Pharmacogenomics

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Pharmacogenomics (a portmanteau of pharmacology and genomics) is the study of the role of genetics in drug response. It deals with the influence of acquired and inherited genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with drug absorption, distribution, metabolism and elimination, as well as drug receptor target effects.[1][2][3] The term pharmacogenomics is often used interchangeably with pharmacogenetics. Although both terms relate to drug response based on genetic influences, pharmacogenetics focuses on single drug-gene interactions, while pharmacogenomics encompasses a more genome-wide association approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response.[4][5][6]

Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects.[7] Through the utilization of pharmacogenomics, it is hoped that drug treatments can deviate from what is dubbed as the “one-dose-fits-all” approach. It attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient’s genes, the functionality of these genes, and how this may affect the efficacy of the patient’s current and/or future treatments (and where applicable, provide an explanation for the failure of past treatments).[4] Such approaches promise the advent of "personalized medicine"; in which drugs and drug combinations are optimized for each individual's unique genetic makeup.[8][9] Whether used to explain a patient’s response or lack thereof to a treatment, or act as a predictive tool, it hopes to achieve better treatment outcomes, greater efficacy, minimization of the occurrence of drug toxicities and adverse drug reactions (ADRs). For patients who have lack of therapeutic response to a treatment, alternative therapies can be prescribed that would best suit their requirements. In order to provide pharmacogenomic-based recommendations for a given drug, two possible types of input can be used: genotyping or exome or whole genome sequencing.[10] Sequencing provides many more data points, including detection of mutations that prematurely terminate the synthesized protein (early stop codon).[10]

Contents

History

Pharmacogenomics was first recognized by Pythagoras around 510 BC when he made a connection between the dangers of fava bean ingestion with hemolytic anemia and oxidative stress. Interestingly, this identification was later validated and attributed to deficiency of G6PD in the 1950s and called favism.[11][12] Although the first official publication dates back to 1961,[13] circa 1950s marked the unofficial beginnings of this science. Reports of prolonged paralysis and fatal reactions linked to genetic variants in patients who lacked butyryl-cholinesterase ('pseudocholinesterase') following administration of succinylcholine injection during anesthesia were first reported in 1956.[1][14] The term pharmacogenetic was first coined in 1959 by Friedrich Vogel of Heidelberg, Germany (although some papers suggest it was 1957). In the late 1960s, twin studies supported the inference of genetic involvement in drug metabolism, with identical twins sharing remarkable similarities to drug response compared to fraternity twins.[15] The term pharmacogenomics first began appearing around the 1990s.[11]

Drug-metabolizing enzymes

There are several known genes which are largely responsible for variances in drug metabolism and response. The focus of this article will remain on the genes that are more widely accepted and utilized clinically for brevity.

- Cytochrome P450s
- VKORC1
- TPMT

Cytochrome P450

The most prevalent drug-metabolizing enzymes (DME) are the Cytochrome P450 (CYP) enzymes. The term Cytochrome P450 was coined by Omura and Sato in 1962 to describe the membrane-bound, heme-containing protein characterized by 450 nm spectral peak when complexed with carbon monoxide.[16] The human CYP family consists of 57 genes, with 18 families and 44 subfamilies. CYP proteins are conveniently arranged into these families and subfamilies on the basis of similarities identified between the amino acid sequences. Enzymes that share 35-40% identity are assigned to the same family by an Arabic numeral, and those that share 55-70% make up a particular subfamily with a designated letter.[17] For example, CYP2D6 refers to family 2, subfamily D, and gene number 6.

From a clinical perspective, the most commonly tested CYPs include: CYP2D6, CYP2C19, CYP2C9, CYP3A4 and CYP3A5. These genes account for the metabolism of approximately 80-90% of currently available prescription drugs.[18][19] The table below provides a summary for some of the medications that take these pathways.

