INTRODUCTION

Pharmacogenomics research typically aims to find genetic variants that affect the pharmacokinetics or the pharmacodynamics of a drug. Pharmacokinetic effects can be very direct, and are therefore easy to understand. Genetic variants can cause loss of function for a metabolic enzyme that can in turn decrease the rate at which a drug is metabolized. This increases the amount of drug delivered to the active site, as well as the half-life of the drug in the system. There is a wider range of pharmacodynamic effects. A variant can change the binding properties of a receptor to which a drug is targeted, and can therefore affect activity. Alternatively, a variant can simply alter the level of expression of some protein that can lead to an indirect effect on drug action. Variants that cause such expression changes can be \textit{cis}, meaning that a variant in the gene has a direct effect on the gene’s expression level. Alternatively, the effect can be \textit{trans}, meaning that variation elsewhere in the genome indirectly affects expression levels for the gene. Genes causing such \textit{trans} effects can be far removed from pathways directly involved in drug action.

The aim of pharmacogenomic research in the cardiac safety area are threefold: (1) to understand variability in safety that is caused by genetics; (2) to develop tools to help evaluate safety of compounds early in clinical trials; and (3) to develop tests to keep
susceptible patients off of inappropriate drugs, or at safe doses. In almost all therapeutic areas there is large variability in both safety and response, and this variability is driven in part by genetics.

The goals of this chapter are to review current knowledge of the genetic factors that can affect the risk of drug-induced torsades de pointes (TdP), and to describe some possible avenues for further research in this area. As we will show, the range of possible genetic risk factors is large, so that we are far from being able to screen all patients for genetic risk prior to drug prescription. However, a more modest goal seems to be in reach: that of being able to understand the cause for outliers in clinical trials (excessive QT prolongation or TdP). From this, it may then be possible to quantify the risk of seeing significant problems with a drug once it goes into larger clinical trials and onto the market.

Currently, there are about 50 drugs on the market that carry some risk of drug-induced TdP that results from drug-induced QT prolongation. The incidence of TdP ranges from very low (on the order of 1 out of 100,000 users of cisapride) (1), to relatively high (e.g., sotalol, which shows a rate of a few percent) (2–4). These drugs span many classes and indications. However, there are some common risk factors however. Virtually all QT-prolonging drugs block the hERG potassium-ion channel (5). Women are at higher risk than men. Hypokalemia and the use of diuretics increase risk. In addition to these and other “phenotypic” risk factors, there are known “pharmacogenomic” risk factors. We will use the term pharmacogenomic loosely to mean instances where we can directly relate clinical risk to an underlying genetic mechanism. Ultimately, with greater understanding of underlying mechanisms, more of the phenotypic risk factors may change their status to pharmacogenomic.

The most well understood classes of pharmacogenomic risks of TdP involve drug metabolism (pharmacokinetics) and the interaction of drugs, directly or indirectly, with cardiac ion channels (pharmacodynamics) (6). Many QT-prolonging drugs are metabolized by the cytochrome P450 class of enzymes. Some individuals inherit defective versions of these enzymes that can lead them to be poor metabolizers. Most metabolic enzymes can also be inhibited by other drugs that can cause patients on multiple medications to receive higher than desired effective concentrations of the drug at the site of action. Both of these situations are well understood. On the pharmacodynamic side, certain individuals have genetic defects that alter the ability of their cardiac potassium and sodium ion channels to conduct. This can lead to the familial Long QT Syndrome (LQTS). The addition of a hERG blocker can be a second hit that will decrease the conductivity of their IKr channel to the point that significant QT prolongation is seen, which in turn increases the risk of TdP. Although it is now well known that mild prolongation of the QT interval is not always a good surrogate for risk of TdP (7), we will discuss both QT prolongation and TdP risk together.

Cisapride offers an example where both pharmacodynamic and pharmacokinetic genetic risk factors were seen to be important enough to make their way into the label (8). This drug was available from 1993 to 2000, when it was removed from active marketing and placed on a compassionate need program as a result of 341 reports of patients with cardiac events, 80 of whom died. All deaths were associated with drug-induced arrhythmias. These cases were reviewed and analyzed by the Food and Drug Administration (8). In 1999, family history of LQTS was added to the label as a contraindication, based on evidence that the drug could be the critical second hit for individuals who had