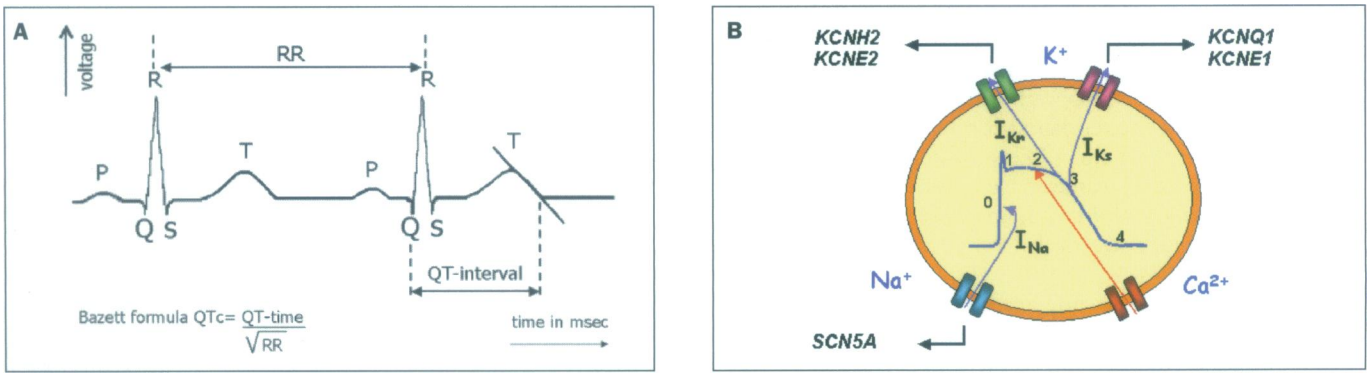

Figure 1A. Reflection of a single heart beat on an ECG in lead II. The QT interval is defined as the distance between the start of the Q wave to the end of the T wave. 1B. Illustration of a single action potential, composed of different K^+ and Na^+ ion channels located in the cell membrane. These channels are encoded by ion channel genes LQT1, 2, 3, 5 and 6. Mutations in one of these genes can lead to a prolongation of the action potential and thereby the QT interval (red dotted line).

terfenadine and cisapride) have been retracted from the market because of unacceptably high incidences of postmarketing TdP reports. Several other drugs classified in group 1 (table 2) may however have a similar or even higher incidence, but are still in use because of the lack of alternative drugs available and/or the severity of the disease treated (e.g. anti-arrhythmic drugs).

Table 3. Reported individual cases of TdP by concomitant medication.

Drug 1	Drug 2	Sex	Age (years)	Symptoms	References
Amiodarone	Loratadine	Female	73	TdP	52
Astemizole	Ketoconazole	Female	63	TdP	53
Astemizole	Erythromycin	Female	30	TdP	54
Astemizole	Cimetidine	Female	77	TdP	55
Terfenadine	Itraconazole	Female	26	TdP	56
Terfenadine	Ketoconazole	Female	39	TdP	57
Terfenadine	Itraconazole	Female	36	TdP	58
Cisapride	Ketoconazole	Female	57	TdP, VF	59
Cisapride	Erythromycin	Female	18	TdP	59
Cisapride	Clarithromycin	Female	77	TdP	60
Cisapride	Clarithromycin	Female	53	TdP	61
Cisapride	Erythromycin	Male	64	TdP	62
Cisapride	Erythromycin	Male	30	TdP	63
Cisapride	Diltiazem	Female	45	Syncope, prolonged QT	64
Cisapride	Erythromycin + fluconazole	Female	8	VT	65
Cisapride	Clarithromycin	Female	52	TdP	66
Cisapride	Clarithromycin	Male	83	TdP	66
Cisapride	Erythromycin	Female	47	TdP	67
Quinidine	Propafenone	Female	77	TdP	68
Quinidine	Erythromycin	Male	95	TdP, cardiac arrest	69
Quinidine	Verapamil	Female	65	TdP	70
Disopyramide	Clarithromycin	Female	76	TdP	71
Pimozide	Clarithromycin	Male	27	SD	72
Mosapride	Flecainide	Male	68	TdP, PM	73
Disopyramide	Clarithromycin	Female	76	TdP	74
Droperidol	Cyclopenzaprine + fluoxetine	Female	59	TdP, VF	75

TdP=torsades de pointes, VF=ventricular fibrillation, VT=ventricular tachycardia, SD=sudden death, PM=pacemaker.