Drug Metabolism of Major CYPs[20][21]		
Enzyme	**Fraction of drug metabolism (%)**	**Example Drugs**
CYP2C9	10	Tolbutamide, ibuprofen, mefenamic acid, tetrahydrocannabinol, losartan, diclofenac
CYP2C19	5	S-mephenytoin, amitriptyline, diazepam, omeprazole, proguanil, hexobarbital, propranolol, imipramine
CYP2D6	20-30	Debrisoquine, metoprolol, sparteine, propranolol, encainide, codeine, dextromethorphan, clozapine, desipramine, haloperidol, amitriptyline, imipramine
CYP3A4	40-45	Erythromycin, ethinyl estradiol, nifedipine, triazolam, cyclosporine, amitriptyline, imipramine
CYP3A5	<1	Erythromycin, ethinyl estradiol, nifedipine, triazolam, cyclosporine, amitriptyline, aldosterone

CYP2D6

Also known as debrisoquine hydroxylase (named after the drug that led to its discovery), CYP2D6 is the most well-known and extensively studied CYP gene.[22] It is a gene of great interest also due to its highly polymorphic nature, and involvement in a high number of medication metabolisms (both as a major and minor pathway). More than 100 CYP2D6 genetic variants have been identified.[21]

CYP2C19

Discovered in the early 1980s, CYP2C19 is the second most extensively studied and well understood gene in pharmacogenomics.[20] Over 28 genetic variants have been identified for CYP2C19,[23] of which affects the metabolism of several classes of drugs, such as antidepressants and proton pump inhibitors.[24]

CYP2C9

CYP2C9 constitutes the majority of the CYP2C subfamily, representing approximately 20% of the liver content. It is involved in the metabolism of approximately 10% of all drugs, which include medications with narrow therapeutic windows such as warfarin and tolbutamide.[24][25] There are approximately 57 genetic variants associated with CYP2C9.[23]

CYP3A4 and CYP3A5

The CYP3A family is the most abundantly found in the liver, with CYP3A4 accounting for 29% of the liver content.[20] These enzymes also cover between 40-50% of the current prescription drugs, with the CYP3A4 accounting for 40-45% of these medications.[12] CYP3A5 has over 11 genetic variants identified at the time of this publication.[23]

VKORC1

The vitamin K epoxide reductase complex subunit 1 (VKORC1) is responsible for the pharmacodynamics of warfarin.[26] VKORC1 along with CYP2C9 are useful for identifying the risk of bleeding during warfarin administration. Warfarin works by inhibiting VKOR, which is encoded by the VKORC1 gene. Individuals with polymorphism in this have an affected response to warfarin treatment.[27]

TPMT

Thiopurine methyltransferase (TPMT) catalyzes the S-methylation of thiopurines, thereby regulating the balance between cytotoxic thioguanine nucleotide and inactive metabolites in hematopoietic cells.[28] TPMT is highly involved in 6-MP metabolism and TMPT activity and TPMT genotype is known to affect the risk of toxicity. Excessive levels of 6-MP can cause myelosuppression and myelotoxicity.[29]

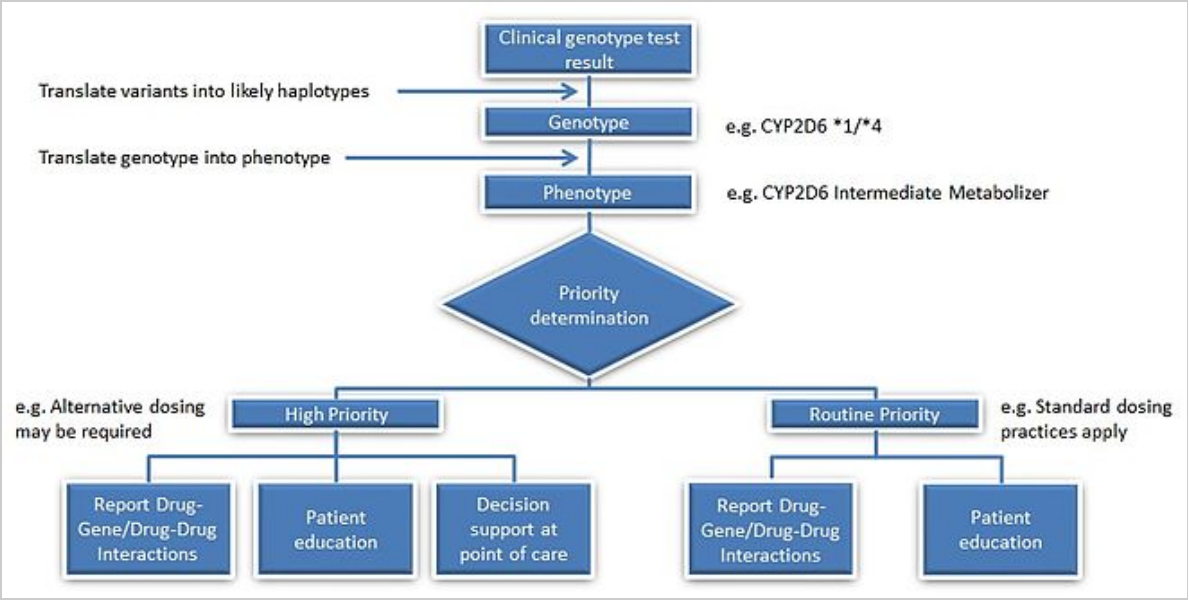
Codeine, clopidogrel, tamoxifen, and warfarin a few examples of medications that follow the above metabolic pathways.

