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# Polymorphisms affecting gene regulation and mRNA processing: Broad implications for pharmacogenetics

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**Abstract**

Functional polymorphisms that alter gene expression and mRNA processing appear to play a critical role in shaping human phenotypic variability. Intensive studies on polymorphisms affecting drug response have revealed multiple modes of altered gene function, frequently involving *cis*-acting regulatory sequence variants. Experimental and in silico methods have advanced the search for such polymorphisms, but considerable challenges remain. Here, a survey of polymorphisms in drug-related genes indicates that: (a) a substantial proportion of genetic variability still remains unaccounted for; (b) a majority of these genes harbors known regulatory polymorphisms; and (c) a portion of polymorphisms affect splicing and mRNA turnover. Pharmacogenetic optimiziation of individual drug therapy may require a complete understanding of all functional sequence variants in key genes. This review surveys known noncoding polymorphisms in genes encoding cytochrome *P*450s and other drug-metabolizing enzymes, drug transporters, and drug targets and receptors. Current methods and challenges associated with the identification and characterization of functional polymorphisms are also discussed.


*Keywords:* *Cis*-Regulatory; Polymorphism; Pharmacogenetics; Pharmacogenomics; SNP; RNA; Allele-specific; Genotype-phenotype; Cytochrome; Review

*Abbreviations*: 5-FU, 5-fluorouracil; 5-HTT, serotonin transporter; 5-HTTLPR, serotonin gene-linked polymorphic region; 6-MP, 6-mercaptopurine; 6-TG, 6-thioguanine; ABCB, ATP-binding cassette (ABC), subfamily B; ACE, angiotensin I converting enzyme (peptidyl-dipeptidase A) 1; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ARE, adenylate-uridylate-rich element; ARED, adenylate-uridylate-rich element database; bp, base pair; BS, binding site; C/EBP, CCAAT/enhancer binding proteins; CAR, constitutive androstane receptor; CGAP, cancer genome anatomy project; CREATE, comprehensive research on expressed alleles in therapeutic evaluation; CRM, *cis*-regulatory module; CYP, cytochrome; DBP, albumin D-site binding protein; DPYD, dihydropyrimidine dehydrogenase; *Drd2*, dopamine D2 receptor; EM, extensive metabolizer; ESE, exonic splicing enhancer; Ets, E twenty six; FXR, farnesol X receptor; haploCHIP, haplotype-specific chromatin immunoprecipitation; hGRα, human glucocorticoid receptor alpha; hGRβ, human glucocorticoid receptor beta; HGVbase, human genome variation database; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HNF, hepatocyte nuclear factor; hnRNA, heterogeneous nuclear RNA; *hPepT2*, human solute carrier family 15 (H+/peptide transporter), member 2 gene; HTR2A, 5-hydroxytryptamine (serotonin) receptor 2a; IM, intermediate metabolizer; IVS, intronic splice site variation; kb, kilobases; LDL, low-density lipoprotein; LIPC, hepatic lipase; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight spectroscopy; MMP, matrix metalloproteinase; NAT, *N*-acetyltransferase; NF-Y, nuclear transcription factor Y; OATP, organic anion-transporting polypeptide; PABA, *para*-aminobenzoic acid; PGA, program for genomic applications; PharmGKB, the pharmacogenetics and pharmacogenomics knowledge base; PM, poor metabolizer; PPAR-α, peroxisome proliferator-activated receptor alpha; PTC, premature termination codon; PTP1N, protein tyrosine phosphatase, nonreceptor type 1; PXR, pregnane X receptor; SIFT, sorting tolerant from intolerant; SLC, solute carrier; SLCO, solute carrier organic anion transporter family; SM12502, (+)-*cis*-3,5-dimethyl-2(3-pyridyl) thiazolidin-4-one hydrochloride; SNP, single nucleotide polymorphism; SP-1, Sp1 transcription factor; SULT, sulfotranferase; TPMT, thiopurine (*S*)-methyltransferase; TSER, thymidylate synthase enhancer region; TYMS, thymidylate synthase; UGT1, UDP-glucuronosyltranferase-1; USF1, upstream transcription factor 1; UTR, unstranslated region; VDR, vitamin D receptor; VNTR, variable number tandem repeat.