A common mechanism for the proarrhythmic effect of these drugs appears to be a blockade of I_{Kr} (HERG, MiRP1), the rapid component of the delayed rectifier current, which is responsible for the outward potassium flow during the repolarisation phase (figure 1B). For the majority of the LQTS-inducing drugs, in vitro and/or in vivo studies have demonstrated that these drugs significantly block I_{Kr} in a dose-dependant manner and at therapeutic levels.[9-11]

During the last decade, researchers have attempted to identify environmental and genetic risk factors that could explain and/or predict the occurrence of drug-induced TdP. The next paragraphs discuss currently known nongenetic and genetic risk factors.

Nongenetic risk factors for drug-induced long-QT syndrome

Drug-drug interactions and drug metabolism

Due to drug-drug interactions, the effectiveness or toxicity of one drug may be altered by the administration of another drug. TdP may arise from two different types of interactions. Firstly, a pharmacodynamic effect between two or more drugs might occur if each of the drugs is individually capable of prolonging the QT interval but no inter-drug interaction is observed.[12] The second possibility is a pharmacokinetic effect in which one drug reduces the clearance of the other co-administered QT-prolonging drug(s), leading to elevated plasma concentrations.[13] These last-mentioned interactions appear to occur frequently in individual case reports of patients suffering from TdP (table 3). For instance, 65% of the published reports on the prokinetic drug cisapride involved concomitant administration of either erythromycin or clarithromycin.[14] These competing interactions for metabolism usually find their way through the cytochrome P450 enzyme system which is responsible for the metabolism of endogenous as well as exogenous compounds.[15] In the human genome, 59 active cytochrome P450 genes are known, of which only six are responsible for 70 to 80% of all phase I dependent metabolism of clinically used drugs.[16] As an example, table 4 provides an overview of frequently reported QT-prolonging drugs belonging to the CYP2D6 and CYP3A metabolic pathways. Most of the drugs implicated in TdP development are metabolised via these hepatic enzyme systems and hence, a combination of drugs that are metabolised via the same CYP450 enzyme may lead to a higher increase in QT prolongation compared with therapeutic dosages of each of the drugs alone.

Although the administered drugs are obviously regarded as the main cause of drug-induced TdP, secondary factors that may facilitate or predispose to its development are involved in the majority of the cases. These commonly reported secondary factors are discussed below.

Table 4. QT-prolonging substrates and inhibitors of CYP450 enzymes.

	CYP2D6	CYP3A (4/5)
Substrates	Propafenone	Amiodarone
	Haloperidol	Astemizole
	Thioridazine	Cisapride
	Mexiletine	Cyclosporin
		Diltiazem
		Diazepam
		Disopyramide
		Erythromycin
		Lidocaine
		Midazolam
		Pimozide
		Propafenone
		Quinidine
		Tamoxifen
		Terfenadine
		Verapamil
Inhibitors	Amiodarone	Amiodarone
	Cimetidine	Cimetidine
	Quinidine	Clarithromycin
	Halofantrine	Diltiazem
		Erythromycin
		Fluconazole
		Itraconazole
		Ketoconazole
		Verapamil

Age and gender

In the total group of all reported drug-induced LQTS cases elderly women are over represented (table 3), which may in part be due to the higher longevity of women that is associated with a higher likelihood of (concomitant) drug intake. The observation that average QT intervals remain longer in women after puberty, as opposed to QT shortening in men, may also be of importance.[17] This hypothesis is strengthened by the fact that in many congenital LQT families adult women have a higher risk of cardiac events than men.[18] Today, the mechanisms for the age- and sex-related differences remain unclear, although preliminary animal studies have indicated that sex hormones may contribute to QT shortening in males or the lack of shortening in females.[19]

Electrolyte disturbances

A shortage of potassium, hypokalaemia, has been reported as a contributing factor in several individual TdP case reports.[20,21] This additional risk factor can be explained by the modulation of the I_{Kr} channel by external potassium.[22] Paradoxically, the magnitude of

Table 5. Mutations and polymorphisms in LQTS genes detected in drug-induced LQTS patients.