Predictive prescribing

Patient genotypes are usually categorized into the following predicted phenotypes:

- Extensive Metabolizer: Normal metabolic activity;
- Intermediate Metabolizer: Patients with reduced metabolic activity;
- Poor Metabolizer: Patients with little to no functional metabolic activity; and
- Ultra-Rapid Metabolizer: Patients with substantially increased metabolic activity.

The two extremes of this spectrum are the Poor Metabolizers and Ultra-Rapid Metabolizers. Efficacy of a medication is not only based on the above metabolic statuses, but also the type of drug consumed. Drugs can be classified into two main groups: active drugs and pro-drugs. Active drugs refer to drugs that are inactivated during metabolism, and Pro-Drugs are inactive until they are metabolized.



An overall process of how pharmacogenomics functions in a clinical practice. From the raw genotype results, this is then translated to the physical trait, the phenotype. Based on these observations, optimal dosing is evaluated.[28]

For example, we have two patients who are taking codeine for pain relief. Codeine is a pro-drug, so it requires conversion from its inactive form to its active form. The active form of codeine is morphine, which provides the therapeutic effect of pain relief. If person A receives one *1 allele each from mother and father to code for the CYP2D6 gene, then that person is considered to have an extensive metabolizer (EM) phenotype, as allele *1 is considered to have a normal-function (this would be represented as CYP2D6 *1/*1). If person B on the other hand had received one *1 allele from the mother and a *4 allele from the father, that individual would be an Intermediate Metabolizer (IM) (the genotype would be CYP2D6 *1/*4). Although both individuals are taking the same dose of codeine, person B could potentially lack the therapeutic benefits of codeine due to the decreased conversion rate of codeine to its active counterpart morphine.

Each phenotype is based upon the allelic variation within the individual genotype. However, several genetic events can influence a same phenotypic trait, and establishing genotype-to-phenotype relationships can thus be far from consensual with many enzymatic patterns. For instance, the influence of the CYP2D6*1/*4 allelic variant on the clinical outcome in patients treated with Tamoxifen remains debated today. In oncology, genes coding for DPD, UGT1A1, TPMT, CDA involved in the pharmacokinetics of 5-FU/capecitabine, irinotecan, 6-mercaptopurine and gemcitabine/cytarabine, respectively, have all been described as being highly polymorphic. A strong body of evidence suggests that patients affected by these genetic polymorphisms will experience severe/lethal toxicities upon drug intake, and that pre-therapeutic screening does help to reduce the risk of treatment-related toxicities through adaptive dosing strategies.[30]

Identification of the genetic basis for polymorphic expression of a gene is done through intronic or exomic SNPs which abolishes the need for different mechanisms for explaining the variability in drug metabolism. The SNPs based variations in membrane receptors lead to multidrug resistance (MDR) and the drug–drug interactions. Even drug induced toxicity and many adverse effects can be explained by genome-wide association studies (GWAS).[31]

Applications

The list below provides a few more commonly known applications of pharmacogenomics:[32]

- Improve drug safety, and reduce ADRs;
- Tailor treatments to meet patients unique genetic pre-disposition, identifying optimal dosing;
- Improve drug discovery targeted to human disease; and
- Improve proof of principle for efficacy trials.