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## 1. Introduction

Regulation at the level of transcription initiation and RNA processing defines downstream biological effects. Such regulation occurs in *cis*, directly affecting the regulated gene, but it can also act in *trans* by altering activity of downstream genes (Fig. 1). Significant interindividual differences in gene expression patterns are common and may result from both environmental factors and *cis*- or *trans*-mediated genetic effects (Singer-Sam et al., 1992; Enard et al., 2002; Whitney et al., 2003; Pastinen & Hudson, 2004). There is growing evidence for abundant polymorphisms in *cis*-acting sequences that influence gene expression (Rockman & Wray, 2002; Yan et al., 2002; Bray et al., 2003; Lo et al., 2003) and indication that a significant portion of functional polymorphisms affect *cis*-acting regulatory elements (Stamatoyannopoulos, 2004; Wittkopp et al., 2004). Identifying the functional alleles that account for interindividual differences remains difficult (Ioannidis, 2003; Page et al., 2003; Sun et al., 2004). The genetic components of complex interindividual differences may require resolution of multiple modest variations in genotype which collectively yield a recognizeable phenotype such as disease susceptibility or drug response.

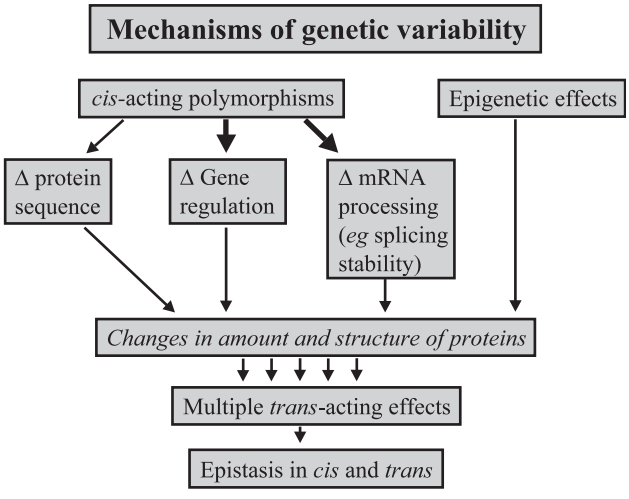


Fig. 1. Human genetic variability, involving *cis*- and *trans*-acting polymorphisms. *Cis*-acting regulatory polymorphisms appear to outnumber functional polymorphisms in coding regions affecting protein sequence. If *cis*-acting polymorphisms alter signaling or transcription factor activity, multiple *trans*-acting changes ensue. Epigenetic changes can mimic *cis*-acting polymorphisms. Lastly, epistatic effects (multiple interacting polymorphisms) are likely to play a role as well. Not shown are regulatory effects exerted by small RNAs, also subject to genetic variability.

Phenotypic differences can arise from genetic polymorphisms acting in *cis* by changing the protein coding sequence or at the level of RNA (Day & Tuite, 1998): affecting transcription (activation or inhibition through regulatory sites or structure of regulatory elements), mRNA processing, pre-mRNA splicing, exonic splicing enhancers (ESEs), exon skipping (Cartegni et al., 2003), mRNA stability (Sheets et al., 1990; Conne et al., 2000; Di Paola et al., 2002; Tebo et al., 2003), mRNA trafficking, or regulatory RNAs (Fig. 1). The most commonly studied polymorphisms, nonsynonymous changes that alter amino acid coding, appear in many cases insufficient to account for interindividual differences in disease aetiology and response to therapies. Further, it is estimated that functional polymorphisms that are *cis*-regulatory in the human genome outnumber those that alter protein sequence, and that the bulk of regulatory polymorphisms remain to be discovered (Ng & Henikoff, 2002; Rockman & Wray, 2002; Stamatoyannopoulos, 2004; Yan & Zhou, 2004). On the other hand, genomewide linkage analysis with mRNA expression as the quantitative trait demonstrates that interindividual differences in mRNA profiles appear to be largely caused by *trans*-acting factors (Morley et al., 2004). These statements are not incompatible since a single *cis*-acting polymorphism in a transcription factor or receptor could affect the expression of numerous other genes (Fig. 1). Therefore, to