Gene	Mutation	Amino acid change	Polymorphism frequency	Drug(s)	Reference
KCNH2	984 C>T	R328C		n.s.	76
	1039 C>T	P347S		Cisapride + clarithromycin	28
	2350 C>T	R784W		Amiodarone	77
KCNE2	22 A>G	T8A*	1.6% (Caucasians)	Sulphamethoxazole	29
				Quinidine	6
				Amiodarone	28
	25 C>G	Q9E		Clarithromycin	6
	161 T>C	M54T		Procainamide	29
	170 T>C	I57T		Oxatomide	29
	347 C>T	A116V		Quinidine + mexilitine	29
KCNQ1	944 A>G	Y315C		Cisapride	78
	1663 C>T	R555C		Terfenadine	79
	1747 C>T	R583C		Dofetilide	77
KCNE1	253 G>A	D85N*	2-7% (US Caucasians)	Sotalol	28
				Quinidine	28
SCN5A	1844 G>A	G615E		Quinidine	77
	1852 C>T	L618F		Quinidine	77
	3305 C>A	S1102Y*	13.2% (African-Americans)	Amiodarone	33
	3748 T>C	F1250L		Sotalol	77
	4999 G>A	V1667I		Halofantrine	80
	5474 T>C	L1825P		Cisapride	81

* Amino acid changes that represent polymorphisms rather than mutations, with a specific frequency in different ethnic populations.

outward HERG (LQT2) current amplitude is reduced upon removal of extracellular K^+, which in turn causes a prolongation of the ventricular repolarisation in these patients. Combined with a drug that blocks the HERG channel, hypokalaemia may exaggerate the effect.[23] Consequently, the administration of potassium supplements can be very useful in hypokalaemic patients when TdP episodes occur.

Other heart disease

It may not be surprising that individuals with structural heart disease are more vulnerable to drug-induced TdP than healthy individuals. QT prolongation in patients recovering from myocardial infarction has been well documented.[24] Other studies suggest that ischaemic, valvular and hypertensive heart disease, and bradycardia may also be involved in triggering TdP.[25]

Genetic factors involved in drug-induced TdP

Mutations in congenital LQTS genes

Because the clinical manifestations of drug-induced LQTS patients resemble those of congenital LQTS patients, it is tempting to speculate that drug-induced patients harbour an as of yet undetected 'mild' mutation in their genes that only shows its potential when challenged by a drug. More than 20 years ago, Moss et al. suggested that genetic variations might influence the susceptibility to develop drug-induced TdP.[26] In this respect, Priori et al. reported that the penetrance of disease-causing mutations in congenital families can be as low as 30%, suggesting that many mutation carriers are asymptomatic under normal circumstances.[27] It is, therefore, indeed reasonable to believe there are individuals highly susceptible to developing TdP in the general population who have not been identified as congenital LQTS patients because of small family size or incomplete penetrance. This hypothesis is further supported by literature reports on several individual cases of TdP development upon drug intake with an underlying mutation in the aminoacid coding sequence of a congenital LQTS-causing gene (table 5 and figure 2). An obvious question is, however, what proportion of drug-induced LQTS patients harbours such a mutation. Today, four independent studies have been performed in larger