Pharmacogenomics may be applied to several areas of medicine, including Pain Management, Cardiology, Oncology, and Psychiatry. A place may also exist in Forensic Pathology, in which pharmacogenomics can be used to determine the cause of death in drug-related deaths where no findings emerge using autopsy.[33]

In cancer treatment, pharmacogenomics tests are used to identify which patients are most likely to respond to certain cancer drugs. In behavioral health, pharmacogenomic tests provide tools for physicians and care givers to better manage medication selection and side effect amelioration. Pharmacogenomics is also known as companion diagnostics, meaning tests being bundled with drugs. Examples include KRAS test with cetuximab and EGFR test with gefitinib. Beside efficacy, germline pharmacogenetics can help to identify patients likely to undergo severe toxicities when given cytotoxics showing impaired detoxification in relation with genetic polymorphism, such as canonical 5-FU.[34]

In cardio vascular disorders, the main concern is response to drugs including warfarin, clopidogrel, beta blockers, and statins.[10]

Example case studies

Case A – Antipsychotic adverse reaction[35]

Patient A suffers from schizophrenia. Their treatment includes a combination of ziprasidone, olanzapine, trazodone and benzotropine. The patient experienced dizziness and sedation, so they were tapered off ziprasidone and olanzapine, and transition to quetiapine. Trazodone was discontinued. The patient then experienced excessive sweating, tachycardia and neck pain, gained considerable weight and had hallucinations. Five months later, quetiapine was tapered and discontinued, with ziprasidone re-introduction into their treatment due to the excessive weight gain. Although the patient lost the excessive weight they gained, they then developed muscle stiffness, cogwheeling, tremor and night sweats. When benztropine was added they experienced blurry vision. After an additional five months, the patient was switched from ziprasidone to aripiprazole. Over the course of 8 months, patient A gradually experienced more weight gain, sedation, developed difficulty with their gait, stiffness, cogwheel and dyskinetic ocular movements. A pharmacogenomics test later proved the patient had a CYP2D6 *1/*41, with has a predicted phenotype of IM and CYP2C19 *1/*2 with predicted phenotype of IM as well.

Case B – Pain Management [36]

Patient B is a woman who gave birth by caesarian section. Her physician prescribed codeine for post-caesarian pain. She took the standard prescribed dose, however experienced nausea and dizziness while she was taking codeine. She also noticed that her breastfed infant was lethargic and feeding poorly. When the patient mentioned these symptoms to her physician, they recommended that she discontinue codeine use. Within a few days, both the patient and her infant's symptoms were no longer present. It is assumed that if the patient underwent a pharmacogenomic test, it would have revealed she may have had a duplication of the gene CYP2D6 placing her in the Ultra-rapid metabolizer (UM) category, explaining her ADRs to codeine use.

Case C – FDA Warning on Codeine Overdose for Infants[37]

On February 20, 2013, the FDA released a statement addressing a serious concern regarding the connection between children who are known as CYP2D6 UM and fatal reactions to codeine following tonsillectomy and/or adenoidectomy (surgery to remove the tonsils and/or adenoids). They released their strongest Boxed Warning to elucidate the dangers of CYP2D6 UMs consuming codeine. Codeine is converted to morphine by CYP2D6, and those who have UM phenotypes are at danger of producing large amounts of morphine due to the increased function of the gene. The morphine can elevate to life-threatening or fatal amounts, as became evident with the death of three children in August 2012.

Polypharmacy

A potential role pharmacogenomics may play would be to reduce the occurrence of polypharmacy. It is theorized that with tailored drug treatments, patients will not have the need to take several medications that are intended to treat the same condition. In doing so, they could potentially minimize the occurrence of ADRs, have improved treatment outcomes, and can save costs by avoiding purchasing extraneous medications. An example of this can be found in Psychiatry, where patients tend to be receiving more medications then even age-matched non-psychiatric patients. This has been associated with an increased risk of inappropriate prescribing.[38]

The need for pharmacogenomics tailored drug therapies may be most evident in a survey conducted by the Slone Epidemiology Center at Boston University from February 1998 to April 2007. The study elucidated that an average of 82% of adults in the United States are taking at least one medication (prescription or nonprescription drug, vitamin/mineral, herbal/natural supplement), and 29% are taking five or more. The study suggested that those aged 65 years or older continue to be the biggest consumers of medications, with 17-19 % in this age group taking at least ten medications in a given week. Polypharmacy has also shown to have increased since 2000 from 23% to 29%.[39]

