that substrate. Individuals with two alleles (variants) encoding for nonfunctional protein make up one group, often termed *poor metabolizers* (PM phenotype); for some genes, many variants can produce such a loss of function, complicating the use of genotyping in clinical practice. Individuals with one functional allele make up a second (*intermediate metabolizers*) and may or may not be distinguishable from those with two functional alleles (*extensive metabolizers*, EMs). *Ultra-rapid metabolizers* with especially high enzymatic activity (occasionally due to gene duplication; Fig. 5-6) have also been described for some traits. Many drugs in widespread use can inhibit specific drug disposition pathways (Table 5-1), and so EM individuals receiving such inhibitors can respond like PM patients (*phenocopying*). Polymorphisms in genes encoding drug uptake or drug efflux transporters may be other contributors to variability in drug delivery to target sites and, hence, in drug effects.

CYP Variants Members of the CYP3A family (CYP3A4, 3A5) metabolize the greatest number of drugs in therapeutic use. CYP3A4 activity is highly variable (up to an order of magnitude) among individuals, but the underlying mechanisms are not well understood. In whites, but not African Americans, there is a common loss-of-function polymorphism in the closely related CYP3A5 gene. Decreased efficacy of the antirejection agent tacrolimus in African-American subjects has been attributed to more rapid elimination due to relatively greater CYP3A5 activity. A lower risk of vincristine-associated neuropathy has been reported in CYP3A5 "expressers."

CYP2D6 is second to CYP3A4 in the number of commonly used drugs that it metabolizes. CYP2D6 activity is polymorphically distributed, with about 7% of European- and African-derived populations (but very few Asians) displaying the PM phenotype (Fig. 5-6). Dozens of loss-of-function variants in the CYP2D6 gene have been described; the PM phenotype arises in individuals with two such alleles. In addition, ultra-rapid metabolizers with multiple functional copies of the CYP2D6 gene have been identified.

Codeine is biotransformed by CYP2D6 to the potent active metabolite morphine, so its effects are blunted in PMs and exaggerated in ultra-rapid metabolizers. In the case of drugs with beta-blocking properties metabolized by CYP2D6, greater signs of beta blockade (e.g., bronchospasm, bradycardia) are seen in PM subjects than in EMs. This can be seen not only with orally administered beta blockers such as metoprolol and carvedilol, but also with ophthalmic timolol and with the sodium channel–blocking antiarrhythmic propafenone, a CYP2D6 substrate with beta-blocking properties. Ultra-rapid metabolizers may require very high dosages of tricyclic antidepressants to achieve a therapeutic effect and, with codeine, may display transient euphoria and nausea due to very rapid generation of morphine. Tamoxifen undergoes CYP2D6-mediated biotransformation to an active metabolite, so its efficacy may be in part related to this polymorphism. In addition, the widespread use of selective serotonin reuptake inhibitors (SSRIs) to treat tamoxifen-related hot flashes may also alter the drug's effects because many SSRIs, notably fluoxetine and paroxetine, are also CYP2D6 inhibitors.

The PM phenotype for CYP2C19 is common (20%) among Asians and rarer (2–3%) in European-derived populations. The impact of polymorphic CYP2C19-mediated metabolism has been demonstrated with the proton pump inhibitor omeprazole, where ulcer cure rates with "standard" dosages were much lower in EM patients (29%) than in PMs (100%). Thus, understanding the importance of this polymorphism would have been important in developing the drug, and knowing a patient's *CYP2C19* genotype should improve therapy. CYP2C19 is responsible for bioactivation of the antiplatelet drug clopidogrel, and several large studies have documented decreased efficacy (e.g., increased myocardial infarction after placement of coronary stents) among Caucasian subjects with reduction of function alleles. In addition, some studies suggest that omeprazole and possibly other proton pump inhibitors phenocopy this effect.

There are common variants of *CYP2C9* that encode proteins with loss of catalytic function. These variant alleles are associated with increased rates of neurologic complications with phenytoin, hypoglycemia with glipizide, and reduced warfarin dose required to maintain stable anticoagulation. The angiotensin-receptor blocker losartan is a prodrug that is bioactivated by CYP2C9; as a result, PMs and those receiving inhibitor drugs may display little response to therapy.

Transferase Variants One of the most extensively studied phase II polymorphisms is the PM trait for thiopurine S-methyltransferase (TPMT). TPMT bioinactivates the antileukemic drug 6-mercaptopurine. Further, 6-mercaptopurine is itself an active metabolite of the immunosuppressive azathioprine. Homozygotes for alleles encoding the inactive TPMT (1 in 300 individuals) predictably exhibit severe and potentially fatal pancytopenia on standard doses of azathioprine or 6-mercaptopurine. On the other hand, homozygotes for fully functional alleles may display less anti-inflammatory or antileukemic effect with the drugs.

N-acetylation is catalyzed by hepatic *N*-acetyl transferase (NAT), which represents the activity of two genes, *NAT-1* and *NAT-2*. Both enzymes transfer an acetyl group from acetyl coenzyme A to the drug; polymorphisms in *NAT-2* are thought to underlie individual differences in the rate at which drugs are acetylated and thus define "rapid acetylators" and "slow acetylators." Slow acetylators make up ~50% of European- and African-derived populations but are less common among Asians. Slow acetylators have an increased incidence of the drug-induced lupus syndrome during procainamide and hydralazine therapy and of hepatitis with isoniazid. Induction of CYPs (e.g., by rifampin) also increases the risk of isoniazid-related hepatitis, likely reflecting generation of reactive metabolites of acetylhydrazine, itself an isoniazid metabolite.

Individuals homozygous for a common promoter polymorphism that reduces transcription of uridine diphosphate glucuronosyltransferase (*UGT1A1*) have benign hyperbilirubinemia (Gilbert's syndrome; Chap. 358). This variant has also been associated with diarrhea and increased bone marrow depression with the antineoplastic prodrug irinotecan, whose active metabolite is normally detoxified by UGT1A1-mediated glucuronidation. The antiretroviral atazanavir is a UGT1A1 inhibitor, and individuals with the Gilbert's variant develop higher bilirubin levels during treatment.

VARIABILITY IN THE MOLECULAR TARGETS WITH WHICH DRUGS INTERACT

Multiple polymorphisms identified in the β_2-adrenergic receptor appear to be linked to specific phenotypes in asthma and congestive heart failure, diseases in which β_2-receptor function might be expected to determine prognosis. Polymorphisms in the β_2-receptor gene have also been associated with response to inhaled β_2-receptor agonists, while those in the β_1-adrenergic receptor gene have been associated with variability in heart rate slowing and blood pressure lowering (Fig. 5-5*B*). In addition, in heart failure, a common polymorphism in the β_1-adrenergic receptor gene has been implicated in variable clinical outcome during therapy with the investigational beta blocker bucindolol. Response to the 5-lipoxygenase inhibitor zileuton in asthma has been linked to polymorphisms that determine the expression level of the 5-lipoxygenase gene.

Drugs may also interact with genetic pathways of disease to elicit or exacerbate symptoms of the underlying conditions. In the porphyrias, CYP inducers are thought to increase the activity of enzymes proximal to the deficient enzyme, exacerbating or triggering attacks (Chap. 430). Deficiency of glucose-6-phosphate dehydrogenase (G6PD), most often in individuals of African, Mediterranean, or South Asian descent, increases the risk of hemolytic anemia in response to the antimalarial primaquine (Chap. 129) and the uric acid–lowering agent rasburicase, which do not cause hemolysis in patients with normal amounts of the enzyme. Patients with mutations in the ryanodine receptor, which controls intracellular calcium in skeletal muscle and