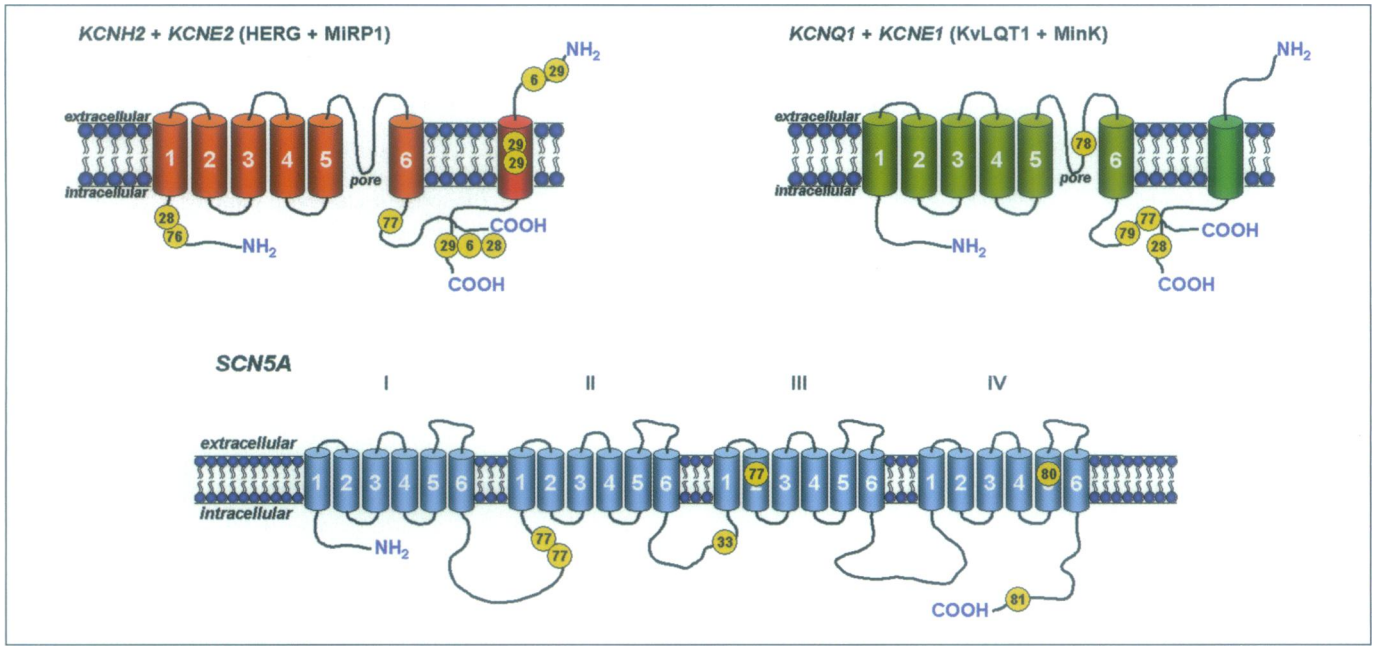

Figure 2. Topology of ion channel proteins (α- and β-subunits). The yellow dots represent mutations or polymorphisms that have been detected in drug-induced long-QT syndrome patients (see table 5). Reference numbers are indicated in the yellow dots.

groups of drug-induced TdP patients, which all showed a similar result: only approximately 10% of the examined patients within the groups could be explained by an underlying 'forme fruste' mutation.[28]

DNA polymorphisms in congenital LQTS genes

Apart from the rare mutations in LQTS genes with a low penetrance as detected in congenital families, DNA polymorphisms exist in those genes with a mild disease phenotype and a relatively higher frequency in the general population. Sesti et al.[29] were the first to report on a T8A variant in the *KCNE2* gene, which was proven to mildly increase the sensitivity towards drug block, and has a prevalence of 1 to 2% in the general Caucasian population (table 5 and figure 2). This variant was later also detected in one of our studies[28] in which we also detected two drug-induced LQTS patients with a D85N polymorphism in the *KCNE1* gene. This last polymorphism was earlier suggested to be a susceptibility factor for drug-induced LQTS,[30] although functional consequences of this polymorphism have not yet been reported in the literature. Interestingly, the reverse effect of a DNA polymorphism has also been reported: the K897T polymorphism in *KCNH2* leads to a shortening of the QT interval due to increased activation and deactivation.[31]

As efforts in genetic research on long-QT syndrome are expanding, also other ethnic groups apart from Caucasians are now being included in studies, which could lead to the identification of other mutations or polymorphisms at different frequencies.[32] For example, Splawski et al. reported on an S1102Y polymorphism in the *SCN5A* gene with an increased susceptibility to drug-induced TdP and a frequency of 13.2% in African-Americans.[33] This polymorphism was, however, not detected in Caucasians and Asians. The role of these ethnic differences was recently also illustrated by Ackerman et al. who showed large differences in polymorphism frequencies in cardiac ion channel genes between black, white, Asian and Hispanic populations.[34]

Genetic variations in drug-metabolising enzyme genes

In addition to the inhibitory effects of concomitant drug administration and the consequently elevated plasma levels of QT-prolonging drugs (see above), genetic variations in the genes encoding these drug-metabolising enzymes may also play a role. The large majority of the drugs involved in drug-induced LQTS are metabolised via the hepatic enzymes CYP2D6 and CYP3A (table 4). The *CYP2D6* gene has been well characterised and is polymorphically expressed. Several variants in this gene abolish the CYP2D6 enzyme function completely, leading to the so-called poor metaboliser (PM) phenotype if both *CYP2D6* gene copies of an individual's genome are affected. This results in substantially higher plasma levels than anticipated, and possibly adverse reactions such as TdP at therapeutic dosages.[35] The population frequency of the PM phenotype ranges from 6 to 10% in Caucasians, and varies with ethnicity (<1% in Asians, 2 to 5% in African-Americans). Four variants (polymorphisms or complete gene deletion) in the *CYP2D6* gene explain up to 98% of the PM phenotypes in Caucasians. Thus, a QT-prolonging drug that is metabolised via CYP2D6