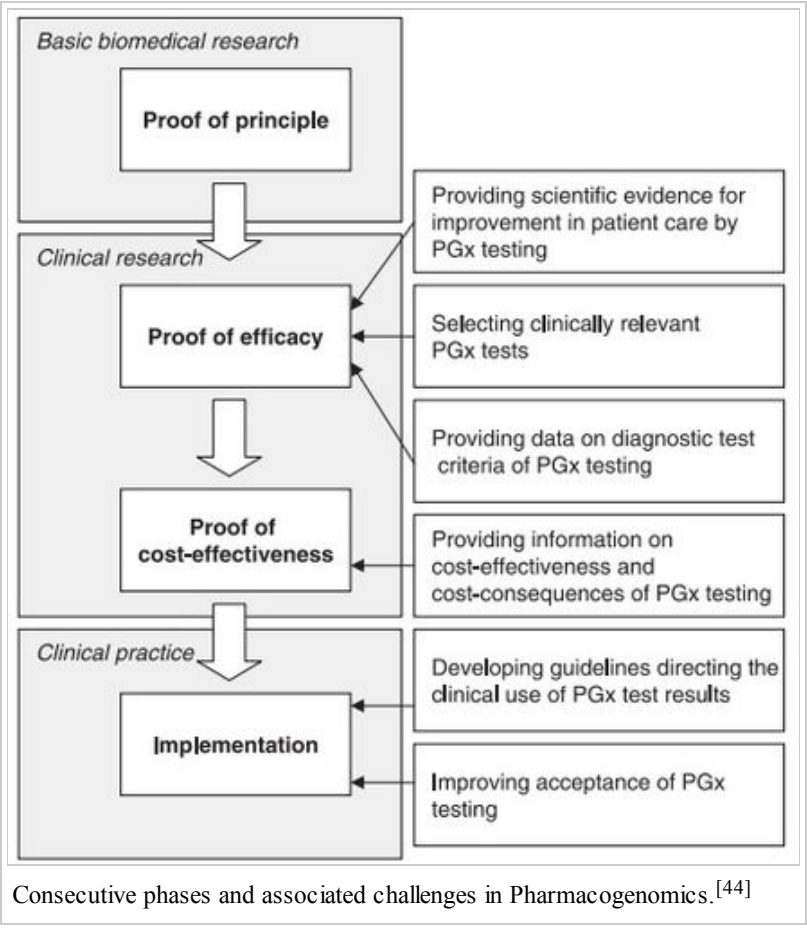
Drug labeling

The U.S. Food and Drug Administration (FDA) appears to be very invested in the science of pharmacogenomics[40] as is demonstrated through the 120 and more FDA-approved drugs that include pharmacogenomic biomarkers in their labels.[41] On May 22, 2005, the FDA issued its first *Guidance for Industry: Pharmacogenomic Data Submissions*, which clarified the type of pharmacogenomic data required to be submitted to the FDA and when.[42] Experts recognized the importance of the FDA's acknowledgement that pharmacogenomics experiments will not bring negative regulatory consequences.[43] The FDA had released its latest guide *Clinical Pharmacogenomics (PGx): Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* in January, 2013. The guide is intended to address the use of genomic information during drug development and regulartory review processes.

Challenges

Although there appears to be a general acceptance of the basic tenet of pharmacogenomics amongst physicians and healthcare professionals,[45] several challenges exist that slow the uptake, implementation, and standardization of pharmacogenomics. Some of the concerns raised by physicians include:[6][45][46]

- Limitation on how to apply the test into clinical practices and treatment;
- A general feeling of lack of availability of the test;
- The understanding and interpretation of evidence-based research; and
- Ethical, legal and social issues.



Consecutive phases and associated challenges in Pharmacogenomics.[44]

Issues surrounding the availability of the test include:[44]

- *The lack of availability of scientific data*: Although there are considerable number of DME involved in the metabolic pathways of drugs, only a fraction have sufficient scientific data to validate their use within a clinical setting; and
- *Demonstrating the cost-effectiveness of pharmacogenomics*: Publications for the pharmacoeconomics of pharmacogenomics are scarce, therefore sufficient evidence does not at this time exist to validate the cost-effectiveness and cost-consequences of the test.

Although other factors contribute to the slow progression of pharmacogenomics (such as developing guidelines for clinical use), the above factors appear to be the most prevalent.

