TABLE 5-2 GENETIC VARIANTS AND DRUG RESPONSES

Gene	Drugs	Effect of Genetic Variants[a]
Variants in Drug Metabolism Pathways		
CYP2C9	Losartan	Decreased bioactivation and effects (PMs)
	Warfarin	Decreased dose requirements; possible increased bleeding risk (PMs)
CYP2C19	Omeprazole, voriconazole	Decreased effect in extensive metabolizers (EMs)
	Celecoxib	Exaggerated effect in PMs
	Clopidogrel	Decreased effect in PMs
CYP2D6	Codeine, tamoxifen	Decreased bioactivation and drug effects in PMs
	Codeine	Morphine-like adverse effects in UMs
	Tricyclic antidepressants	Increased adverse effects in PMs; decreased therapeutic effects in UMs
	Metoprolol, carvedilol, timolol, propafenone	Increased beta blockade in PMs
CYP3A5	Tacrolimus, vincristine	Decreased drug concentrations and effect
Dihydropyrimidine dehydrogenase	Capecitabine, fluorouracil	Possible severe toxicity (PMs)
NAT2	Rifampin, isoniazid, pyrazinamide, hydralazine, procainamide	Increased risk of toxicity in PMs
Thiopurine S-methyltransferase (*TPMT*)	Azathioprine, 6-mercaptopurine	*3A/*3A (PMs): increased risk of bone marrow aplasia; wild-type homozygote: possible decreased drug action at usual dosages
Uridine diphosphate glucuronosyltransferase (*UGT1A1*)	Irinotecan	*28/*28 PM homozygotes: increased risk of severe adverse effects (diarrhea, bone marrow aplasia)
Variants in Other Genes		
Glucose 6-phosphate dehydrogenase (G6PD)	Rasburicase, primaquine, chloroquine	Increased risk of hemolytic anemia in G6PD-deficient subjects
HLA-B*1501	Carbamazepine	Carriers (1 or 2 alleles) at increased risk of severe skin toxicity
HLA-B*5701	Abacavir	Carriers (1 or 2 alleles) at increased risk of severe skin toxicity
IL28B	Interferon	Variable response in hepatitis C therapy
IL15	Childhood leukemia therapy	Variability in response
SLCO1B1	Simvastatin	Encodes a drug uptake transporter; variant non-synonymous single nucleotide polymorphism increases myopathy risk
VKORC1	Warfarin	Decreased dose requirements with variant promoter haplotype
ITPA	Ribavirin	Variants modulate risk for hemolytic anemia
Variants in Other Genomes (Infectious Agents, Tumors)		
Chemokine C-C motif receptor (CCR5)	Maraviroc	Drug effective only in HIV strains with CCR5 detectible
C-KIT	Imatinib	In gastrointestinal stromal tumors, drug indicated only with c-kit–positive cases
Epidermal growth factor receptor (EGFR)	Cetuximab	Clinical trials conducted in patients with EGFR-positive tumors
Her2/neu overexpression	Trastuzumab, lapatinib	Drugs indicated only with tumor overexpression
K-ras mutation	Panitumumab, cetuximab	Lack of efficacy with *KRAS* mutation
Philadelphia chromosome	Busulfan, dasatinib, nilotinib, imatinib	Decreased efficacy in Philadelphia chromosome–negative chronic myelogenous leukemia

[a]Drug effect in homozygotes unless otherwise specified.

Note: EM, extensive metabolizer (normal enzymatic activity); PM, poor metabolizer (homozygote for reduced or loss of function allele); UM, ultra-rapid metabolizer (enzymatic activity much greater than normal, e.g., with gene duplication, Fig. 5-6). Further data at U.S. Food and Drug Administration: *http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm*; or Pharmacogenetics Research Network/Knowledge Base: *http://www.pharmgkb.org*.

uptake into the liver, which accounts for 60% of myopathy risk. GWA approaches have also implicated interferon variants in antileukemic responses and in response to therapy in hepatitis C. Ribavirin, used as therapy in hepatitis C, causes hemolytic anemia, and this has been linked to variants in *ITPA*, encoding inosine triphosphatase.

GENETIC VARIANTS AFFECTING PHARMACOKINETICS

Clinically important genetic variants have been described in multiple molecular pathways of drug disposition (Table 5-2). A distinct multimodal distribution of drug disposition (as shown in Fig. 5-6) argues for a predominant effect of variants in a single gene in the metabolism of