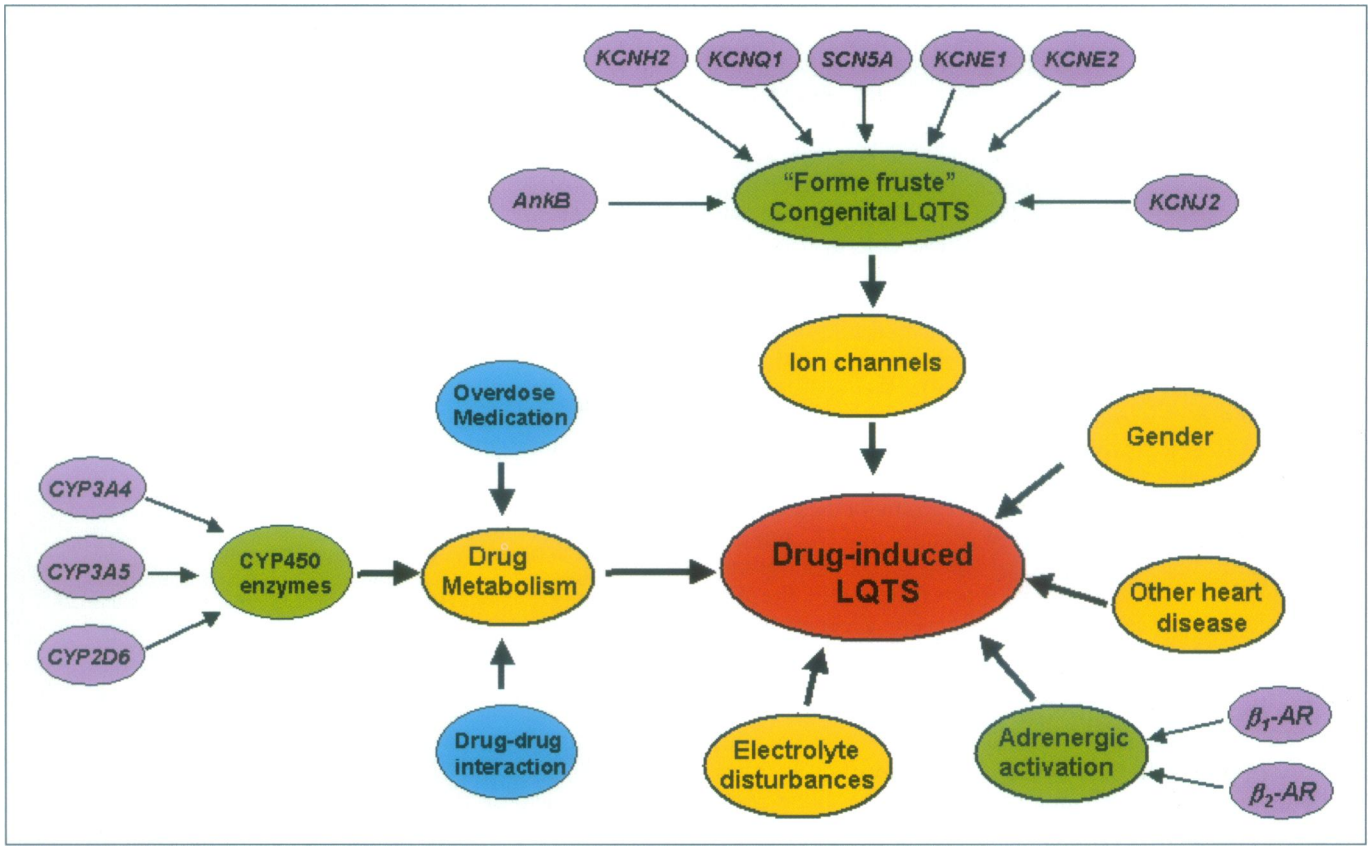

Figure 3. Representation of currently known factors involved in the development of torsades de pointes, including the genes that (may) play a role in these factors.

and that is prescribed to an individual with the PM genotype could possibly contribute to an increased susceptibility to TdP development.

The CYP3A isoenzyme family is one of the most important drug-metabolising enzymes, being responsible for over 50% of all clinically used drugs.[15] Of the two forms expressed during adulthood (CYP3A4 and CYP3A5) only CYP3A5 is polymorphically expressed. Earlier experiments detected two polymorphisms in the *CYP3A5P1* pseudogene promoter that could explain bimodal CYP3A5 expression.[36] Later, these polymorphisms were found to be in linkage disequilibrium (in Caucasians) with a splice site variant in intron 3 of the *CYP3A5* gene, causing a low CYP3A5 expression in 70% of Caucasians.[37] Interestingly, Gibbs et al.[38] showed that liver microsomes with a high amount of CYP3A5 expression were less susceptible to ketoconazole and fluconazole inhibition, which may suggest that CYP3A5 could be an important genetic contributor to interindividual differences in drug response and TdP development.