Controversies

Some alleles that vary in frequency between specific populations have been shown to be associated with differential responses to specific drugs. The beta blocker Atenolol is an anti-hypertensive medication that is shown to more significantly lower the blood pressure of Caucasian patients than African American patients in the United States. This observation suggests that Caucasian and African American populations have different alleles governing oleic acid biochemistry, which react differentially with Atenolol.[47] Similarly, hypersensitivity to the antiretroviral drug abacavir is strongly associated with a single-nucleotide polymorphism that varies in frequency between populations.[48]

The FDA approval of the drug BiDil with a label specifying African-Americans with congestive heart failure, produced a storm of controversy over race-based medicine[49] and fears of genetic stereotyping, even though the label for BiDil did not specify any genetic variants but was based on racial self-identification.[50][51]

Future of Pharmacogenomics

Computational advances in Pharmacogenomics has proven to be a blessing in research. As a simple example, for nearly a decade the ability to store more information on a hard drive has enabled us to investigate a human genome sequence cheaper and in more detail with regards to the effects/risks/safety concerns of drugs and other such substances. Such computational advances are expected to continue in the future.[52] The aim is to use the genome sequence data to effectively make decisions in order to minimise the negative impacts on say, a patient or the health industry in general. A large amount of research in the biomedical sciences regarding Pharmacogenomics as of late stems from combinatorial chemistry,[53] genomic mining, omic technologies and high throughput screening. In order for the field to grow rich knowledge enterprises and business must work more closely together and adopt simulation strategies. Consequently more importance must be placed on the role of computational biology with regards to safety and risk assessments. Here we can find the growing need and importance of being able to manage large, complex data sets, being able to extract information by integrating disparate data so that developments can be made in improving human health.

Education

With the growing trend of incorporating pharmacogenomics into clinical practices, several courses have been designed to accommodate health professionals in understanding and using pharmacogenomics. Some of the institutions that offer pharmacogenomics-related coursework in the U.S. are shown below.

Pharmacogenomics Courses (U.S.)	
Institution	**Course/Subject**
University of California, San Diego	PharmGenEd™ - PGx Principles and Concepts and Clinical Applications of Pharmacogenomics
University of California, San Francisco	PhD Program in Pharmaceutical Sciences and Pharmacogenomics
Stanford University	Principles of Pharmacogenomics
The George Washington University	Health Sciences Program
University of Utah	Exploring Pharmacogenomics

In addition to the above, medical schools such as Harvard and the Mayo Clinic also include pharmacogenomics-related medical training.[40] The FDA has also created a training program for genomics with self-teaching tutorials. The American Academy of Family Physicians had also launched a series of workshops with the US National Institutes of Health and the Centers of Disease Control and Prevention. This initiative had resulted in the education of 90,000 family doctors on how to use genetic information in patient care.[42]

Web-based resources

Web Resources for Pharmacogenomics[54][55]		
Data Source	**Main Use**	**URL**

Cytochrome P450 (CYP) Allele Nomenclature Database	A comprehensive list of genes and SNPs identified in the area of pharmacogenomics	http://www.cypalleles.ki.se/
SuperCYP Bioinformatics Tool	Containing 1170 drugs with more than 3800 interactions, and approximately 2000 known SNPs. These SNPs are listed and ordered according to their effect on expression and/or activity	http://bioinformatics.charite.de/supercyp/
PharmGKB	The Pharmacogenomics Knowledge Base (PharmGKB) is an interactive tool for researchers investigating how genetic variation affects drug response	https://www.pharmgkb.org/
dbSNP database	A repository of SNPs and other variants that have been reported after discovery, compiled and officially named. These are SNPs across the board	http://www.ncbi.nlm.nih.gov/SNP/
FINDbase	Repository of allele frequencies of pharmacogenetic markers in different populations	http://www.findbase.org/
Pharmacogenomics Biomarkers in Drug Labelling	A table that identifies which FDA-approved drugs have pharmacogenomics-related warning labels	http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
SNPedia	A wiki-based bioinformatics database of SNPs	http://www.snpedia.com/index.php/SNPedia

See also

- Genomics
  - Pharmacogenetics
  - Toxicogenomics
  - Clinomics
  - Genetic engineering
- Population groups in biomedicine
- Toxgnostics

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