Other genetic factors

Because only a few mutations in congenital LQTS genes were detected in larger groups of drug-induced LQTS patients, it seems worthwhile to search for additional genes that might (indirectly) be involved in QT prolongation and TdP development. Kanki et al. screened the β-adrenergic receptor 1 and 2 genes (β_1-AR, β_2-AR) in drug-induced LQTS patients, because of the sympathetic activation trigger for TdP in many congenital patients and the increase in heart rate in drug-induced LQTS patients just prior to TdP development.[39] So far, however, none of the detected missense polymorphisms in these genes have been shown predictive of drug-induced TdP. Matsuoka et al.[40] reported on a mitochondrial DNA mutation (3394 T>C) in the NADH dehydrogenase subunit 1 (*ND1*) gene in a congenital LQTS family, resulting in reduced complex I activity and oxygen consumption. The authors hypothesised that this may lead to depletion of ATP and an increase in Ca^{2+} cytosolic concentration, thereby prolonging the QTU intervals in both congenital and drug-induced LQTS patients.

Conclusions

The list with drugs that have been reported to cause marked QT-interval prolongation and TdP is expanding continuously. In addition to several antiarrhythmic drugs, of which it is well recognised that 1 to 8% of the patients receiving them develop TdP, a

growing number of noncardiovascular agents is on this list of LQTS-inducing drugs, including antihistamines, antibiotics and antipsychotics. Thanks to many studies, the risk factors contributing to drug-induced LQTS are becoming better understood, and comprise among other things gender, electrolyte disturbances, other heart disease, concomitant medication and underlying mutations in congenital LQTS genes (figure 3). Despite the knowledge of these risk factors, the development of TdP in an individual patient still remains very unpredictable.

The discovery of genes implicated in congenital long-QT syndrome has provided a better insight into the molecular basis of this ventricular arrhythmia. However, mutation screening of the currently known cLQTS genes explains only a minority of the cases of drug-induced LQTS. This number could perhaps be increased by a more thorough screening of these genes, including the promoter and untranslated (5' and 3') regions. In this respect, a first report on the cloning and characterisation of the promoter of one of the ion channel genes (*SCN5A*) has very recently been reported, including the identification of a polymorphism in this region affecting promoter activity.[41] Although this discovery is important because it could shed new light on the regulation of ion channel expression, it is reasonable to assume that other modulating or secondary factors will be involved in the development of the disease in many individual patients. Despite the clear scientific value of mutation screening in drug-induced LQTS patients, it is less clear how mutation screening could be implemented as a tool to prevent drug-induced LQTS in the clinical situation. Unfortunately, a number of factors make its use as a predictive diagnostic tool rather limited: drug-induced LQTS is a rare disorder which can be induced by a large variety of different drugs, and only a small number of these patients can be explained by the results of the mutation screening of at least five different genes. Given the high costs for mutation screening today, it is very questionable whether it is economically feasible to perform these analyses in a large population of patients before they start taking potentially drug-inducing medication, especially since it can be anticipated that less than 20% of drug-induced LQTS patients can be identified. However, for the more frequent polymorphisms (D85N in *KCNE1*, T8A in *KCNE2*) that have already been identified as susceptibility factors for drug-induced LQTS, genotyping of new cases should be considered in order to further investigate the contribution of these polymorphisms to the occurrence of TdP, which might eventually lead to the development of a pharmacogenetic test predictive of an increased risk to develop drug-induced LQTS.

Metabolism of QT-prolonging drugs could be an important risk factor since not only combinations of drugs competing for the same drug metabolising enzyme can lead to elevated plasma levels, but also variations in drug metabolising enzyme genes have been proven to affect the availability of the active enzyme. Future screening of these genes in drug-induced LQTS patients might elucidate the significance of inter-individual differences in drug metabolism.

Other factors that influence QT prolongation, such as adrenergic stimulation triggers, hormones, electrolyte disturbances and other heart disease, have not yet revealed any significant genes or polymorphisms, although it is expected that more sophisticated genotyping technologies will make it feasible to fully screen candidate genes for drug-induced long-QT syndrome. ■

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